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Cost of Illness Handbook

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PLEASE NOTE: Some of the documents mentioned in this Section are in Adobe's Portable Document Format (PDF). To view or print them you will need to have the Adobe Acrobat Reader program installed on your computer. The Reader can be downloaded and used with no charge; check here for more information on the Adobe Acrobat Reader.

Appendices

- Appendix A: Inflation and Discounting Factors [PDF, 28 KB]

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EXECUTIVE SUMMARY

The societal benefits of environmental regulations and programs are typically manifested by the reduction in adverse health effects. These reductions are associated with decreased exposure to environmental agents. Ideally, valuation of these human health benefits would include all costs to society associated with the benefits, including medical costs, work-related costs, educational costs, the cost of support services required by medical conditions, and the willingness of individuals to pay to avoid the health risks. These factors can be referred to in aggregate as society's total willingness to pay to avoid an illness. Many of these categories of information are difficult to obtain. In particular, obtaining an accurate measure of a society's total willingness-to-pay to avoid illnesses is often not possible. Consequently, analysts often use alternative measures of the costs saved when illnesses are avoided. Direct medical costs, which measure non-subjective aspects of an illness — the expenditures on medical care — are often used as a lower-bound estimate of avoiding an illness.

This handbook, developed by the U.S. Environmental Protection Agency, provides direct per capita incremental medical costs of illnesses associated with environmental pollutants.[1] The handbook was developed in response to the Agency's desire to provide information on the benefits associated with disease avoidance resulting from environmental programs or regulations. The data can be used in economic analyses, policy development or evaluation, and various decision-making activities. Improvements in human health frequently constitute a major portion of the benefits resulting from environmental regulations. While there are a variety of approaches to estimating the value of these benefits, one of the more straightforward approaches is to calculate the medical and related costs avoided. The medical costs in this handbook provide a relatively simple and efficient lower-bound estimate of the costs of illnesses.

The cost of illness data provided in this handbook include some, but not all components of the total benefit of avoiding a disease. Those outside the scope of this analysis are direct *non*-medical costs, the opportunity costs of patients, family members or other unpaid caregivers, and what the patient and others would be willing to pay to avoid the anxiety, pain, and suffering associated with the illness. Due to the seriousness of most illnesses in this handbook, these components may be substantial. The

[1] This handbook was developed by the Office of Pollution Prevention and Toxics under the direction of Dr. Nicolaas Bouwes (EPA WAM) by Abt Associates, Cambridge, Massachusetts (Dr. K. Cunningham, Project Manager).

values reported in this handbook must therefore be viewed as partial estimates of the economic costs, and are useful primarily as lower-bound estimates of cost.

EPA selected diseases for inclusion in this handbook based on the known or anticipated need for disease cost estimates for regulatory or policy activities and a review of the environmental health literature. Estimates of medical costs are provided for the following illnesses (click on the illness name to link to the relevant chapter; click on the section numbers to reach the introductory chapters):

Section II: Cancers[2]

- stomach cancer
- breast cancer
- kidney cancer
- lung cancer
- skin cancer
- colorectal cancer
- bladder cancer

Section III: Developmental Illnesses and Disabilities

- low birth weight
- cleft lip and palette
- limb reductions
- cardiac abnormalities
- spina bifida
- cerebral palsy
- Down syndrome
- high blood lead levels

Section IV: Respiratory Diseases

- asthma
- acute respiratory illnesses
- middle ear infections

Section V: Symptoms

- symptom groups

The diseases are organized into handbook sections with similar types of diseases, as shown in the list above. Each chapter contains background information in the illness, method used to estimate medical costs, and present value cost estimates discounted at zero, three, five, and seven percent over the duration of the disease. Costs are provided which were current in the year in which the chapter was written or revised (1996 and

[2]Bone and liver cancer costs are also briefly discussed in the introductory cancer chapter (Chapter II.1).

forward). The costs can be updated to the current year using the Consumer Price Index (CPI) Medical Services inflation data provided in Appendix A: Inflation and Discounting Factors.

Link to Appendix A

Matrices with preliminary information on environmental agents that may be associated with cancer and birth defects are provided in the chapters that introduce each of those disease categories. Each chapter also discusses causality and especially susceptible subgroups of the population.

A core of information is provided in each chapter on the methodology, costs, sources of uncertainty, and background information on the illness. The handbook was developed over many years, and the cost estimates for each illness were developed to address specific program requirements within the Agency. Consequently, the type of information provided and level of detail involved in the analyses vary among the illnesses.

The direct medical costs incurred as the result of an illness were estimated for the duration of the illness, i.e., from diagnosis to cure or patient death. Expected costs are estimated for each year post-diagnosis until cure or death, incorporating information on the likelihood and timing of receiving specific treatments, as well as survival data, information on the age of onset of the disease, and life expectancy data. Medical cost estimates are subject to advances in medical practice and changes in the costs of both services and materials. Most cost estimates are based on recent evaluations of medical practice; the handbook provides dates when cost and treatment data were obtained and descriptive information regarding disease definition and treatment. The user should consider changes in practice over time, however, if recent advances or changes in treatment have been reported.

The goal of the handbook is to provide cost estimates that are generalizable to any area of the United States. To obtain cost data representative of the nation as a whole, standard disease treatment methods, using generally acceptable practices, and the average patient experience regarding prognosis and survival (e.g., life expectancy) were used in cost estimates.

As noted above, the costs provided in this handbook do not include many non-medical costs, which may be substantial and should be included in a comprehensive benefit evaluation. Although non-medical costs may be an important component of overall benefit, direct medical costs are likely to comprise a substantial portion of the cost to society for the diseases included in this handbook. Thus, the medical cost estimates provided in the handbook offer reasonable lower-bound estimates for many illnesses of environmental concern.

It is anticipated that the contents will continue to be supplemented with new illnesses, and with revisions to illnesses currently included in the Handbook. In addition, links will be made to other sources of information on this topic. EPA welcomes the submission of new data, comments, and recommendations from users of this Handbook.

CHAPTER I.1. INTRODUCTION TO THE COST OF ILLNESS HANDBOOK

Clicking on the sections below will take you to the relevant text.

CHAPTER I.1. INTRODUCTION TO THE COST OF ILLNESS HANDBOOK

This handbook is provided through EPA's website. All chapters in the handbook have links to this chapter because it contains basic information on objectives, content of the handbook, analytical methodology, limitations, and results. It is anticipated that the web site will be updated continuously and this chapter will be modified as new information becomes available. As shown in the example below, you can use sidebars appearing at the left to link to resources that may be useful while reading and using the Chapters. These include the table of contents (which can be used to link to any chapter), a glossary with abbreviation definitions, inflation and discounting factors, an executive summary, and other useful websites (e.g., OPPT).

Sidebar example:
Click here to link to the Table of Contents

The cost of illness is an estimate of the incremental direct medical costs associated with medical diagnosis, treatment, and follow-up care. This includes various cost elements, such as physician visits, hospitalization, and pharmaceuticals. This Handbook does not estimate the costs in lost time or wages that may be incurred by either a patient or his or her unpaid caregiver. The costs also do not include pain and suffering, which may be substantial. Rather, this Handbook provides information on medical treatments and their costs, usually aggregated over the lifetime of the patient. These costs are inflated to the current year, and summarized at various discount rates.[1] A discussion of willingness-to-pay, which is presented later in this chapter, outlines in more detail the cost elements that are and are not included in the Handbook.

A normative approach is used to estimate costs, whereby the average age at diagnosis, the average life expectancy, and other average or mean values are used to estimate costs. The text notes situations which may arise that would lead to higher or lower costs than those estimated in this Handbook.

Due to the variability in medical costs geographically and over time, there is considerable uncertainty associated with estimating direct medical costs. An estimate of costs is often useful, however, when considering planning, decision-making, and regulatory development. As such, it can provide an efficient lower-bound estimate of the benefits of avoiding an illness.

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[1] The chapters were developed over many years and the costs are presented in the current dollar value for the year the chapters were written. Inflation factors based on the Consumer Price Index can be accessed by clicking on the lefthand sidebar and used to inflate the costs to any year up to the present.

Link to inflation factors: Appendix A

I.1.A Overview

Improvements in human health in the form of avoiding adverse health effects frequently constitute a major portion of the benefits resulting from environmental regulations. There are a variety of approaches to estimating the value of these benefits, but one of the simplest and more straightforward approaches is to calculate the medical and related costs avoided because of the health improvements.

The purpose of this handbook is to present information on the direct medical costs resulting from illnesses that are associated with exposure to environmental agents.[2] These cost data can be used for policy and regulatory development and evaluation, benefits assessments (e.g., RIAs), and other applications where there is interest in either medical costs avoided due to pollution prevention or costs incurred due to a lack of pollution control. Direct medical costs represent only a portion of the total benefits associated with pollution prevention/reduction, but in many cases these lower-bound estimates may be sufficient for decision-making purposes.

This handbook has been developed over many years, beginning in 1991. The level of sophistication and complexity in the field of health economics has evolved and the approaches taken in the chapters has likewise evolved. In addition, the needs of the Agency and the requirements of benefit cost analysis have changed with the advancing field of economics. To address specific Agency needs, the chapters have been tailored to address program requirements. For example, some chapters (e.g., stomach cancer) provide direct medical cost information for survivors and nonsurvivors separately, while other chapters dealing with other cancers contain medical costs averaged over all patients with the disease. In each case, the approach was designed to meet the specific requirements of the Office within the Agency for whom the cost estimates were prepared. Consequently, although all chapters contain information on direct medical costs, the approaches and level of detail vary, depending on when the chapter was written and the specific requirements that the analyses were designed to address.

Many offices within EPA have funded the analyses of medical costs discussed in this handbook. These include Office of Pollution Prevention and Toxics (the primary funding office), the Indoor Environment Division within the Office of Air and Radiation, the Office of Policy Planning and Evaluation, and the Office of Water.

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[2] For simplicity and brevity's sake, illnesses in the Handbook refer to diseases, birth defects, and other acute and chronic conditions requiring medical attention.

I.1.B Willingness to Pay and Cost Components

When calculating the value of human health benefits, the ideal approach would be to estimate the value of these improvements in health to everyone affected by an illness (e.g., the patient, family, friends, community). Economists measure this value in terms of how much they are willing to pay for it. Obtaining the detailed information necessary to comprehensively estimate willingness to pay (WTP), however, is complex and expensive. In addition, some components of WTP, such as the value of avoiding pain and suffering, are very difficult to estimate with accuracy. As an alternative to estimating WTP, the direct medical costs of treating diseases provides a lower-bound estimate of the benefits of reducing exposure to harmful pollutants.

I.1.B.1. Definition of Willingness to Pay

WTP is a measure of value based on the premise, central to economic theory, that the value of a good is simply what it is worth to those who consume it or benefit from it. The amount an individual is willing to pay for a particular good may be higher, or lower, than the cost of that good. WTP for a good will vary from one individual to another and may decline with how much of the good an individual already has. In the case of market goods, the comparison between the price of the good and the individual's WTP for it determines whether or not he or she buys the good. If the price is lower than his WTP, he will buy the good at less than he would have been willing to pay for it, receiving what economists call "consumer surplus." If the price exactly equals his WTP, then the individual will be equally happy whether he keeps the money and forgoes the good or pays the money and gets the good. If the price exceeds the individual's WTP, he will not buy the good.

In the context of environmental regulations and policy, economists define the value of a reduction in health risks as the sum of all individuals' WTP for it. Most people would be willing to pay something for a reduction in risk to themselves, but many people would also be willing to pay for a reduction in risk to others. Most parents, for example, would probably be willing to pay for a reduction in the risk of their children incurring a serious illness. These altruistic components of WTP may be insignificant in many cases, but they may be substantial in the case of serious diseases or disabilities. The total value of a risk reduction, then, is the sum of all WTPs for it.

Environmental contaminants generally cannot be linked with certainty to specific health effects experienced by specific individuals. Instead, the contaminants increase the *likelihood*, for all exposed individuals, of contracting specific diseases. Rather than summing the WTPs for a given

risk reduction over all those who enjoy the risk reduction, however, it is often easier to think in terms of the value of an adverse health effect avoided. Some people who would have contracted the illness will now avoid contracting it. The total value of an avoided illness is what the otherwise-afflicted individual would be willing to pay to avoid it plus what others would be willing to pay for him or her to avoid it. The sum of these WTPs is the total value of the avoided case of illness, referred to here as total WTP. In practice, average WTPs are used to value adverse health effects avoided because WTP will vary from one individual to another.

The crosswalk between valuing risk reductions and valuing a case avoided can be made by valuing a *statistical* case avoided. For example, suppose that a regulation is passed that reduces the risk of contracting pneumonia by a factor of 0.001. That means that one fewer individual out of every 1,000 people whom the regulation affects would be expected to contract pneumonia. Suppose each person has some positive WTP for this risk reduction of 0.001, and that the average WTP is $5. The total willingness to pay to avoid the one case of pneumonia that would otherwise be expected to occur per 1,000 people is $5,000 ($5 per person × 1,000 people). That is, the value of a statistical case of pneumonia avoided would be $5,000. Regulations typically affect cities of substantially greater size than 1,000 people, however, so there are typically many cases avoided. For example, if a regulation reduced the risk of contracting pneumonia by 0.001 in a city with 3 million people, there would be 3,000 (0.001 × 3,000,000) fewer cases of pneumonia expected to occur in the city as a result of the regulation. If the value of a statistical case of pneumonia avoided in that city is $5,000, the pneumonia-related benefit of the regulation in that city would be 3,000 statistical cases avoided × $5,000 per statistical case avoided = $15 million.

In theory, nonmarket goods should be valued in exactly the same way as market goods — in terms of what people would be willing to pay for them, (i.e., their willingness to pay). Unlike most market goods, many nonmarket goods are public goods, from which many people benefit simultaneously. A reduction in the risk of an adverse health effect is such a public good, because all the exposed individuals will experience a decrease in the likelihood of contracting the disease.

I.1.B.2 Components of Willingness to Pay

WTP to avoid an illness contains several components. Illness imposes both direct and indirect costs that would not be borne if the illness was avoided. Direct costs result from the increased resource utilization caused by the illness, and may be medical or non-medical. For example, the cost of an ambulance used to transport a person to the hospital is a direct medical cost, while child care and housekeeping expenses required due to illness are non-medical direct costs. In addition to the direct costs, there are

opportunity costs (the value of productive and leisure time lost) to the patient and possibly to others.[3] Finally, illness causes anxiety, pain, and suffering, the cost of which, although difficult to measure, is very real and may be very large. Most people would be willing to pay something to avoid the pain and suffering that comes with illness, as well as to see loved ones avoid pain and suffering. There is also a perceived value to most individuals of maintaining public health (i.e., most people would place some value on reducing the number of children with asthma, the number of people with cancer, the incidence of birth defects, and the occurrence of most illnesses).

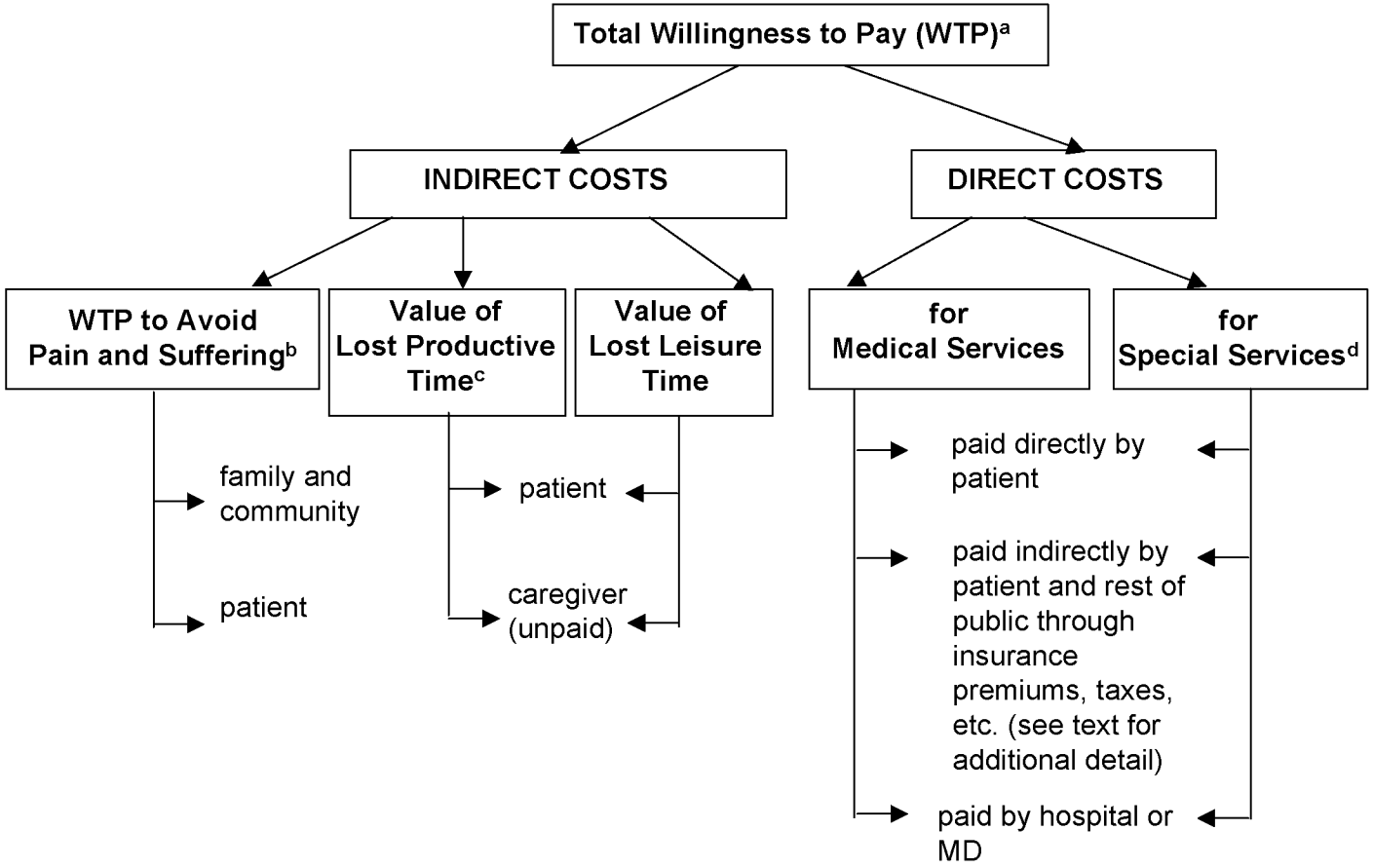
Finally, in some cases people may take precautionary actions to avoid contracting environmentally-related illnesses. People may buy bottled water, for example, if their water supply is contaminated or if they believe it may be. In these cases, there are not only costs associated with the occurrence of the illness, but costs incurred in efforts to prevent the illness. These costs would be avoided or reduced if the risk of the illness were reduced. The components of total WTP are shown in Figure I.1-1.

I.1.B.3 Approaches to Measuring Willingness to Pay

The challenge confronting the analyst is to measure the total value associated with avoiding an illness. This is a difficult challenge due to the variability in human perceptions, responses, and the complexities involved in measuring individual attitudes and extrapolating to a larger group. Economists have developed several ways to measure the value of morbidity avoided; each method has advantages and disadvantages.

[3] Opportunity cost is the cost associated with forgone opportunities. Time spent in the hospital, for example, is time that would otherwise have been spent in productive and/or leisure activities. The opportunity cost of a hospital stay is the value of the productive and/or leisure time lost during the hospital stay.

Figure I.1-1. Elements of Willingness to Pay



a. See text for a discussion of cost elements. The cost components above are associated with contracting a disease. People who avoid disease by employing averting behavior may incur other costs (e.g., the cost of buying bottled water). Both the cost components listed above, and those associated with risk avoidance would be reduced or eliminated if the risks were reduced or eliminated.

b. Heightened morbidity or other adverse effects associated with a lack of treatment (e.g., due to insufficient resources) may increase pain and suffering. This indirect cost category is very difficult to measure.

c. Lost time includes a partial or complete loss of the ability to carry out activities (paid or unpaid).

d. Includes special education (children); worker retraining (adults); workers' disability; and/or specialized equipment, transportation, and other services required due to the illness.

I.1.B.3.1 Averting Behavior.

One approach to valuing WTP relies on the averting behavior of people. This "averting behavior" approach provides estimates of WTP based on actual behavior in markets. The major drawbacks of this method, however, are that (1) it is limited to situations in which averting behavior is possible (i.e., not all contaminants can be avoided), and (2) it is difficult to isolate WTP for improved health from WTP for other aspects of the averting behavior. For example, while use of an air conditioner may reduce exposure to ambient air pollutants, it also cools the house.

Evaluation of averting behavior may be complex because pollution avoidance costs are situation dependent. Using the air conditioning example, community factors that influence air conditioner use include the extent of public notification about pollution problems, ambient temperatures, etc. Individual decision factors include a subjective rating of the pollutant's health risks.

I.1.B.3.2 Contingent Valuation

A second method, contingent valuation, is to simply ask people how much they are willing to pay for a good or service that is not traded on the market. The valuation is contingent upon establishing the market. This method involves designing surveys that present people with hypothetical situations in which they are queried about how much they would be willing to pay for a specified nonmarket good (such as to avoid a case of pneumonia). The advantage of the contingent valuation method is that it attempts to estimate the right thing — individuals' WTP. In addition, in contrast to the averting behavior approach, it can be applied to any risk reduction or adverse health effect. It is a controversial method because it of necessity elicits responses to a hypothetical situation. The reliability of the estimates obtained through contingent valuation methods is questioned by many economists and by others. The approach is resource intensive and costly. It requires careful questionnaire design and interpretation of responses. In spite of its drawbacks, it may be a useful tool for obtaining valuation data, and has the potential for contributing to a variety of planning, evaluation, and regulatory activities.

I.1.B.4 Conclusions

The cost of illness method used in this handbook estimates the direct medical costs associated with an illness. This method has several advantages. It is straightforward to implement and easy to understand. In addition, it is likely to result in relatively accurate estimates of the components of total WTP that it attempts to measure, the medical cost component. The major drawback of the cost of illness method is that it omits several components of total WTP, most notably the WTP of the patient and of others to avoid the anxiety, pain, and suffering associated with the illness. These components may be substantial, especially for

serious illnesses. In addition, this handbook does not include direct *non*-medical costs, the opportunity costs of family members or other unpaid caregivers, or time lost for the patient. Consequently, the values reported here are only a partial estimation of the cost of illness, which, as described above, is itself an underestimate of the total economic costs associated with the diseases considered. Because it omits these components, the cost of illness method provides an underestimate of WTP to avoid the disease.[4]

I.1.C Organization of Handbook.

This handbook is organized into sections based on common features of illnesses and the type of illnesses discussed, such as cancer, developmental illnesses and disabilities, diseases of specific organ systems (i.e., respiratory), and acute illnesses. They were organized in this manner because the diseases contained in these categories are similar in important aspects, including: cost calculation methods; biomedical data on disease definition, causality, susceptible subgroups, and treatment; survival patterns; and the types of medical services required and their costs. For example, cancers frequently require similar types of medical intervention, share similar characteristics regarding survival data, and have many causative agents in common. Developmental effects also share many characteristics; they manifest early in childhood, involve protracted treatment, occur in clusters, require both medical and other professional intervention, and may have similar causative agents. For both cancer and developmental effects, toxicological data are often not organ-specific, and providing general information regarding chemical associations in an introductory chapter was most appropriate. Most sections begin with a chapter that discusses the common characteristics of a disease group with respect to background medical data, cost, and causality.

[4] Some researchers (Crocker and Agee, 1995) have suggested that the cost of illness approach may not always underestimate costs (e.g., when treatments are painful and consequences are limited, patients or their caregivers may have ambivalent attitudes). If this is true, however, it is likely to be expected to be the exception rather than the norm under circumstances of fully informed medical information, because most individuals place a higher value on regaining their health (in the case of non-terminal diseases) than on avoiding medical procedures.

I.1.C.1 Illnesses Covered in the Handbook

Medical costs are provided for the following illnesses:

Cancers[5]
- breast cancer
- kidney cancer
- lung cancer
- skin cancer
- stomach cancer
- colorectal cancer
- bladder cancer

Developmental Illnesses and Disabilities
- low birth weight
- cleft lip and palette
- limb reductions
- cardiac abnormalities
- spina bifida
- cerebral palsy
- Down syndrome
- high blood lead levels

Respiratory Diseases
- asthma
- acute respiratory illnesses

Symptoms

Some of these chapters are currently in development or undergoing revisions (e.g., skin cancer).

I.1.C.2 Chapter Format

Each chapter covering a specific illness follows the same general format; the level of detail provided depends on the availability of information and the goals of the analysis. First, the chapter provides the reader with background information on the disease (Section A), including a definition and description of the disease, adverse effects related to the disease, associations with environmental pollutants, common medical approaches, and likely disease outcomes (prognosis).

The second portion of each chapter (Section B) provides specific cost information, including the methodology used to estimate costs, sources of the data, and cost estimates. Costs are provided that were current in the year in which the chapter was written or revised (1996 and forward). The

[5]Bone and liver cancer costs are also briefly discussed in the introductory cancer chapter (Chapter II.1).

Link to Chapter II.1

costs can be updated to the current year using the Consumer Price Index (CPI) Medical Services inflation data provided in "Appendix A: Inflation and Discounting Factors" on the sidebar at left.

Link to Appendix A

Section B of each chapter also discusses results and limitations of the methods used. In some cases an uncertainty and/or sensitivity analyses is also provided. Studies that provide alternative cost estimates are presented and discussed, when available. When more than one set of results is discussed, recommendations for data use are given in a section titled "Conclusions."

The headings that appear in the format of each disease chapter are listed below and described in the text that follows:

A Background
A.1 Description
A.2 Concurrent Effects
A.3 Causality & Special Susceptibilities
A.4 Treatments and Services
A.5 Prognosis

B Costs of Treatment and Services
B.1 Methodology
B.2 Results
B.3 Limitations
B.4 Other Studies
B.5 Conclusions

The chapters introducing each part of the handbook, such as cancer and developmental effects, do not follow this format because they do not deal with a specific disease.

I.1.C.3 Section Contents

The contents of each section are as follows:

A. Background:

A.1 Description: provides a clear definition of the disease and what subcategories of an illness are omitted. This section may also include data on occurrence for some diseases, depending on the needs of the sponsoring office.

A.2 Concurrent Effects: often there are other diseases associated with a given disease. These may be attributable to the same causes (e.g.,

environmental pollution). If the concurrent effects have been reported in the reviewed medical literature, then they are listed in this section. Treatment often incurs additional risk; radiation treatment, anti-cancer drugs, and other therapies can cause serious illness while curing the target disease. These secondary illnesses usually constitute a separate disease, however, so their costs are not provided in the same chapter. In some cases, the costs of these diseases are discussed in other chapters within the handbook. Concurrent effects are listed even when cost data are not provided, so that the analyst using the data can report the underestimate and uncertainty associated with additional anticipated illness.

A.3 Causality and Special Susceptibilities: information on the associations between environmental agents and diseases is presented in this category. Factors that may increase susceptibility are also discussed; these include many pre-existing conditions. Data are limited, however, on special susceptibilities. A comprehensive evaluation of illnesses that would increase susceptibility or severity of a disease was beyond the scope of this analysis. In general, a pre-existing disease in the target organ causes additional medical complications and higher costs. For example, coronary artery disease in someone with pre-existing heart disease is likely to be much more serious and costly.

1.4 Treatment and Services: includes a brief description of common treatments and related services. In most cases, this description does not include support services, such as specialized occupational training required for rehabilitation. This information was available for some the chapters that cover childhood diseases and disabilities, and so is included as supplemental cost data.

1.5 Prognosis: contains quantitative or qualitative information on likely disease outcomes. This information is important because survival probabilities, and the duration between diagnosis and death among those who do not survive, are used in cost of illness evaluations and have an impact on the cost of a disease.

B. Costs of Treatment and Services: contains medical cost data and methods used to estimate costs.

B.1 Methodology: describes methods used in calculating the costs of medical treatments and services, and the basic information used to calculate costs.

B.2 Results: summarizes cost estimates. Discounted costs at zero, three, five, and seven percent are provided for most illnesses.

B.3 Limitations: describes shortcomings of the methodology and results. These typically include a discussion of factors such as the age of the data,

sources of information, assumptions regarding treatment, and other factors that may affect the applicability or accuracy of cost estimates.

B.4 Other Studies: when other study results are available, they are presented and the advantages and disadvantages of the various studies are discussed. In all cases, the study results recommended for use are presented first and described in detail in the "Methodology" and "Results" sections. Those studies with results of limited use are presented later in this section.

B.5 Conclusions: when more than one set of results is discussed in the medical cost and/or time sections, the final recommendations regarding the optimal results are given in this section. The section is not included in chapters having only one set of study results.

I.1.C.4 Selection of Illnesses

EPA selected diseases for inclusion in this handbook based on 1) the known need for disease cost estimates for regulatory or policy activities, or 2) the anticipated need based on a review of the environmental health literature and Agency activities.

Regulations and policy evaluations often require cost and benefit information for specific illnesses anticipated to be affected by a rule or policy. Because reductions in exposure to pollutants will result in improvements in human health, evaluations of rules or policy changes may incorporate consideration of the impacts on human health, including the benefits of illness avoidance. For example, the medical cost estimates for stomach, bladder, and lung cancer provided in this handbook were developed in 1998, in response to a need for economic data for Office of Water rules covering radon and arsenic.

Illnesses were also selected based on their likely occurrence as a result of exposure to environmental pollution and anticipated future needs of the Agency for cost data. Many illnesses that are frequently associated with environmental pollutants, or that are clearly linked to pollution episodes (e.g., asthma) were evaluated and included in the handbook. For these health-based selections, the environmental health literature (i.e., toxicology and epidemiology) was consulted. The illnesses in this handbook have been linked to exposure to environmental hazards including both chemical (e.g., PCBs) and physical (e.g., radiation) hazards.

The health-based selection process included the following considerations:

- a link to environmental exposures in the toxicological and/or epidemiological literature;[6]

[6]Toxicological and epidemiological studies may strongly suggest, but rarely provide, unequivocal evidence for links between exposure and effects. Credible studies in the peer-reviewed literature that demonstrated statistically significant associations between exposure and effects were considered adequate

- illnesses that could reasonably be linked to exposure levels likely to occur in the environment;
- the availability of costing data for an illness (either in the form of multiple mergeable databases, or in the economic literature);
- occurrence linked to multiple chemicals, ubiquitous chemicals, or those of particular interest to EPA based on policy considerations (e.g., lead, mercury);
- an illness that does not result in death shortly after onset.

Professional journals were consulted for information on health effects. In addition, some federal sources, such as the Hazardous Substances Data Base (HSDB), the Integrated Risk Information System (IRIS), the Health Effects Assessment Summary Tables (HEAST), and the Agency for Toxic Substances and Disease Registry's (ATSDR) Toxicological Profiles, were used as the sources of data linking illnesses and exposure to environmental pollutants.[7] In selecting illnesses, a convergence was sought between the likelihood of an illness based on environmental exposure levels and the availability of good quality aggregate cost data from databases and research papers. For high priority illnesses, it was sometimes necessary to construct cost estimates using a theoretical approach when aggregate data were not available.

I.1.C.5 Linking Diseases to Agents

Matrices with preliminary information on environmental agents associated with cancers and with birth defects are provided in Chapters II.1 and III.1, respectively. These contain lists of hundreds of agents that have been associated with the disease categories in either toxicological or epidemiological data, or both.

Some of the agents were identified with a single disease during research on a single disease or disease category (e.g., birth defects) and have not been reviewed regarding the induction of other diseases in the Handbook. In some cases, the diseases were studied as a result of their link to an agent. For example, the costs associated with stomach cancer were evaluated for

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evidence for inclusion in this handbook. The associations listed in this handbook are presented at the screening level; risk assessments and health evaluations require an in-depth review of the literature on each chemical.

[7] HSDB is an on-line toxicological database maintained by EPA and available through the National Library of Medicine's TOXNET. IRIS and HEAST, developed by EPA, contain data regarding carcinogenic and non-carcinogenic effects of chemicals.

a proposed radon rule. Consequently, when the stomach cancer chapter was written, an extensive search for other stomach carcinogens was not conducted.

In addition to those chemicals listed because the data were obtained for a specific chapter, data on chemicals associated with health risks were collected specifically for the matrix from general toxicological sources. Most linkages between chemicals listed and categories of effects (i.e., cancer and birth defects) did not involve an extensive search of the literature, and are often based on a quick review of relevant databases. The reader should assume that the matrices do NOT list all adverse effects of an agent, or all agents that can cause a disease. This limitation is due to the very sizable scope of the work that would be required to fully evaluate all potential effects of the hundreds of chemicals listed in the matrices. In the future additional data may be added to the matrices.

Links to Chapters II.1 and III.1

I.1.D Methods used to Estimate Direct Medical Costs

As noted above, total costs associated with an illness incorporate many elements. This handbook focuses on direct medical costs. The direct medical costs of illness are calculated for the life cycle of each illness, (i.e., from diagnosis to cure or patient death). The goal of this handbook is to provide cost estimates that are generalizable to any area of the United States; therefore, cost data representative of the nation as a whole were sought. Standard disease treatment methods, using generally acceptable practices, were also considered appropriate. Finally, the average patient experience regarding prognosis and survival was used in the cost estimate. This approach is expected to yield representative cost estimates that are generally applicable. They may be modified by changes in technology or cost structure.

I.1.D.1 Overview of Method

Six basic steps are necessary to calculate direct medical costs:

1. Identify a cohort who has received the standard treatment for the disease. If costs are to be determined by treatment component, list the standard treatment elements.

2. Determine the costs of each phase of treatment or for each treatment component and the timing of these costs.

3. Combine the cost estimates with probability data regarding the likelihood of receiving specific treatments and their timing.

Incorporate survival data in probability estimates based on the age of onset of the disease and life expectancy.

4. If total medical costs are used (rather than disease-specific cost elements), determine the background medical costs that would be incurred in the absence of the disease.[8] Modify the disease-related costs as needed to obtain incremental costs.

5. Discount the stream of treatment costs over time to estimate present value treatment costs. All costs in the handbook are adjusted to 1996 dollars using the medical care cost component of the Consumer Price Index.

6. Aggregate the discounted stream to obtain an estimate of the total medical costs of the disease.

Ideally, this process is carried out for both survivors and nonsurvivors of the disease (these two subgroups are discussed below). These basic cost estimation activities are carried out for all illnesses. As discussed above, results reported in the literature are used for many of the diseases. In a few cases, these steps were carried out specifically for the development of chapters in this handbook.

The data obtained in the various steps above are used in a single aggregating equation described by Hartunian et al. (1981) to calculate the expected direct present value costs (PVC) for any individual of a given sex, impairment category, and age at onset of impairment:

$$PVC = \sum_{n=l}^{99} \frac{P^{i}_{l,s}(n)\ DC^{i}_{l,s}(n - l + 1)}{(1 + r)^{n-l}}$$

where:

n	=	the various ages of the individual,
l	=	the age at impairment onset,
$P^{i}_{l,s}(n)$	=	the probability that a person of sex s who acquires condition i at age l will survive to age n,
$DC^{i}_{l,s}(n\text{-}l\text{+}1)$	=	the dollar value of the average annual incremental direct costs generated by such persons during year $n\text{-}l\text{+}1$ following impairment onset, and
r	=	the discount rate.

[8] Background costs are the average costs incurred by a population matched (e.g., in age, sex, etc.) for those with the disease, and include care for both healthy and diseased people in the population.

In reality, data rarely exist regarding the probability of survival and direct costs for a specific disease for each age of diagnosis and sex. If there were such data, however, the estimated average direct costs would be calculated by weighting the direct costs for each age and sex by the percentage of incidence in each sex/age grouping.

Appendix I.1-A, "Equations Describing the Expected Present Discounted Value of the Per Capita Lifetime Stream of Costs Associated with a Given Illness," contains a listing of equations and their input parameters used to estimate the expected present discounted value of the per capita lifetime stream of medical costs. The appendix includes more detail than is provided in this section.

Link to Appendix I.1-A.

I.1.D.2 Survivors and Nonsurvivors

Medical costs associated with a disease differ for those who survive a disease and those who die of it. For purposes of the cost analysis in this handbook, survivors are defined as those people who are diagnosed with a disease, but do not die of it (although they may die of another cause). Nonsurvivors are those who die of the disease at any point after diagnosis. Separate cost estimates for survivors and nonsurvivors are provided in the handbook for a few types of cancer, due to a specific Agency program need. These estimates are listed separately in cases where it is important to distinguish between the differing costs for the two groups, and in cases where the value of a statistical life (VSL) is used for nonsurvivors. When the VSL is used for nonsurvivors, their medical costs have already been incorporated into the cost estimate. Under these circumstances, it would be appropriate to use the medical and time (and any other costs) for survivors, but not for nonsurvivors. The use of cost data depends on the composite of all cost calculations that are being carried out for a benefits assessment.

A patient's probability of receiving specific treatments is modified by the likelihood that he or she will survive to receive that treatment. Survivors incur initial treatment costs but not charges for services, such as terminal care associated with the disease. They may die of other causes during the treatment period, and their probability of receiving treatment is modified by the probability that they will die of another cause. This probability is determined from the background mortality rates for the U.S. population, as reported by the Department of Health and Human Services publication series, *Vital Statistics in the United States* (DHHS, 1994). The probability of death due to the disease is determined from the medical literature (e.g., from the National Cancer Institute for cancers) for nonsurvivors. Determining survivorship for some illnesses, such as asthma, is very difficult due to rapid advances in treatments and the confounding effects of

limited access to care among some socioeconomic groups. When survival data are provided in a chapter, the source and confounding effects are discussed.

The methods used to calculate medical costs for survivors and nonsurvivors are described briefly below. Numerous additional calculations are often required to determine survival rates, life expectancy, etc., and are discussed in chapters where required.

I.1.D.2.1 Survivors (those who do not die of the disease)

The average cost among survivors of a disease for each year post-diagnosis may be expressed as:

Average *n*th Year Costs = medical costs for *n*th year treatment × probability of survival through the *n*th year + medical costs for *n*th year of treatment /2 × probability of mortality in the *n*th year

As this description indicates, the costs decline as the population decreases due to mortality. Costs are discounted back to the year of diagnosis. Costs for those who die are calculated for one half year because they are assumed to die at the midpoint of the year. Their survival rate is equal to the background mortality rate at each age in the U.S. population as reported in vital statistics reports (e.g., *Vital Statistics of the United States*, DHHS, 1994).

The yearly costs are aggregated over the remaining life of the "average" patient. For example, if the average age of a patient is 40 and medical visits and drug treatment for asthma are anticipated to be required over the expected lifetime for a 40-year-old in the general population, the costs for each year are calculated, discounted from the time of diagnosis, and summed over a lifetime. This generates a lifetime stream of costs.

Average Lifetime cost = Average 1st year cost + the sum of the (discounted) average subsequent year costs

If there is a point at which treatment ceases (e.g., ten years after diagnosis and treatment for cancer), the costs will be aggregated over time up to that point. When this approach is compared to the equation supplied by Hartunian et al. (1981) shown in section I.1.D.1, it can be seen that the overall cost estimation method is the same.

Link to Section I.1.D.1

I.1.D.2.2 Nonsurvivors (those who die of the disease)

The method for calculating medical costs for nonsurvivors is similar to that shown above for survivors, but the costs themselves are often different, and the probabilities used to calculate costs differ. For nonsurvivors, the

probability of treatment is contingent on surviving the study disease for each year after disease onset. The general descriptions are the same as those shown above.

I.1.D.2.3 Average Costs for Survivors and Nonsurvivors

The average lifetime medical costs of a disease are estimated for survivors and for nonsurvivors separately. The average cost for both together is calculated as a weighted average of costs for the two groups, using the proportion of patients in each group. This can be expressed as:

Average Lifetime medical costs = costs for survivors × proportion of survivors + lifetime costs for nonsurvivors × proportion of nonsurvivors

I.1.D.3 Data Sources

Most cost estimates provided in this Handbook rely on an evaluation of databases of actual costs incurred, either for this Handbook or by previous researchers. Each chapter describes how various data sources were used to calculate the final results, and contains a discussion of uncertainties associated with data sources.

Well-designed studies in the literature that supplied recent cost estimates were located for most illnesses and were preferred over data collection and evaluation for the sake of efficiency. For example, many of the childhood disease chapters in this handbook are based on work done by Waitzman et al. This research group used 12 databases to accurately construct their cost estimates.

Link to Chapter II.2

Using the results of these studies is more efficient than constructing costs directly from multiple databases. Extensive resources are required to evaluate national databases, and confidentiality is often an issue that requires a lengthy timetable for clearances. Most chapters use a combination of data obtained from the literature and directly from data sources. Results reported in the literature are supplemented by survival or other essential data to obtain cost estimates.[9]

[9] For example, Baker et al. (1989 and 1991) were used as a source of basic cost information for many of the cancer chapters. Additional data required for the cost analyses regarding survival and mortality estimates and cancer rates were obtained directly from the National Cancer Institute's databases. These combined sources were used to calculate cost estimates.

Cost estimates were developed for some diseases by constructing a typical treatment course through physician panels, and evaluating the cost of each treatment component using sources such as the Medicare database. This approach relies on expert judgment by physicians who determine treatments that the average patient receives, the timing of treatments, and the likelihood that a percentage of patients will receive a particular treatment. Survival data are obtained from a secondary source.

Limitations to this approach include physician errors in recall, physician experience with a non-representative population, and incomplete knowledge of variations in treatment patterns geographically and among physician specialties. In addition, the approach tends to estimate ideal costs because physician panels describe the treatment and costs that a person with a disease *should* receive, whereas the direct cost estimation approach described above is based upon actual costs. For example, skin cancer costs were evaluated using physician recommendations. The protocol described is one that provides the most appropriate care; it is not necessarily the most expensive, but assumes that everyone receives the services that would address their medical needs adequately. In practice this does not happen, due to a variety of factors (e.g., limited access or funds, avoidance of diagnosis).

Consequently, the chapters based on physician recommendations for treatment describe costs associated with sound medical practice, and these values may be higher than the "average" for the U.S. Adequate care for all patients probably reduces time loss, however, so that what is theoretically spent on complete medical care may be balanced by related reductions in unnecessary morbidity and mortality. When these types of analyses have been done, they generally find that preventive and/or adequate medical care costs are more than offset by reductions in future morbidity, time loss, and special services required (e.g., special education).

Due to the limitations of the approach and the resources required to carry out an analysis based on this type of cost evaluation, it was used for very few chapters in this handbook.

I. 1.E Susceptible Subpopulations

Many diseases affect subgroups of the population disproportionately. The subgroups may be defined by age, gender, racial, ethnic, socioeconomic, or other differences within the U.S. population. For example, asthma is most often reported and treated in children and the elderly. Most cancers occur with increasing frequency in older populations (some leukemias being notable exceptions). Very few diseases affect all population groups (ages, sexes, races) equally. For purposes of evaluating costs and potential benefits to different segments of the population, it is useful to evaluate

whether there are susceptible subpopulations that require consideration. Their benefits may be considerably higher than those of the average member of the general population.

Each chapter contains a section titled "Causality and Special Susceptibilities" that contains information gathered to address this issue. An exhaustive search was not carried out for these data, however, and new information is being generated rapidly in this field. Consequently, there may be susceptible subgroups not identified in this section. In addition, there are usually pre-existing medical conditions that will increase susceptibility to most diseases (as noted previously), such as a pre-existing disease in the same organ.

Special susceptibilities are often indicated by higher-than-average rates of the disease of interest. Increases in the rates of reported diseases may be due to a variety of factors. Some of these indicate an increased susceptibility; others are matters of personal choice and may not be considered relevant to cost calculations. One way to approach this issue is to evaluate increased susceptibility when it is based on an increased risk of disease due to factors *reasonably beyond the control of the subpopulation*. Factors that are usually beyond the control of the individual that may cause increased susceptibility include:

- constitutional limitations (e.g., illnesses, genetic abnormalities, birth defects such as enzyme deficiencies);
- concurrent synergistic exposures that cannot reasonably be controlled (e.g., at home or in the workplace);
- normal constitutional differences (i.e., differences based on sex, age, race, ethnicity, etc).

Other factors that are not usually considered beyond the individual's control include personal choices, such as smoking, drinking, and drug use. These factors may be included in an analysis depending on the goals of the analysis. Which types of factors should be included in an analysis is a policy decision. Personal choice typically does not include the place of residence or work, since these are not reasonably changed by many people. For example, asthmatic smokers who increase their risk of asthma are not discussed at length as susceptible subpopulations; however, asthmatic residents of an area with high levels of acid aerosols may require additional analysis of their risk of asthma and benefits of asthma avoidance. It may be useful to evaluate the medical costs of people in the latter group using different underlying risk factors than would be appropriate for the overall U.S. population.

These types of considerations are not used directly in the cost calculations presented in this handbook. Much of the information regarding special susceptibilities is incorporated, however, into the medical information provided in the background sections of each chapter. In addition, sensitivity analyses in some chapters include an analysis of the impact on subgroups at highest risk.[10] The data may be used in a variety of ways, depending on the nature of the benefits assessment.

The degree to which special susceptibilities should be considered in an assessment depends on the extent of impact that is expected in the cost analysis (e.g., whether the differences will be substantial or minimal), as well as equity considerations. For example, the rate of stomach cancer in African-Americans is much greater than in non-African-Americans. There is no conclusive information regarding the cause of this increase, so it is assumed that it may be due to a genetically determined increase in susceptibility to stomach cancer. Because these differences are consistent across the ages, there is no modification required in the *per capita* cost estimates for stomach cancer. If an area that was predominantly African-American was the subject of a benefits assessment, however, the increased risk in that area would merit consideration in the benefits assessment. If risk factors for the general population were used with the per capita costs, then the impact on the area would be estimated incorrectly. Most chapters contain some information regarding known increases in susceptibility. Some have considerable detail, such as the chapter on stomach cancer (Chapter II.2) where basic information on differences in stomach cancer rates based on race and sex from the National Cancer Institute are provided. These data could be used by risk assessors or epidemiologists to evaluate the potential for increased risk.[11] Their results, together with the economic data, could then be used in a benefits assessment. This same approach may be used for any diseases for which a susceptible subgroup of interest has been identified.

Link to Section I.1.B
Link to Chapter II.2

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[10] This type of analysis was begun in 1998 in response to specific needs regarding high-risk subgroups. It is not contained in earlier chapters, but may be added in the future.

[11] This type of analysis is complex because it requires an evaluation of the proportion of cases expected in the population subgroup as well as in the overall population. This requires calculation of the conditional probabilities of stomach cancer based on race. Because the overall stomach cancer rates incorporate the rates for both blacks and non-blacks, the likelihood of occurrence in each of these two groups would need to be determined. This information would be used with the racial distribution in the target population to determine the estimated potential risk.

I.1.F Limitations

The limitations of the data provided in this handbook are related to two primary constraints:

1) the scope of the analysis, and

2) uncertainty regarding the data used in the analysis.

The scope of the analysis, described in the introduction to this chapter, includes only direct medical costs. Many aspects of the willingness to pay to avoid these illnesses are not covered in the handbook, including direct non-medical costs and pain and suffering (see discussion in Section I.1.B and Figure I.1-1).

Link to Figure I.1-1

There are numerous sources of uncertainty associated with the values presented in this handbook. The background and cost sections of the chapters provide definitions and information on the "average" medical experience and costs for a disease. Outside this experience, however, numerous factors impact the costs associated with specific diseases and lead to uncertainty in the cost estimates. The sources of uncertainty specific to each disease cost analysis (i.e., the databases used in an analysis, the methods of the analysis) are discussed in the individual disease chapters. Those common to all diseases are discussed in this section.

I.1.F.1 Uncertainties Regarding the Market Value of Medical Goods and Services

As noted above, direct medical costs are provided in this handbook as a component of WTP and may be used as a lower estimate of WTP. For a variety of reasons, however, the price of medical services and the mix of services purchased may not accurately reflect the market demand and value for these services. These reasons are related to the nature of what is purchased when buying medical services, and the way in which medical services are paid for in the U.S.

I.1.F.1.1 The Nature of Medical Service Purchases

The nature of what is being purchased is often unclear when obtaining medical services. Although a specific service or good is usually being obtained at a point in time (e.g., surgery, a pharmaceutical, an X-ray), the ultimate goal of the purchase is invariably an improvement in health. The latter, often purchased through multiple related services and goods, is generally far more valuable to the individual than the individual service or item. For example, when faced with a serious illness, individuals would

expend the maximum funds they have available to avoid death or permanent disability.[12]

Just as individuals may be willing to bear almost any medical costs required for serious illnesses, society is often willing to spend very large sums to avoid illness or death among otherwise healthy individuals. Extensive and expensive health programs for indigent populations illustrate the interest in the overall health of the population. This may be both the provision of a public good and a self-protective strategy. Likewise, societies are often willing pay very large medical costs under special circumstances. For example, communities have raised millions of dollars to provide cancer treatments for a relatively small number of children. What a society or individual would be willing to pay for medical services may be strongly affected by a society's response to potentially drastic consequences. The willingness to pay very large medical costs to avoid dire consequences is expressed both by the individual with the illness and by those who are aware of the individual's plight.[13]

There is an interactive relationship between what medical costs society is willing to pay and standard medical practice (which dictates costs), which often reflects societal values. This dynamic may further diminish individual control over the purchase of medical services and their impact on the market for medical services. When insurance companies, the government, or medical practice standards determine access to care or determine what constitutes appropriate treatment, individual choice may be limited; this may also affect cost. For example, both the costs of treating a disease such as breast cancer and access to care for that disease may be quite different for patients of different ages or with different health status (i.e., AIDS vs good health).

I.1.F.1.2 The Sources of Payment for Medical Services

A second major source of possible inequality between medical costs and market values is the system of medical payments in the U.S. The system creates institutional reasons for a disjunction between costs, payments, and WTP for both individuals and society. As Figure I.1-1 shows, there are often a multitude of sources of payment for medical costs. In the case of medical services, people have typically prepaid insurance premiums or taxes (e.g., for Medicare and Medicaid) that are used as the source of payment. This prepayment may affect the demand for and the costs of

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[12] This discussion generally addresses people who prefer a cure over death. Although the latter may occur, it is not the norm and is not directly relevant to determining willingness to pay for services to improve health.

[13] Alternatively, there is often opposition to high medical costs associated with prolonging life for the very elderly, terminally ill, or those with certain types of health problems.

services at the time the service is rendered, since the funds have already been expended.

Link to Figure I.1-1

In addition, prepaid premiums or taxes are not designated for specific services, but are held to be distributed on an as-needed basis (with need being controversial in some cases). Consequently, insurance payments are not provided equally to all premium holders due to differences in medical services required. Thus, the premium holders have purchased an assurance that their medical bills (or some portion of them) will be paid rather than paying for a specific service. This is quite different than payment for a specific treatment at the time it is needed based on decisions regarding its value to the individual. There is no direct connection between payment for and receipt of a good or service.[14]

When costs are high and exceed the amount of the premium (or individual taxes), the excess is borne by a group rather than by the patient. This system of payment also reinforces the concept that when the general public purchases insurance or approves funding for public health programs, it is buying some assurance of good health rather than specific services. Patients may be willing to pay more for an improvement in health status than for a specific service.

For some individuals and groups, the payment system is quite complex, and determination of the costs of medical services and WTP is even more difficult. For example, elderly patients, who comprise the majority of those who suffer from cancer, chronic obstructive pulmonary diseases, heart disease, and many other illnesses covered in this handbook, often have multiple sources of payment, including Medicare (for which they often pay premiums and taxes), private insurance, free clinic care for some services (paid for by local funds), and direct out-of-pocket expenditures.

I.1.F.1.3 Conclusions Regarding the Market Value

These factors distort the simple connection between the price paid and the actual costs that exists for purchasing many other goods and services. Under these circumstances, it is difficult to determine precisely what an average patient would be willing to pay. Although such uncertainties may lead to an over- or underestimate of WTP, the illnesses in this handbook are very serious in nature (i.e., either life-threatening or capable of resulting in very debilitating conditions), and people are likely to be willing to pay much more than they currently pay out-of-pocket or indirectly (e.g., through insurance premiums). The value to the afflicted individual and/or friends and family of avoiding the anxiety, pain, and suffering associated

[14] As Figure I.1-1 shows, there are some direct payments of medical services by the patient; however, full payment for major illnesses by a patient is relatively uncommon.

with the illness (see Figure I.1-1) may be considerably greater than those cost components included in the cost-of-illness approach.

Link to Figure I.1-1

Because the payment of medical costs comes from multiple sources, both direct and indirect, the purchase of medical services is actually determined by multiple and diverse groups. Those who have a role in determining medical costs and standard services for illnesses include insurance premium payers; taxpayers and their elected representatives (who are involved in determining payments for publicly funded services); state, local, and national agencies, whose staff are also publicly accountable; corporations with stockholders; medical personnel; and others. The overall cost of living, employment characteristics, and cost for durable goods also play a role. Consequently, although there are disjunctions and complications in the determination of medical costs, the diversity of decision-makers in the cost-setting process provide some assurance that medical costs reflect the preferences of society.

I.1.F.2 Differences in Critical Patient Characteristics.

Some factors are related to individual characteristics. They introduce uncertainty into the use of cost only if the population of concern (e.g., the study population for a benefits assessment) has characteristics that differ from those of the "average" members of the population with the disease. These factors include:

- the organ systems affected by the disease (e.g., which systems, multiple versus single systems);
- the severity of the disease (may be related to the above);
- the general health of the patients aside from the disease in question;
- other complicating medical conditions in the patients; and
- the life expectancy of the patients (this affects the length of treatment)

I.1.F.3 Geographic Differences in Medical Practices and Services

Other factors that impact costs are associated with medical practices and services in a geographic area. These factors may differ substantially among various areas of the U.S. For example, urban areas generally have higher direct medical costs than rural areas.

Factors of concern regarding differences in medical practices and services include:

- the specific treatment protocols chosen;
- the hospital and professional fee rate structure in a particular area; and
- the support systems that provide care at no cost (e.g., home care).

Access to care is a particularly difficult factor in evaluating medical costs and has a complex role in their calculation. Consequently, is it usually discussed only qualitatively as a source of uncertainty. Its actual cost impacts are rarely known. Access to services varies on a geographic and socioeconomic basis and often increases both risks and costs for economically disadvantaged patients. For example, access to medical care has been found to be a critical factor in survival among people with asthma, with limited access to care being closely linked to poverty status in some major cities.

Access to care has multiple components. It includes the physical availability of services. A one-hour bus trip to a clinic may be a major impediment to care, and be replaced by the use of ambulance transport to an emergency room rather than a doctor's office because an "emergency" is required to obtain transportation (given that the bus ride is not a reasonable option for someone who is sick). Moderately ill people who could be seen in a clinic may be seen in a much more expensive emergency room due to lack of access to designated Medicare/Medicaid clinics.

A second, and often more costly impact of limited access to care, is the condition of the patient when he or she receives services. Access issues may lead to delays in obtaining care so that disease management is poorer. This care differential impacts the outcome and often leads to higher mortality (as mentioned above with respect to asthma). The overall costs of this factor, in direct and indirect costs (including pain and suffering), is substantial. The vast majority of deaths from asthma occur among children and the elderly who are below the poverty line.

When evaluating benefits, some aspects of the impacts of access to care and other problems related to socioeconomic status may be relevant, especially for chronic low-level diseases (e.g., COPD, asthma, cardiovascular diseases). They are also relevant to cancers in which the late diagnosis, in part due to less frequent medical checkups, is often noted as a contributing factor to the higher mortality rate among lower socioeconomic groups. An example is the strong positive association between the probability of mammograms and family income. The reduced use of this diagnostic tool among poorer women is linked to their increased

risk of breast cancer being diagnosed at later stages of the disease. This delay leads to a poorer overall survival, higher medical costs, and increases in lost time.

As noted previously, differences in medical practices and services will be relevant ONLY if a benefits analysis focuses on an area or population subgroup within the U.S. where the practices and services differ from the "average" in the U.S. Most cost estimates in the handbook are derived from databases that cover a wide socioeconomic and geographic spectrum.

I.1.F.4 Uncertainty Regarding the Application And/or Accuracy of Input Data

Varied data sources are used for most cost analyses. These sources range from scientific papers reported in the medical economics literature to census and National Cancer Institute (NCI) data regarding demographics and background rates of mortality, cancer diagnosis, and patient survival. The quality and applicability of the input data are relevant to all uses of the cost data. Uncertainty regarding the inputs to the cost estimates fall into the following categories:

- accuracy of estimates from primary sources,
- accuracy of "background" cost estimates used with the disease cost estimates to calculate the incremental costs,
- accuracy of life expectancy estimates for patients who are either survivors or nonsurvivors of the disease,
- accuracy of estimates of the percent of survivors and nonsurvivors,
- accuracy of the estimates of survival among people without the disease (used for background calculations),

I.1.F.4.1 Geographically Representative Data

As noted previously, national data were sought to obtain the best "average" estimate for each input parameter. Estimates were usually obtained through the use of data on a cross-section of people with a similar mix of ages, sexes, races, etc., to that of the overall U.S. population. Often a subset of a national database was used, or the entire database for specific years was obtained. This national approach provides a reasonably good estimate of costs. As always with sampling, there is a small chance that the data selected will not be entirely representative, thereby introducing some uncertainty. This is not likely, however, to be a major source of uncertainty.

Some diseases were evaluated based on data from a specific geographic area. For example, some chapters on birth defects (e.g., cleft lip and

palate) were obtained from a detailed analysis conducted by Waitzman et al. (1996) that used 18 databases in California to obtain a complex and comprehensive description of direct and some indirect costs of the disorders. California is economically and demographically diverse, and so, as noted in the chapter, it is believed that the cost estimates are reasonable approximations of a national average. Still, the use of location- or population-specific data introduces additional uncertainty. When data were used that generate this type of uncertainty, relevant concerns are described in the chapter.

I.1.F.4.2 Treatment Estimates

As discussed previously, a few chapters rely on treatment protocols provided by physicians to estimate medical costs. These protocols cause uncertainty in estimating medical costs, due to the assumption that all patients receive timely and adequate medical care, which is not always the case in practice. Some patients don't seek care, some delay treatment, and others are treated for only a short time. These behaviors are due to a variety of factors. Evaluating the impact of this approach on costs is difficult because a delay in care, while reducing immediate costs, usually leads to increased costs in treating a more severe form of the disease and a longer disability period, or in early mortality and an associated increase in lost time. Rather than determining the direction of impact on costs (higher or lower), it is simply noted that the cost estimate based on a physician protocol introduces additional uncertainty.

I.1.F.4.3 Conversions and Calculations

Other types of uncertainty are introduced by the use of data that are relevant, but not expressed in the units required for this analysis. Agencies and researchers typically provide data in a format that is most useful for their goals; this often does not match the requirements for cost estimation. Consequently, the raw data obtained often require additional modifications using inputs from multiple sources. For example, survival among cancer patients is expressed as a relative survival rate (RSR) in the NCI databases. It was necessary to convert the relative survival rate to an absolute survival rate to carry out essential cost calculations. RSRs incorporate a background mortality rate from the general population, as well as other inputs, in their derivation. Various sources were consulted for the inputs (e.g., the U.S. Census Bureau, mortality probabilities from NCI) and the absolute survival rate was calculated. This type of calculation, which is a derivation of a critical value, introduces uncertainty regarding the result. The outcome is not likely to have substantial error, but there is not the certainty that would be obtained if the absolute rates were available from a primary source.

I.1.F.4.4 Changes in Medical Services Provision and Medical Costs

The most common source of uncertainty is introduced by the use of data that are not "current." There is no single definition of "current" because the relevant concern is whether the cost estimates reflect ongoing practices and costs. Medical approaches for some diseases have changed considerably in recent years, while others remain very similar for many years. Services and costs reflect changes and improvements in the technical aspects of how medical care is delivered.

In addition to technical changes in how medicine is practiced, there have been numerous changes in the way medical services are provided and in medical costs during the 1980s and 1990s. Medical cost containment is a relatively recent focus of private sector payers (e.g., insurance companies, managed care providers) and has been the subject of considerable effort at the federal level since the outset of the Medicare and Medicaid programs. The rapidly escalating medical costs of the 1970s and 1980s led to a national recognition of the need for medical cost containment. New systems of care management and payment have evolved in recent years and continue to evolve. Consequently, it is difficult to compare current costs directly with those of the past. This is relevant to the costs presented in the Handbook because many of the cost estimates are based on data collected in past years.

Changes in payment structures and cost containment efforts proceeded hand-in-hand with changes in the way in which services are provided. In many cases, cost containment is partially accomplished through limitations on the types of services or the specialty of the physicians to which a patient has access. Thus, cost control efforts have been directed both at slowing the increase in cost for a specific service, and in limiting the access to expensive services. The consumer price index (CPI) medical care component is used in the Handbook to inflate costs obtained in past years to the most recent year available. The CPI was designed to estimate the increases in costs associated with a specific service or item. It does not address the issue of access to services. Although there have been studies of the impacts of access limitation and other cost containment strategies, there is not a single agreed-upon value that can be applied to compare either services for a specific disease, or costs for that disease over time, independent of factors other than access limitation.

Wicker et al (1999) contains a discussion of cost containment programs' impact on patterns of care and the readmission of patients with respect to children. They discussed utilization management (UM), which provides for review and authorization of both inpatient and outpatient care for more than 90 percent of enrollees in group insurance plans (HMOs, preferred provide organizations, etc). Their study pointed out an ongoing problem related to this cost reduction strategy: by limiting care through the review

process, UM decreases initial inpatient costs but increases the rate of hospital readmission. This was noted in particular for low birth weight infants and those with depression or drug or alcohol dependence problems (Wicker et al., 1999). These are very common chronic conditions among children and adolescents, and are also among the more costly conditions due to their chronic nature. Consequently, the dynamic observed for these conditions is potentially relevant to most chronic conditions. A similar dynamic has been observed in adult patients, for whom delays in referrals to specialists and specialized treatment led to more serious illnesses requiring more costly care than would have originally been required. In the most extreme cases, denial of services had led to death (and subsequent court settlements).

What Wicker et al. and other studies suggest is that cost reductions using resource limitation strategies may not reduce costs overall, at least in some cases. In addition, the application of UM and other similar strategies varies greatly in implementation, and its application is not universal. Making simple assessments the impacts of trends in medical services, management, and costs on the overall lifetime costs of an illness is therefore difficult. The Handbook attempts to clearly state both the source of cost data and limitations in the methods of data collection, study design, and other factors that may affect how the cost data can be applied currently. It is often not known if the costs for an illness are over- or underestimates of current costs. Where new treatments are known to be offered and their likely cost impact is known, however, that information is provided (usually qualitatively).

When evaluating changes over time in costs and services, it is important to consider all inputs to cost. For example, when the data on breast cancer costs were collected, bone marrow transplants were not yet being done. Now they are offered for the most advanced cases of the disease and they are very expensive. Because they are provided to a small percentage of women with the disease, they will not have a substantial impact on the overall costs; however, bone marrow transplants may slightly increase the average cost of treatment. Balancing this is the fact that women receiving this treatment are less likely to die. Consequently, any application of mortality percentages and the value of statistical life (VSL) to breast cancer patients may overestimate the mortality-associated costs. In addition, there is some evidence that women are being diagnosed with breast cancer at earlier stages, which decreases the risk of death but also increases the direct medical costs because they are living longer and requiring additional services. Given the difficulty in evaluating changes in services and costs over time, and the extreme difficulty in obtaining a national average lifetime medical cost for most diseases, the cost estimates provided in this Handbook offer a reasonable approximation, with the limitations associated with the estimates acknowledged.

Appendix I.1-A Equations Describing the Expected Present Discounted Value of the Per Capita Lifetime Stream of Costs Associated with a Given Illness

Illnesses are costly in many ways and often over long periods of time.[15] Many illnesses result in costs for years after onset; some illnesses result in a lifetime of costs. Some of these costs, such as hospitalization charges and physician fees, are obvious. Other costs, such as the value of lost time due to the illness, are less obvious but just as real. A complete accounting of the total cost of an illness includes *all* the costs incurred as a result of the illness from the time of onset to the time of cure or the death of the individual — that is, the lifetime stream of costs associated with the illness.[16]

Properly estimating the total value of this lifetime stream of costs requires understanding several key considerations, including:

- costs incurred at a later time should be discounted,
- there are several different kinds of cost, and
- the costs of an illness are incremental costs.

The lifetime stream of costs associated with an illness will vary from one individual to another for a variety of reasons, including, for example, the age of onset of the illness. For each year post-diagnosis, moreover, direct costs can be incurred during that year only if the individual survives to that year.[17] If the individual dies in that year, then indirect costs are incurred. The number of years of survival post-diagnosis, however, will also vary from one individual to another. A fourth consideration, then, is that:

- it is not "a lifetime stream of costs" that is of interest, but rather the *expected*, or average, lifetime stream of costs.

To estimate this average value, it is necessary to know the probabilities of survival for each year post-diagnosis.

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[15] Birth defects are included within "illnesses."

[16] Even a complete accounting of all costs of an illness will yield an underestimate of the true social value of avoiding the illness, because it does not take into account the value of avoiding the pain and suffering associated with the illness.

[17] Estimates of the costs of an illness are usually used as lower-bound estimates of morbidity costs rather than as estimates of the value of avoiding premature mortality from the illness. Estimates of the value of avoiding premature mortality are generally substantially higher than cost of illness estimates.

The expected present discounted value of per capita lifetime incremental costs of an illness can be constructed from its component parts. Each of the expressions or parameters used in this construction is explained in the table below. When an expression is derived from other expressions and/or parameters, the derivation is given in the table. All costs are average per capita costs and are incremental (i.e., the costs of the illness beyond those expected to be incurred by the same individual in the absence of the illness).

Table I.1.A-1: Estimation of the Expected Present Discounted Value of Per Capita Lifetime Incremental Costs of an Illness		
Parameter		**Derivation**
The cost of heightened morbidity:		
j	number of years post-diagnosis (an index)	
$dc_j^{medical}$	direct medical costs j years post-diagnosis	
$dc_j^{nonmedical}$	direct nonmedical costs j years post-diagnosis	
ic_j^{vlphm}	indirect costs j years post-diagnosis: value of lost time due to heightened morbidity, estimated as the number of units of productive time (e.g., hours or days) lost in the jth year post-diagnosis due to the illness times the value per unit time.	
ic_j^{vllthm}	indirect costs j years post-diagnosis: value of lost leisure time due to heightened morbidity, estimated as the number of units of leisure time (e.g., hours or days) lost in the jth year post-diagnosis due to the illness times the value per unit time.	
$cost_j^{hm}$	total costs of heightened morbidity incurred j years post-diagnosis. $Cost_j^{hm}$ is an *average* cost among all those with the illness who survive j years post-diagnosis. Any of the components of $cost_j^{hm}$ may vary from one individual to another because of factors such as sex or age.	$cost_j^{hm} = dc_j^{medical} + dc_j^{nonmedical} + ic_j^{vlphm} + ic_j^{vllthm}$
The cost of premature mortality:		
r	discount rate, reflecting individuals' positive rate of time preference.	
x	age of onset of the illness	
d	age of death from the illness	If death from the illness occurs j years post-diagnosis, d=x+j.
m	expected age of death, in the absence of the illness	

Table I.1.A-1: Estimation of the Expected Present Discounted Value of Per Capita Lifetime Incremental Costs of an Illness		
Parameter		**Derivation**
vp_k	value of time at age k (in the absence of the illness), estimated as the number of units of time (e.g., days or hours) of time at age k times the value per unit time.	
vlt_k	value of leisure time at age k (in the absence of the illness), estimated as the number of units of leisure time (e.g., days or hours) at age k times the value per unit time.	
ic^{vlppm}	indirect costs: value of lost time due to premature mortality. This is the sum of discounted values of time for each year that the individual would be expected to live in the absence of the illness but did not live — i.e., from the age at death (d) to the expected age at death (m).	$$ic^{vlppm} = \sum_{k=d}^{m} \frac{vp_k}{(1+r)^{k-d}}$$
ic^{vlltpm}	indirect costs: value of lost leisure time due to premature mortality. This is the sum of discounted values of leisure time for each year that the individual would be expected to live in the absence of the illness but did not live — i.e., from the age at death (d) to the expected age at death (m).	$$ic^{vlltpm} = \sum_{k=d}^{m} \frac{vlt_k}{(1+r)^{k-d}}$$
$cost_j^{pm}$	total costs of premature mortality for an individual who dies j years post-diagnosis. $Cost_j^{pm}$ is an *average* cost among all those who die from the illness j years post-diagnosis. Any of the components of $cost_j^{pm}$ may vary from one individual to another because of factors such as sex or age. As noted above, if death from the illness occurs j years post-diagnosis, then age at death is d=x+j. Medical costs included in $cost_j^{pm}$ are those medical costs that would not have been incurred in the absence of death from the illness (e.g., terminal care costs of cancer).	$$cost_j^{pm} = dc_j^{medical} + ic_j^{vlppm} + ic_j^{vlltpm}$$ where $$ic_j^{vlppm} = \sum_{k=d}^{m} \frac{vp_k}{(1+r)^{k-d}}, \quad d = x+j$$ and similarly for ic_j^{vlltpm}

Table I.1.A-1: Estimation of the Expected Present Discounted Value of Per Capita Lifetime Incremental Costs of an Illness		
Parameter		**Derivation**
Expected costs:		
ps_j	probability of surviving j years post-diagnosis	
pd_j	probability of dying j years post-diagnosis	$pd_j = ps_{j-1} * (1 - ps_j)$
$E(cost_j)$	expected costs incurred j years post-diagnosis. This is the *average* cost of the illness j years post-diagnosis — the average cost of heightened morbidity times the probability of surviving j years post-diagnosis plus the average cost of premature mortality times the probability of dying j years post-diagnosis.	$E(cost_j) = ps_j * cost_j^{hm} + pd_j * cost_j^{pm}$
Age-of-onset-dependent costs: *The costs and probabilities of surviving or dying j years post-diagnosis may depend not only on j but on the age of onset of the illness, or, equivalently, on the individual's age (x+j) j years post-diagnosis. The probability of someone who gets lung cancer at age 45 surviving to age 46, for example, may be very different from the probability of someone who gets lung cancer at age 70 surviving to age 71. The above parameters are therefore further refined below.*		
$cost_{j,x}^{hm}$	total costs of heightened morbidity incurred j years post-diagnosis, given that age of onset is x. This is a refinement of $cost_j^{hm}$ which acknowledges that one or more components of the costs of heightened morbidity may depend not only on the number of years post-diagnosis but also on the age of onset or, equivalently, on current age (x+j).	$cost_{j,x}^{hm} = dc_{j,x}^{medical} + dc_{j,x}^{nonmedical} + ic_{j,x}^{vlphm} + ic_{j,x}^{vllthm}$
$cost_{j,x}^{pm}$	total costs of premature mortality for an individual who dies j years post-diagnosis, given that age of onset is x. This is a refinement of $cost_j^{pm}$ which acknowledges that the components of the costs of premature mortality may depend not only on the number of years post-diagnosis but also on the age of onset, or, equivalently, on current age (x+j).	$cost_{j,x}^{pm} = dc_{j,x}^{medical} + ic_{j,x}^{vlppm} + ic_{j,x}^{vlltpm}$

Table I.1.A-1: Estimation of the Expected Present Discounted Value of Per Capita Lifetime Incremental Costs of an Illness		
Parameter		**Derivation**
$ps_{j,x}$	probability of surviving j years post-diagnosis, given that age of onset is x.	
$pd_{j,x}$	probability of dying j years post-diagnosis, given that age of onset is x.	$pd_{j,x} = ps_{j-1,x} * (1 - ps_{j,x})$
$E(cost_{j,x})$	expected total costs incurred j years post-diagnosis, given that age of onset is x.	$E(cost_{j,x}) = ps_{j,x} * cost_{j,x}^{hm} + pd_{j,x} * cost_{j,x}^{pm}$
Discounted expected costs: *Expected costs incurred j years post-diagnosis are discounted back to the time of diagnosis (onset) of the illness.*		
$PDVEC_{j,x}$	present discounted value of expected costs incurred j years post-diagnosis, given age of onset x.	$PDVEC_{j,x} = \frac{E(cost_{j,x})}{(1 + r)^j}$
$PDVEC_x$	present discounted value of the *lifetime stream* of expected costs when age of onset is x. This is the sum of discounted expected costs from onset of the illness at age x until either cure or the death of the individual.	$PDVEC_x = \sum_{j=0} PDVEC_{j,x} = \sum_{j=0} \frac{E(cost_{j,x})}{(1 + r)^j}$
p_x	probability that the age of onset of the illness is x	

Table I.1.A-1: Estimation of the Expected Present Discounted Value of Per Capita Lifetime Incremental Costs of an Illness		
Parameter		**Derivation**
EPDVEC	*expected* present discounted value of lifetime costs, i.e., the average over all possible ages of onset.	$EPDVEC = \sum_{x=0} p_x PDVEC_x = \sum_{x=0} p_x \sum_{j=0} \frac{E(cost_{j,x})}{(1+r)^j}$
Approximations or alternatives to EPDVEC:		
av	the average age of onset of the illness	
$PDVEC_{av}$	present discounted value of the *lifetime stream* of expected costs when age of onset is the average age of onset. $PDVEC_{av}$ is $PDVEC_x$, where age of onset is the average age of onset; av. $PDVEC_{av}$ is an approximation to EPDVEC.	$PDVEC_{av} = \sum_{j=0} PDVEC_{j,av} = \sum_{j=0} \frac{E(cost_{j,av})}{(1+r)^j}$
n	average number of years post-diagnosis at which cure or death occurs	
$PDVC_{avg}{}^{hm}$	present discounted value of the lifetime stream of costs of heightened morbidity associated with the illness for the "average individual" diagnosed with the illness.	$PDVC_{avg}{}^{hm} = \sum_{j=0}^{n-1} \frac{cost_{j,av}{}^{hm}}{(1+r)^j}$
$PDVC_{avg}$	present discounted value of the lifetime stream of costs (including both heightened morbidity and premature mortality costs) associated with the illness for the "average individual" whose age of onset is av and who dies from the illness at n years post-diagnosis. $PDVC_{avg}$ is a simplification of $PDVEC_{av}$. It sets $ps_{j,av} = 1$ for $j<n$ and $ps_{j,av} = 0$ for $j \geq n$.	$PDVC_{avg} = \sum_{j=0}^{n-1} \frac{cost_{j,av}{}^{hm}}{(1+r)^j} + \frac{cost_{n,av}{}^{pm}}{(1+r)^n}$

The hypothetical example below considers an "average individual" who becomes ill at age 60 and who survives to age 68. The hypothetical incremental costs incurred by this individual at each year post-onset, the discounted age-specific costs, and the sum of these discounted costs (the present discounted value of this average individual's costs at the time of onset) are shown in the table below. Because the individual dies of the illness at age 68, the value of lost leisure time for each year that he or she would otherwise have lived is discounted back to age 68 and the discounted values summed ($95,009).

For those individuals who ultimately die of an illness, it could be argued that the value of a statistical life lost is the appropriate cost. This value would subsume the cost-of-illness estimate. Based on evidence from numerous value-of-life studies, the value of a statistical life far exceeds any cost-of-illness estimates that might be derived from estimates of the four cost components discussed above. For those individuals who do not die of the illness, there will be no terminal care costs, nor will there be any lost time or lost leisure time attributable to the individual dying prematurely. Costs incurred during a period of remission, however, could exceed those for terminal cases, if the remission period is substantially longer.

Table I.1.A-2: The Present Discounted Value of the Lifetime Stream of Hypothetical Costs of an Illness of a Hypothetical Average Individual						
	Costs					
	Direct		Indirect			
Age	Medical	Nonmedical	Value of Lost Time	Value of Lost Leisure Time	Age-specific Costs	Discounted Age-specific Costs**
60*	$30,000	$5,000	$20,000	$7,000	$62,000	$62,000
61	$10,000	$5,000	$20,000	$7,000	$42,000	$40,000
62	$2,000	$1,000	$200	$0	$3,200	$2,902
63	$2,000	$1,000	$200	$0	$3,200	$2,764
64	$2,000	$1,000	$200	$0	$3,200	$2,633
65	$2,000	$1,000	$200	$0	$3,200	$2,507
66	$2,000	$1,000	$0	$200	$3,200	$2,388
67	$2,000	$1000	$0	$200	$3,200	$2,274
68	$40,000	$500	$0	$95,009	$135,509	$91,718
					Present discounted value of costs:	$209,187

*Average age of onset.
** Using a discount rate of 5 percent, discounted back to the age of onset. For example, to get the present discounted value (at age of onset) of the costs at age 63, these costs are divided by $(1+0.05)^3$

CHAPTER II.1: INTRODUCTION TO THE COSTS OF CANCERS

Clicking on the sections below will take you to the relevant text.

CHAPTER II.1: INTRODUCTION TO THE COSTS OF CANCERS

This section of the handbook contains chapters that describe costs of medical treatments for a variety of cancers that have been associated with exposure to environmental agents. Cancer is one of the three leading causes of death in the United States and throughout the world (Williams and Weisburger, 1993). It is a serious illness that has been associated with environmental exposures in both human and animal studies. Cancers often have similar treatment options (e.g., radiation, chemotherapy, surgery, reconstructive and physical therapy treatments), and generally require long-term medical care. Most occur with much greater frequency in individuals in the second half of life.

This section contains an overview of the environmental causes of cancer and general issues related to economic valuation of the medical treatment of cancer. It also contains an estimate of the cost of a "typical" cancer case and examples of how the typical cost estimates can be modified to obtain more information on specific cancers (using liver and bone cancers as examples). This chapter is followed by chapters containing medical cost information on specific types of cancer that may be associated with exposure to environmental agents.

II.1.A. Description

Cancer is the common term for all malignant tumors and includes carcinomas and sarcomas, depending on the tissue of origin. Cancer is characterized by abnormal growth that preys on the host. It may metasticize to other locations in the body and often leads to debilitation and/or death if left untreated. A critical distinction among tumors is made between benign and malignant tumors. Although benign tumors may be medically important and sometimes become malignant (Robbins et al., 1984), they are not considered cancerous, and so are not included in the cost estimates presented in this section.

II.1.B. Concurrent Effects

Concurrent effects commonly occur with cancer. These effects usually arise from two main causes: 1) as a result of a metastatic (spreading) process, leading to cancers at more than one site in the body, 2) as a result of the impaired health status of the cancer patient. Impaired health can arise from either the cancer's interference with normal functioning, or the adverse effects associated with chemotherapy, radiation treatment, surgery, or other medical treatments. Many of the side effects of cancer treatment are well known. For example, the antineoplastic drug adriamycin causes damage to the heart muscle. Radiation therapy may cause toxicity (e.g., sterility) and additional cancers while limiting the spread of cancer at the

original site. A variety of other effects are associated with cancer therapies. One focus in oncology is on balancing the toxic properties of the anticancer therapies in the health portions of the body against the need to cause toxicity to the tumor cells.

Because there are no benign cancer therapies, and cancer is often a metastatic process, there are invariably some costs associated with cancer that are not considered when only the direct medical costs of treating the primary cancer are considered. Some researchers (e.g. Baker et al., 1989 and 1991) have taken many of the costs of concurrent effects into account by evaluating the costs associated with the treatment of cancer patients in relation to medical costs of individuals without cancer (referred to as background medical costs). When background costs are subtracted from the total medical costs to cancer patients, the remaining incremental costs to cancer patients include costs of treating side effects, as well as the original cancer treatment costs. Baker et al.'s values are reported in Chapters II.2., II.3, II.4, II.5, II.7, and II.8.

This incremental approach captures medical costs associated with side effects that occur during treatment for the original cancer, but those that occur at a later date may not be included. For example, medical costs associated with a second cancer that occurs years later, induced by radiation therapy, would not be included using this approach. There are currently no very long-term follow-up data on these types of costs. This omission is likely to lead to an underestimate of total medical costs.

II.1.C. Causality and Special Susceptibilities

Carcinogens may act directly in causing cancer (initiators), or with other chemicals or individual characteristics to promote the development of cancer (promoters). Both initiators and promoters increase cancer risk. Cancer involves a change in cells that eliminates the normal controls on the growth of cells (Williams and Weisburger, 1993). Most carcinogens interact with DNA to alter the basic genetic directions of cells. Common characteristics of these carcinogens are that their effects are persistent, cumulative, and delayed (Ibid). The delay in effects, often for decades, make their identification and the quantification of their risks to humans difficult.

Although thousands of studies of the carcinogenicity of chemicals are conducted, most are carried out in animals due to:

1) the long delay after exposure in the development of tumors in humans, as noted above;

2) ethical issues;

3) costs of conducting human studies; and

4) difficulties with the confounding effects of carcinogens not under study.[1]

Animals are used because they provide a controlled set of subjects whose exposure can be measured accurately. Due to their relatively short life span, cancer can be observed and quantified in a reasonable amount of time in animals, especially in rodents. They are typically given large doses because this allows a relatively small number of animals to be used (e.g., 50 or 100) to obtain a statistically significant result. The results are then scaled to a human dose and response.

The chemical induction of cancer in animals is generally assumed to be evidence that the chemical may pose cancer risks to humans. EPA's *Proposed Guidelines for Cancer Risk Assessment* state that:

> "The default assumption is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans. Thus if no adequate human data are present, positive effects in animal cancer studies are a basis for assessing the carcinogenic hazard to humans... The assumption is supported by the fact that nearly all of the agents known to cause cancer in humans are carcinogenic in animals in tests with adequate protocols... Further support is provided by research on the molecular biology of cancer processes, which has shown that the mechanisms of control of cell growth and differentiation are remarkably homologous among species..." (EPA 1996).

These proposed guidelines are very similar to those which have been in force for the last decade (EPA 1986).[2]

Although the assumption is made that cancer induction in animals may indicate cancer risk in humans, it is not assumed that cancer will occur in the same organ(s) in humans as in animals (EPA 1996). In addition, carcinogens often act non-specifically, being capable of acting on multiple organ systems throughout the body. Consequently, most cancer studies

[1] The absolute prohibition against exposure to non-beneficial chemicals (e.g., pharmaceuticals) that exists for humans does not exist for animals, and most chemicals of toxicological interest continue to be tested on animals. Ethical issues still persist, however, when animal studies are conducted, due to procedures that raise serious ethical concerns.

[2] Many specific criteria are used in determining whether a chemical is carcinogenic. See the proposed cancer guidelines for more information (EPA 1996).

cannot be used to determine the specific site where cancer is likely to occur in humans, but can be used to strongly suggest that a cancer risk exists.[3] Because positive cancer study results in animals may be relevant to many types of cancer in humans, the results of cancer studies in animals are listed in this introductory cancer chapter rather than in the individual cancer chapters that deal with a specific organ (e.g., kidney cancer, lung cancer).

II.1.D. Chemicals Associated with Cancer Induction

Table II.1-1 lists chemicals that have been associated with carcinogenic effects in either animal or human studies, based on EPA's review of the carcinogenicity data. The chemicals listed in Table II.1-1 have been identified as potential human carcinogens in one or more of EPA's large toxicity databases: HSDB, IRIS, or HEAST. The table, compiled in 1996, is *not* a comprehensive list of all carcinogens.

The chemicals listed in Table II.1-1 are a sample of the potential environmental agents associated with this disease. Although the table contains many chemicals, it is incomplete for two reasons:

1. It does not include toxicological data from sources other than HSDB, IRIS, and HEAST. The toxicological literature currently available is vast, and a thorough review was beyond the scope of this analysis.

2. Many chemicals have not been tested, or the results of the tests are inconclusive. Consequently, the human health effects of many environmental hazards are unknown, especially at concentrations found in the environment.

[3] When portal-of-entry effects or other location-specific interactions occur, cancer sites can be more specifically predicted.

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
ACENAPHTHENE	HSDB
ACENAPHTHYLENE	HSDB
ACEPHATE*	IRIS
ACRYLAMIDE*	IRIS
ACRYLONITRILE*	HSDB, IRIS
ALACHLOR*	HEAST
ALDRIN*	IRIS
ALKANOLAMINE SALTS, 2,4-D,	HSDB
ALUMINUM*	HSDB
ALUMINUM FLUORIDE	HSDB
ALUMINUM OXIDE*	HSDB
ALUMINUM SODIUM FLUORIDE	HSDB
AMMONIUM CHROMATE	HSDB
AMMONIUM DICHROMATE	HSDB
AMOSITE	HSDB
AMPICILLIN	HSDB
ANILINE*	IRIS
ARAMITE	IRIS
ARSENIC*	HSDB, IRIS
ARSENIC ACID*	HSDB
ARSENIC PENTOXIDE*	HSDB
ARSENIC TRIBROMIDE*	HSDB
ARSENIC TRICHLORIDE*	HSDB
ARSENIC TRIIODIDE*	HSDB
ARSENIC TRIOXIDE*	HSDB
ARSENIC TRISULFIDE*	HSDB
ARSINE	HSDB
ASBESTOS*	HSDB
ASPHALT	HSDB
ATRAZINE*	HEAST
ATTAPULGITE	HSDB
AZOBENZENE	IRIS
BENZENE*	HSDB, IRIS
BENZENE HEXACHLORIDE	HSDB
BENZIDINE*	HSDB, IRIS
BENZO(A)PYRENE*	HSDB
BENZO(B)FLUORANTHENE*	HSDB
BENZOTRICHLORIDE	HSDB, IRIS
BENZOYL CHLORIDE*	HSDB
BENZO[A]PYRENE	IRIS
BENZYL CHLORIDE*	IRIS
BERYLLIUM*	HSDB, IRIS
BERYLLIUM CHLORIDE*	HSDB
BERYLLIUM FLUORIDE*	HSDB
BERYLLIUM HYDROXIDE*	HSDB
BERYLLIUM NITRATE*	HSDB
BERYLLIUM OXIDE*	HSDB
BERYLLIUM PHOSPHATE*	HSDB

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
BERYLLIUM SULFATE*	HSDB
BIS(2-CHLOROETHYL) ETHER*	HEAST
BIS(2-CHLOROETHYL)SULFIDE	HSDB
BIS(CHLOROETHYL)ETHER	IRIS
BIS(CHLOROMETHYL) ETHER*	HSDB, IRIS
BROMO-2-CHLORO-1,1,1-TRIFLUOROETHANE, 2-	HSDB
BROMOCHLORODIFLUOROMETHANE*	HSDB
BROMODICHLOROMETHANE	IRIS
BROMOETHENE (VINYL BROMIDE)*	HEAST
BROMOFORM*	IRIS
BUTADIENE, 1,3-*	HSDB
BUTYRIC ACID, 4-(2,4-DICHLOROPHENOXY)	HSDB
CALCIUM ARSENATE	HSDB
CALCIUM ARSENITE	HSDB
CALCIUM CHROMATE	HSDB
CAPTAFOL	HEAST
CAPTAN*	HEAST
CARBAZOLE	HEAST
CARBON BLACK	HSDB
CARBON TETRACHLORIDE*	HSDB, IRIS
CHLORAMBUCIL	HSDB
CHLORAMPHENICOL	HSDB
CHLORANIL	HEAST
CHLORDANE	HSDB, IRIS
CHLORO-1,1,1,2-TETRAFLUOROETHANE, 2-*	HSDB
CHLORO-1,3-BUTADIENE, 2-	HSDB
CHLORO-2-FLUOROETHANE, 1-	HSDB
CHLORO-2-METHYLANALINE, 4-	HEAST
CHLORO-2-METHYLANILINE HYDROCHLORIDE	HEAST
CHLORO-2-METHYLPHENOL, 4-	HSDB
CHLOROBENZILATE*	HEAST
CHLORODIFLUOROMETHANE*	HSDB
CHLOROFORM*	IRIS
CHLOROMETHANE*	HEAST
CHLOROMETHYL METHYL ETHER*	HSDB
CHLORONITROBENZENE, O-	HEAST
CHLORONITROBENZENE, P-	HEAST
CHLOROPENTAFLUOROETHANE	HSDB
CHLOROTETRAFLUOROETHANE	HSDB
CHLOROTHALONIL	HEAST
CHROMIC ACID, CHROMIUM(3+) SALT	HSDB
CHROMIC OXIDE	HSDB
CHROMIC SULFATE	HSDB
CHROMIC TRIOXIDE	HSDB
CHROMITE	HSDB
CHROMIUM*	HSDB
CHROMIUM CHROMATE*	HSDB
CHROMIUM DIOXIDE*	HSDB
CHROMIUM TRIHYDROXIDE*	HSDB
CHROMIUM(III) ACETATE*	HSDB
CHROMOUS CHLORIDE	HSDB

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
CHROMOUS OXALATE	HSDB
CHROMYL CHLORIDE	HSDB
CHRYSOTILE ASBESTOS	HSDB
CIS-DIAMINEDICHLOROPLATINUM	HSDB
CLOMIPHENE	HSDB
CLOZARIL	HSDB
COAL TAR USP	HSDB
COAL TAR CREOSOTE*	HSDB
COAL TAR	HSDB
COPPER*	HSDB
CREOSOTE, WOOD*	HSDB
CYANAZINE*	HEAST
CYCLOPHOSPHAMIDE	HSDB
D, 2,4-*	HSDB
D BUTOXYETHYL ESTER, 2,4-*	HSDB
D, BUTOXYPROPYL ESTER, 2,4-*	HSDB
D BUTYL ESTER, 2,4-*	HSDB
D CHLOROCROTYL ESTER, 2,4-*	HSDB
D, DIMETHYLAMINE, 2,4-*	HSDB
D ISOOCTYL ESTERS, 2,4-*	HSDB
D ISOPROPYL ESTER, 2,4-*	HSDB
D, PROPYLENE GLYCOL BUTYL ETHER ESTER, 2,4-*	HSDB
DAUNORUBICIN	HSDB
DDT	HSDB
DI(2-ETHYLHEXYL)ADIPATE	IRIS
DI(2-ETHYLHEXYL)PHTHALATE*	IRIS
DIALLATE*	HEAST
DIBENZ(A,H)ACRIDINE*	HSDB
DIBENZ(A,J)ACRIDINE*	HSDB
DIBENZO(A,E)PYRENE*	HSDB
DIBENZO(A,H)PYRENE*	HSDB
DIBENZO(A,L)PYRENE*	HSDB
DIBENZO(C,G)CARBAZOLE, 7H-*	HSDB
DIBROMO-3-CHLOROPROPANE, 1,2*	HEAST
DIBROMOCHLOROMETHANE	IRIS
DIBROMOETHANE, 1,2-*	IRIS
DIBROMOTETRAFLUOROETHANE, 1,2-	HSDB
DICHLORFOP-METHYL	HSDB
DICHLORO-1,1,2-TRIFLUOROETHANE*	HSDB
DICHLORO-1,1,1-TRIFLUOROETHANE, 2,2-*	HSDB
DICHLORO-1,1,2,2-TETRAFLUOROETHANE, 1,2-	HSDB
DICHLORO-1,1-DIFLUOROETHANE, 1,2-*	HSDB
DICHLORO-1-FLUOROETHANE, 1,1-*	HSDB
DICHLORO-2-BUTENE, 1,4-*	HEAST
DICHLOROBENZENE*	HSDB
DICHLOROBENZENE, 1,4-*	HSDB
DICHLOROBENZENE, 1,2-*	HSDB
DICHLOROBENZENE, 1,3-*	HSDB
DICHLOROBENZENE, 1,4-*	HEAST
DICHLOROBENZIDINE, 3,3'-*	HSDB, IRIS
DICHLORODIFLUOROMETHANE*	HSDB

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
DICHLORODIPHENYL DICHLOROETHANE, P,P'-	IRIS
DICHLORODIPHENYLDICHLOROETHYLENE, P,P'-	IRIS
DICHLORODIPHENYLTRICHLOROETHANE, P,P'-	IRIS
DICHLOROETHANE, 1,2-*	IRIS
DICHLOROETHYLENE, 1,1-	IRIS
DICHLOROMETHANE*	HSDB, IRIS
DICHLOROPHENOL, 2,4-*	HSDB
DICHLOROPROPANE, 1,2-*	HEAST
DICHLOROPROPENE, 1,3-	HSDB
DICHLOROTRIFLUOROETHANE*	HSDB
DICHLORVOS*	HSDB, IRIS
DIELDRIN	IRIS
DIENESTROL	HSDB
DIETHYLSTILBESTROL	HEAST
DIMEHTYLBENZIDINE, 3,3-*	HEAST
DIMETHOXYBENZIDINE, 3,3-*	HEAST
DIMETHYL SULFATE*	HSDB
DIMETHYLANALINE HYDROCHLORIDE, 2,4-	HEAST
DIMETHYLANILINE, 2.4-	HEAST
DIMETHYLCARBAMOYL CHLORIDE*	HSDB
DINITROTOLUENE MIXTURE, 2,4-/2,6-*	IRIS
DIOXANE, 1,4-*	IRIS
DIPHENYLHYDRAZINE, 1,2-*	IRIS
DIRECT BLACK 38*	HEAST
DIRECT BLUE 6*	HEAST
DIRECT BROWN *95	HEAST
EPICHLOROHYDRIN*	HSDB, IRIS
ESTRONE	HSDB
ETHANOL	HSDB
ETHYL ACRYLATE*	HEAST
ETHYL CARBAMATE	HSDB
ETHYLENE GLYCOL DINITRATE	HSDB
ETHYLENE OXIDE*	HEAST, HSDB
ETHYLENE THIOUREA*	HEAST
FERRIC ARSENATE	HSDB
FERRIC OXIDE	HSDB
FERROUS ARSENATE	HSDB
FLUOROURACIL*	HSDB
FOLPET*	IRIS
FOMESAFEN*	IRIS
FORMALDEHYDE*	HSDB
FURAZOLIDONE	HEAST
FURIUM	HEAST
FURMECYCLOX	IRIS
GASOLINE	HSDB
GILSONITE	HSDB
HCFC-123A *	HSDB
HCFC-123B*	HSDB
HCFC-124A*	HSDB
HEMATITE	HSDB
HEPTACHLOR*	HSDB, IRIS

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
HEPTACHLOR EPOXIDE	IRIS
HEXACHLOROBENZENE*	IRIS
HEXACHLOROBUTADIENE	IRIS
HEXACHLOROCYCLOHEXANE, ALPHA-	IRIS
HEXACHLOROCYCLOHEXANE, BETA-	IRIS
HEXACHLOROCYCLOHEXANE, GAMMA-	HEAST
HEXACHLOROCYCLOHEXANE, TECHNICAL	IRIS
HEXACHLORODIBENZO-P-DIOXIN*	IRIS
HEXACHLOROETHANE*	IRIS
HEXAHYDRO-1,3,5-TRINITRO-1,3,5-TRIAZINE	IRIS
HYDRAZINE*	HSDB
HYDRAZINE/HYDRAZINE SULFATE*	IRIS
ISOPHORONE	IRIS
KEROSENE	HSDB
LEAD ARSENATE*	HSDB
LEAD CHROMATE*	HSDB
LEAD PHOSPHATE*	HSDB
LITHIUM CHROMATE	HSDB
MAGNESIUM ARSENATE	HSDB
MECHLORETHAMINE	HSDB
MELPHALAN	HSDB
MERCURY, ELEMENTAL*	HEAST
METHALLENESTRIL	HSDB
METHOXSALEN	HSDB
METHOXY-5-NITROANILINE, 2-	HEAST
METHOXYPSORALEN, 5-	HSDB
METHYL ISOBUTYL KETONE*	HSDB
METHYL-5-NITROANILINE, 2-	HEAST
METHYLANILINE, 2-	HEAST
METHYLANILINE HYDROCHLORIDE, 2-	HEAST
METHYLENE BIS(N,N'-DIMETHYL)ANILINE, 4,4'-	IRIS
MOLYBDATE ORANGE	HSDB
NAPHTHYLAMINE, 2-	HSDB
NICKEL*	HSDB
NICKEL CARBONATE*	HSDB
NICKEL CARBONYL*	HSDB
NICKEL CHLORIDE*	HSDB
NICKEL FORMATE*	HSDB
NICKEL HYDROXIDE*	HSDB
NICKEL OXIDE*	HSDB
NICKEL SULFATE*	HSDB
NITROFURAZONE	HEAST
NITROPROPANE, 2-*	HEAST
NITROQUINOLINE-N-OXIDE, 4-	HSDB
NITROSO-DI-N-BUTYLAMINE, N-*	IRIS
NITROSO-M-ETHYLUREA, N-	HEAST
NITROSO-N-METHYLETHYLAMINE, N-	IRIS
NITROSODI-N-PROPYLAMINE, N-*	IRIS
NITROSODIETHANOLAMINE, N-	IRIS
NITROSODIETHYLAMINE, N-**	IRIS
NITROSODIMETHYLAMINE, N-*	IRIS

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
NITROSODIPHENYLAMINE, N-*	IRIS
NITROSOPYRROLIDINE, N-	IRIS
OCHRATOXIN A	HSDB
ORYZALIN*	HSDB
OXYPHENBUTAZONE	HSDB
PENTABROMO-6-CHLOROCYCLOHEXANE, 1,2,3,4,5-	HEAST
PENTACHLORONITROBENZENE	HEAST
PENTACHLOROPHENOL*	HSDB, IRIS
PENTACHLOROPHENOL, SODIUM SALT*	HSDB
PETROLEUM ETHER	HSDB
PHENOBARBITAL	HSDB
PHENYLBUTAZONE	HSDB
PHENYLENEDIAMINE, O-	HEAST
PHENYLPHENOL, 2-*	HEAST
POLYBROMINATED BIPHENYLS*	HEAST
POLYCHLORINATED BIPHENYLS*	IRIS
POLYVINYL CHLORIDE	HSDB
POTASSIUM ARSENATE	HSDB
POTASSIUM ARSENITE	HSDB
PROCHLORAZ	IRIS
PROPIONIC ACID, 2-(3-CHLOROPHENOXY)	HSDB
PROPYL THIOURACIL	HSDB
PROPYLENE OXIDE*	IRIS
QUINOLINE*	HEAST
RADIUM	HSDB
RADON	HSDB
SILICON DIOXIDE	HSDB
SIMAZINE*	HEAST
SODIUM ARSENATE	HSDB
SODIUM ARSENITE	HSDB
SODIUM CHROMATE	HSDB
SODIUM DICHROMATE	HSDB
SODIUM DIETHYLDITHIOCARBAMATE*	HEAST
STREPTOZOTOCIN	HSDB
STRONTIUM	HSDB
STRONTIUM CHROMATE	HSDB
T, 2,4,5-	HSDB
TALC	HSDB
TETRACHLORODIBENZO-P-DIOXIN, 2,3,7,8- *	HSDB, HEAST
TETRACHLOROETHANE, 1,1,1,2-*	IRIS
TETRACHLOROETHANE, 1,1,2,2-*	IRIS
TETRACHLOROPHENOL, 2,3,4,6-	HSDB
TETRACHLOROTOLUENE, PARA, ALPHA, ALPHA, ALPHA-	HEAST
TETRACHLOROVINPHOS/(STIROFOS)	HEAST
TETRAETHYL LEAD	HSDB
THIO-TEPA	HSDB
THORIUM DIOXIDE*	HSDB
TITANIUM DIOXIDE	HSDB
TOLUENE-2,4-DIAMINE	HEAST
TOLUIDINE, P-	HEAST
TOXAPHENE*	HSDB, IRIS

Table II.1-1. SUSPECTED CARCINOGENS LISTED IN IRIS, HEAST, AND HSDB

Chemicals are listed alphabetically and TRI chemicals as of August 2000 are shown with an asterisk. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. See text for discussion of inclusion criteria. This is not a comprehensive list of all carcinogens.

CHEMICAL	SOURCE(S)
TP, 2,4,5-	HSDB
TREMOLITE ASBESTOS	HSDB
TRICHLOROANILINE, 2,4,6-	HEAST
TRICHLOROANILINE HYDROCHLORIDE, 2,4,6-	HEAST
TRICHLOROETHANE, 1,1,2-*	IRIS
TRICHLOROFLUOROMETHANE*	HSDB
TRICHLOROPHENOL, 2,4,5-*	HSDB
TRICHLOROPHENOL, 2,4,6-*	IRIS
TRICHLOROPROPANE, 1,2,3-	HEAST
TRIFLURALIN*	IRIS
TRIMETHYL PHOSPHATE	HEAST
TRINICKEL DISULFIDE	HSDB
TRINITROTOLUENE, 2,4,6-	IRIS
URANIUM	HSDB
URANYL ACETATE	HSDB
URANYL NITRATE	HSDB
URANYL SULFATE	HSDB
VINCRISTINE	HSDB
VINYL CHLORIDE*	HEAST, HSDB
VITAMIN A	HSDB
ZINC CHROMATE*	HSDB
ZINC CHROMATE HYDROXIDE*	HSDB
ZINC DICHROMATE*	HSDB
ZINC POTASSIUM CHROMATE*	HSDB

For these reasons, Table II.1-1 should not be used as a definitive source of information on the links between chemicals and cancer. A comprehensive literature search is necessary to identify the dose-response relationships between chemicals of concern and this or other health effects.

The chemicals with asterisks in Table II.1-1 are TRI chemicals (subject to reporting under the Toxics Release Inventory, Section 313 of the Emergency Planning and Community Right-to-Know Act). When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals. Chemicals included on the TRI due to their human health effects are known or reasonably anticipated to cause either significant adverse acute health effects or chronic health effects as a condition of their listing on TRI.

The route of exposure (e.g., oral, inhalation, dermal) is often considered when evaluating whether a chemicals poses a carcinogenic risk. The routes of exposure are not listed in Table II.1-1 for two reasons:

1. A chemical that is carcinogenic by one route of exposure will usually be assumed to be carcinogenic by other routes of exposure. EPA's proposed cancer guidelines state that it is assumed "that an agent that causes internal tumors by one route of exposure will be carcinogenic by another route if it is absorbed by the second route to give an internal dose" (EPA 1996). In effect, most carcinogens will fall under this assumption under most circumstances.

2. This table provides preliminary information on many chemicals identified as potential human carcinogens. Risk or health assessment, however, requires considerably more information than that provided in the table. Consequently, additional information must be collected and evaluated by researchers to fully evaluate cancer risks; an analysis of route-specific data is a part of this evaluation.

In considering the potential impacts of carcinogens, it is useful to note that a number of them are known to cross the placental barrier, and some cancers are likely to be the result of this type of exposure (Williams and Weisburger,1993).

II.1. E. Genotoxicity

Genotoxicity assays usually provide information regarding a chemical's ability to interact with DNA. Genotoxicity may be associated with cancer induction because, in most cases, the alteration in the cells' normal replication methods allows uncontrolled growth that characterizes cancer. Table II.1-2 contains a listing of chemicals associated with genotoxic effects listed in a variety of sources.[4] These chemicals have yielded positive results in genotoxicity assays, which are usually cell-level studies of a chemical's interaction with the genetic material (DNA) within a cell and/or its ability to cause mutations. Genotoxins are not all necessarily carcinogenic to humans; however, genotoxicity indicates the potential for actions that may cause cancer. Table II.1-2 contains only a small percentage of all the chemicals that have had positive genotoxicity assays. As of 1990, the Environmental Mutagen Information Center in Oak Ridge, Tennessee, maintained mutagenicity data on 21,000 chemicals (Hoffmann,1991). The size of the database indicates the magnitude of the chemicals of potential interest regarding their carcinogenic capabilities.[5]

[4] Table II.1-1 contains both genotoxic and non-genotoxic carcinogens with the criteria for inclusion being a positive carcinogenicity assay. A positive genotoxicity assay was the criterion for inclusion in Table II.1-2.

[5] Not all carcinogens are genotoxic (e.g., hormonally-mediated carcinogens). See EPA (1996) for a discussion of this distinction.

Chapter III.1 contains an additional discussion of genotoxicity relevant to birth defects.

Link to III.I.C.4

Table II.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS
DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.

CHEMICAL	REFERENCES
ACETONE*	5
ACROLEIN*	4
ACRYLIC ACID*	7
ACRYLONITRILE*	5
ALACHLOR*	1
ALDICARB*	1
AMINOPTERIN	3
AMITRAZ*	6
AMITROLE*	5
ANTU	5
AROCLOR 1016 (A PCB)*	7
ARSENIC COMPOUNDS*	6
ARSENIC*	6
ASULAM	7
ATRAZINE*	9
AVERMECTIN B1	7
BENOMYL *	1,7
BENZENE*	5
BENZO(A)PYRENE*	14
BIORESMETHRIN	1
BISULFAN	14
BORIC ACID	5
BRADIFACOUM	1
BUSULFAN	3
BUTACHLOR	4
CADMIUM*	14
CAPROLACTAM	7
CAPTAFAL	6
CAPTAN*	7,6
CARBARYL*	6
CARBOFURAN*	6
CARBON TETRACHLORIDE*	1
CARBON DISULFIDE*	5
CARBOPHENOTHION	1
CHLORDANE*	12
CHLORDECONE	1
CHLORDIMEFORM	6
CHLORFENVINPHOS	6
CHLORMEQUAT	5
CHLOROBENZILATE*	7
CHLOROBIPHENYLS (INCLUDES PCBS)*	3
CHLOROFORM*	1
CHLOROPHACINONE	1
CHLOROPROPHAM	7
CHLOROTHALONIL*	1
CHLORPROPHONE	1
CHROMIUM*	16
COPPER SULFATE*	5

Table II.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.	
CHEMICAL	**REFERENCES**
COUMACHLOR	1
COUMAFURYL	1
COUMATETRALYL	1
CYANIDES*	1
CYCLOHEXANE*	5
CYCLOHEXANONE	5
CYCLOHEXIMIDE	5
CYCLOPENTAPYRENE	2
CYCLOPHOSPHAMIDE	14
CYHALOTHRIN*	7
2,4-D*	6
DALAPON	5
DECAMETHRIN	1
DEET (DIETHYLTOLUAMIDE)	5
DI(2-ETHYL HEXYL) ADIPATE	7
DIBROMOCHLOROPROPANE*	5,6
DICAMBA*	7
DICHLOBENIL	1
O-DICHLOROBENZENE*	1
P-DICHLOROBENZENE*	5
DICHLOROETHYL ETHER	5
1,3-DICHLOROROPENE (2,3 ON TRI)	5
DICHLORVOS*	13
DIETHYLSTILBESTROL (DES)	3
DIFENACOUM	1
DIMETHOATE*	6
DIMETHYL SULFOXIDE	5
DINOSEB	14
DIOXANE *	5
DIPHACINONE	1
DIPHENYLHYDANTOIN	3
DIQUAT	5
DISULFOTON	1
DIURON*	5
ENDRIN	6
EPICHLOROHYDRIN*	5
EPN	1
EPTC	7
ETHANOL	14
ETHYL BENZENE *	
ETHYLENE DIBROMIDE	8,6
ETHYLENE DICHLORIDE*	5
ETHYLENE THIOUREA*	14
ETHYLENE OXIDE*	5
ETHYLNITROSUREA	3
EUGENAL	5
FENBUTATIN OXIDE*	1
FERBAM*	1
FLUOMETURON*	6
FLURPRIMIDOL	7
FLUTOLANIL	7
FOLPET*	8
FORMALDEHYDE*	5
GLYCEROL FORMAL	1

Table II.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.	
CHEMICAL	**REFERENCES**
GLYPHOSATE	7
HALOXYFOP METHYL	7
HEXACHLOROBENZENE*	5
HEXACHLOROPHENE*	1
LEAD*	14
LINDANE*	1
LINURON*	5
LITHIUM (TRI LISTED AS LITHIUM CARBONATE)*	3
MALATHION*	1
MALEIC HYDRAZIDE*	5
MANEB*	6
MCPA*	1
MERCURY*	7
MERCURY COMPOUNDS*	15
METALDEHYDE	5
METHIDATHION	1
METHIMAZOLE	3
METHOMYL	6
METHOXYCHLOR*	5,7
METHYL ETHYL KETONE (MEK) *	7
METHYL BROMIDE	1
METHYL METHACRYLATE*	5
METHYLCHOLANTHRENE*	14
METHYLENE CHLORIDE	5
METOLACHLOR	1,7
MEXACARBATE	1
MIREX	14
MNNG	3
MOLINATE*	1
NABAM*	5
NAPHTHALENES*	1
NAPROPAMIDE	7
NICKEL*	15
NICOTINES*	1
NITRATE*	7
NITRITE	7
NITROFEN*	4
NITROGUANIDINE	7
OXYFLUORFEN*	6
PARAQUAT*	5
PARATHION*	1
PCBS*	
PENTACHLORONITROBENZENE	1
PENTACHLOROPHENOL*	1
PERCHLOROETHYLENE*	1
PERMETHRIN*	1
PHENMEDIPHAM	1
PHENOL*	1,7
O-PHENYLPHENOL*	5
PHOSMET	1
PICLORAM*	1
PIDRIN	7
PINDONE	1
PIPERONYL BUTOXIDE*	1

Table II.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.	
CHEMICAL	**REFERENCES**
PIRIMICARB	1
PIRIMIPHOS-ETHYL	1
PIRIMIPHOS-METHYL*	6
2-PIVALYL-1,3 INDANDIONE	1
PROPACHLOR*	4
PROPARGITE*	7
PROPHAM	1
PROPOXUR*	1
PROPYLENE OXIDE*	5
PROPYLENE DICHLORIDE	5
PYRAZON	1
PYRIDINE*	5
RADIONUCLIDES (ALPHA, BETA, & GAMMA EMITTERS)	3
RESMETHRIN*	7
RONNEL	1
ROTENONE	1
SODIUM CHLORATE	5
STRYCHNINE*	5
SULFUR DIOXIDE	5
TCDD	14
2,4,5-T	1
2,4,5-TP	1
TETRACHLORVINPHOS*	1
TETRACYCLINES	3
THIABENDAZOLE*	5
THIOPHANATE-METHYL 6*	6
THIRAM*	1
TOLUENE*	5
TOXAPHENE*	6
TRICHLORFON*	13
1,2,4-TRICHLOROBENZENE*	7
1,1,1-TRICHLOROETHANE*	5
TRICHLOROETHYLENE*	5
TRIDIPHANE	7
TRIFLURALIN*	6
TRIFORINE*	1
TRIMETHADONE	3
URETHANE*	14
VALPROIC ACID	3
VERNAM	7
WARFARIN*	1
WHITE PHOSPHORUS*	
XYLENE*	5
ZINEB*	5
ZIRAM	1

Table II.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS
DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.

* = Listed in TRI as of August 2000 . When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals

References

1. Cunningham and Hallenbeck (1985).
2. Archer and Livingston (1983).
3. Doull et al .(1980).
4. U.S. EPA 1983).
5. U.S. Department of Health and Human Services, NIOSH (1983).
6. U.S. EPA (1983).
7. IRIS, U.S. EPA online database.
8. Clayton and Clayton (1982).
9. Hayes (1982).
10. Vettorazzi (1979).
11. Council on Environmental Quality (1981).
12. International Agency for Research on Cancer (1979).
13. Chambers and Yarbrough (1982)
14. Key et al. (1977).
15. Tice et al. (1996).
16. U.S. Department of Health and Human Services, ATSDR (1993).

II.1.F. Selection of Diseases

The selection of cancers included in this section was based on input from a variety of sources (as discussed in Chapter I.1). It is anticipated that additional cancers will be added in the future.

Link to Chapter I.1

II.1.G. Prognosis

II.1.G.1 General Issues

Cancers vary widely in the course of the diseases. Some types of cancer have a relatively good prognosis (e.g., non-Hodgkins lymphoma), with most patients surviving the course of the disease. Others, such as lung cancer, are much more often fatal. Although generalizations can be made regarding the "average" prognosis for each cancer, the prognosis for survival and the length of time over which treatment is required vary among individuals, even for the same type of cancer. This variability is observed for all types of cancer. Consequently, the cost estimates presented in the chapters in this section utilize estimates of the average survival rates to obtain representative estimates of the medical costs.

In addition to the individual variability in survival, patterns in survival for specific types of cancer are based on patient characteristics. For example, elderly patients with breast cancer typically have slower tumor growth than younger patients. There may also be differences related to gender and race. Although this type of pattern evaluation was beyond the scope of this handbook, it may have an impact on the cost of medical treatment. (When information was available in texts reviewed for other purposes, survival patterns are reported.) Consequently, if an analysis is being conducted on a homogeneous population (similar age, ethnicity, etc.), then it is advisable to survey the literature to determine if patterns in disease course or survival exist that may be relevant to an economic evaluation.

II.1.G.2 Survival Estimates

It is often important to obtain estimates of survival and mortality that are as accurate as possible because medical costs depend on the duration of treatment and whether patients are survivors or nonsurvivors. For example, the value of a statistical life may be used for nonsurvivors, whereas the summed direct medical and other costs may be used for survivors. Obtaining accurate estimates of mortality due to a disease is difficult unless the disease has a very short duration prior to death.[6] When the illness is protracted, as it is for most cancers, it is necessary to evaluate multiple years of vital statistics for patients to obtain reliable mortality estimates. For many illnesses there are scant data of this type; however, the National Cancer Institute (NCI) maintains this data for most cancers through their Surveillance, Epidemiology, and End Results (SEER) Program and database, which is available both on line and in documents published through the Biometry Branch of NCI.

Survival and mortality data are reported in SEER as the Relative Survival Rate (RSR) for each cancer for each year post-diagnosis. It is usually reported for the years 1973 to 1993, but for rare cancers may only be provided for five years post-diagnosis. The stomach cancer chapter in this handbook contains a detailed discussion of RSRs, and their derivation. They are statistics based on the survival of cancer patients in relation to the general population of the same age (hence the term "relative"). For purposes of determining the percent of patients who are survivors and nonsurvivors, a complex process that is described in the stomach cancer chapter can be used to obtain a precise estimate of these percents. For most uses, however, the RSRs provide a sufficiently close approximation

[6] Mortality here refers to the risk that death will occur due to the illness under study, and can be expressed as a rate (e.g., the percentage of all patients who ultimately die of the disease).

of survival and mortality percents to be used without modification. An example of a simplified approach to survival estimates is provided in the discussion of bone and liver cancer in this chapter (Section II.1.H.6.4).

Links to Chapter II.2 for detailed discussion of RSRs and Section II.1.H.6.4

II.1.H Typical Cancer Costs

Although cancer costs among individuals vary widely, there are similarities in the average costs reported for cancers. This section reports and analyzes some of these costs. The data in this section may be useful when evaluating a cancer for which cost data aren't available (e.g., a rare cancer such as bone cancer), or when the specific type of cancer is not known but a cancer risk is projected (i.e. from an animal study) and a typical value is sought.

The cost estimate provided in this section is referred to as a "typical cancer" cost rather than an average cost because it is not a statistical average of all cancer costs. Rather, the estimate is based on the average cost calculated from the only long-term study of cancer costs available (Baker et al., 1989). The costs reported here cannot be represented as average costs because they are not based on an average of either all cancers or a random sample of cancers. Cost estimates are based on a group of cancers that represent the vast majority of cancers that occur in the U.S., however, and so offer a reliable estimate of typical costs.

II.1.H.1. Source

The most recent source located for lifetime direct medical costs of a number of cancers is Baker et al. (1989). Baker et al. evaluated the continuous Medicare history sample file (CMHSF) from the Health Care Financing Administration. The file contains a random sample of five percent of all Medicare beneficiaries enrolled in 1974 in the United States, and includes all Medicare activity from 1974 to 1981. They chose CMHSF because:

1) it is a nationally representative sample of the Medicare population (five percent), covering over 1.6 million patients;
2) it is longitudinal, dating from 1974 to 1981; and
3) it captures the majority of medical expenses for each beneficiary.

Five Medicare files are included in the CMHSF, which cover:
1) inpatient hospital stays,
2) skilled nursing facility stays,
3) home health agency charges,

4) physicians' services, and
5) outpatient and other medical services.[7]

Because CMHSF provides no indication of initial diagnosis, Baker et al. assumed that disease onset occurred when a diagnosis of cancer was listed on a hospitalization record following a minimum of one year without a cancer diagnosis. This assumption is reasonable due to the high frequency of hospitalization associated with these diseases (i.e., individuals diagnosed with cancer would usually be hospitalized).[8]

Baker et al. assigned costs associated with each cancer to three post-diagnostic time periods:

- initial treatment, during the first three months following diagnosis;
- maintenance care, between initial and terminal treatment; and
- terminal treatment during the final six months prior to death.

Initial treatment includes all diagnostic work, and any treatments provided in the first three months after diagnosis. This treatment may include radiation therapy, surgery, antineoplastic drugs, etc. Terminal care includes care provided only in the last six months of life. The care may be palliative or aggressive in nature and covers the spectrum of all potential cancer treatments. Maintenance care is defined as that care provided between the initial care phase and terminal treatment (for nonsurvivors) or cessation of care (for survivors). Maintenance includes any care provided after the first three months, excluding terminal care. It may include surgery, continued aggressive treatment with radiation or chemotherapy, diagnostics to determine the patient's progress, or be limited to ongoing monitoring and preventive therapies in cases where the cancer has been minimized or eliminated.

II.1.H.2. Modifications to the Data

There are a number of limitations to using Medicare data; these were addressed by Baker et al. with a variety of strategies. As noted in Chapter I.1, the amount paid for service may differ from the actual medical costs because many insurers and federal programs either 1) pay only a portion of

[7] See Baker et al. (1989 and 1991) for further details.

[8] Although there are some exceptions to this generalization, such as non-melanoma type skin cancers, very few cancers exist for which hospitalization is not required. (Medical costs for non-melanoma skin cancers are provided in this handbook in Chapter II..6)

Link to Chapter II.6

total costs or 2) pay more than actual costs to underwrite the care providers' losses due to underpayment from other sources. Baker et al. used provider charges, rather than Medicare reimbursements (which represent only a portion of most total charges), thus providing a more accurate cost estimate.

Link to Chapter I-1

To improve the accuracy of the cost estimates, Baker et al. included the costs of coinsurance, deductibles, and other cost components. They made four adjustments to the cost estimates calculated from the CMHSF:

- First, charges were added for skilled nursing facilities (SNFs) not covered by Medicare by multiplying the "length of stay" at an SNF (computed from admission and discharge dates) by the average daily SNF charge.

- Second, the annual Medicare Part B deductible of $60 was added to the reimbursed charges in the database.

- Third, since Medicare pays only 80 percent of physicians' charges, Baker et al. scaled these reimbursements to 100 percent of physicians' charges to better reflect costs.

- Finally, they inflated all dollar values to 1984 dollars using the Medical Care component of the Consumer Price Index.

Costs that were not included are outpatient prescription medications and nursing home care below the skilled level. The Mor et al. (1990) analysis of the CMHSF data notes that including costs incurred only after the initial diagnosis omits costs associated with prediagnostic tests and treatment. Although these costs could be significant, substantial medical treatment (e.g., tests requiring hospitalization) would also likely result in a diagnosis and thus be included in Baker et al.'s estimates. This omission may lead to an underestimate of costs by Baker et al. It is not likely to be substantial when viewed in the context of the overall costs of treatment.

II.1.H.3. Total Non-incremental Costs of Treatment Phases

Costs were evaluated for initial care and for each year post-diagnosis (i.e., the patient may have been in any year post-diagnosis to be included in the analysis). Patients with an initial diagnosis of cancer prior to or during the 1974 to 1981 time period numbered 125,832. Thirteen types of cancer had sufficient Medicare beneficiaries (more than 1,000) to be analyzed.

Table II.1-3 lists the cancer types; the number of patients diagnosed; and the costs of initial, maintenance, and terminal phases of care in 1984

dollars. As Table II.1-3 shows, there is a relatively small variation in costs among the cancers. Initial care costs vary by approximately a factor of 2, continuing care by a factor of approximately 1.8, and terminal care by a factor of approximately 1.3.

Table II.1-3 Cancer Types, Number of Study Subjects and Treatment Phase Costs[a]

		Treatment Phase Costs in 1984 Dollars[b]		
Cancer Type (ICD9 Code)	# Patients	Initial	Maintenance (per year)	Terminal
Colorectal (153-154)	19,673	$14,190	$572	$15,776
Lung (162)	15,381	$12,916	$690	$15,565
Prostate (185)	14,002	$8,112	$560	$14,613
Breast (174)	12,486	$7,606	$483	$15,136
Bladder (188)	6,843	$8,470	$766	$18,577
Leukemia (204-208)	3,740	$9,068	$676	$19,777
Pancreas (157)	3,231	$14,009	$677	$14,790
Stomach (151)	3,228	$14,443	$660	$16,132
Uterine corpus (182)	3,042	$9,260	$424	$17,623
Kidney (189)	1,953	$12,608	$670	$19,302
Ovary (183)	1,605	$11,055	$647	$18,650
Uterine cervix (180)	1,448	$8,979	$493	$16,414
Melanoma (172)	1,105	$6,954	$488	$16,194
Mean Costs		$10,590	$600	$16,811

a. Based on Baker et al., 1989. These are non-incremental and not discounted.
b. See text for definitions of treatment phases.

II.1.H.4. Maintenance Phase Costs

One complicating factor in evaluating cancer costs using the Baker et al. data is determining a value for maintenance care. As Table II.1-3 shows, this value is reported as a yearly cost. The duration of maintenance care for each cancer is not provided by the authors. It should be noted that maintenance care refers to a time period rather than to the nature of the care, and may include diagnostic tests, surgery, care during relapses, etc., and any other care provided more than three months after diagnosis and more than six months prior to death due to the cancer (but not due to other causes). Consequently, costs of maintenance care can vary widely among patients. It may occur for only a few months or for decades, due to variations in human disease patterns, disabilities, etc.

A variety of strategies can be used to estimate an average maintenance period. The most precise would be to determine the average length of maintenance care for survivors and non-survivors of different ages, either from the literature or through a national survey of medical practitioners for each type of cancer. Literature has not been located with statistics on maintenance care durations, and a survey of practitioners would be time-consuming, expensive, and have considerable uncertainty. It would be necessary to ascertain both how long a patient would be expected to live (for both survivors and non-survivors) and how long they would receive care if they lived for an extended time period. Some patients would not live as long as the "recommended" period of maintenance care, due to either death from cancer or from some other cause (i.e., background mortality). The typical cancer costs estimated in this section are to be used primarily for rare cancers that lack data; consequently, the necessary information on mortality and care is not generally available.

Given the unknowns, some simplifying assumptions were made to estimate maintenance costs for purposes of this "typical cancer" analysis. Rather than evaluate maintenance care for each cancer separately, an average duration of care was selected and an average cost calculated. Two simplifying assumptions were used:

1) It was assumed that the average patient (survivors and nonsurvivors combined) receives five years of maintenance care post-diagnosis.

2) Terminal costs were assumed to be applicable to 50 percent of patients (a 50 percent mortality rate); survival actually varies widely by cancer type.

Many patients will survive beyond the five-year maintenance period assumed in this analysis and continue to incur cost due to diagnostic tests, drugs, etc.[9] Five years, however, is a reasonable estimate for follow-up when non-survivors are included. Most cancers have a relatively high mortality rate, as reflected in the 50 percent mortality rate used as an assumption in this analysis. As a result of the two assumptions listed above, the average maintenance cost for five years was added to the initial costs plus one half of the terminal costs to obtain an estimate of the total cost.

[9] For example, the average age of diagnosis for most cancers is about 70 years. At this age the average member of the general population has a life expectancy of 14 years. Patients may incur additional costs over the full course of their lifespan.

II.1.H.5. Incremental Costs of Treatment Phases

The costs shown in Table II.1.3 are *all* medical costs incurred by a patient with a cancer diagnosis. Consequently, the costs must be adjusted for background medical expenses to obtain the incremental costs of cancer treatment. Baker et al. (1991) provides an estimated background cost per year of $2,988 (in 1984 dollars). The costs of each treatment phase were adjusted for background costs, based on the duration of the treatment phase, and the assumptions regarding maintenance care and survival discussed above in sections II.1.H.3 and II.1.H.4. For example, the initial care, which covers a three-month period, has a background medical cost of $747 ($2,988 per year × 3/12 months). This background cost was subtracted from the total cost for initial care of $10,590, to obtain an incremental cost of $9,843.

Link to Sections II.1.H.3 and II.1.H.4

The costs have also been updated to 1996 using the Medical Care Component of the Consumer Price Index (1984:1996 = 2.14). The results are shown in Table II.1-4. The final value in the table, $82,581, is the undiscounted estimate of the lifetime incremental direct medical costs for a cancer case.

Depending on how this value is to be used, it may be possible to adjust the cost components to better reflect the cancer(s) of interest. For example, if it is known that there is a substantially higher mortality rate (50 percent was used here), then the terminal cost component could be adjusted accordingly. Any application should clearly state that this value was based on numerous assumptions and represents and average of many, but not all, cancers that occur in the U.S.

Table II.1-4 Incremental Undiscounted Direct Medical Costs for a Typical Cancer				
Treatment Phase	Total Medical Costs (1984$)	Incremental Medical Costs[a]	Incremental Medical Costs in 1996 Dollars[b]	Lifetime Incremental Costs[c]
Initial (3 months)	$10,590.00	$9,843.00	$21,064.02	$21,064.02
Maintenance	$600.46 (per month)	$351.46 (per month)	$752.12 (per month)	$45,127.46 (5 years)
Terminal (6 months)	$16,811.46	$15,317.46	$32,779.36	$16,389.68
Total Lifetime Costs in 1996 Dollars[d]				$82,581.16

a Adjusted for background medical costs of $2,988 per year (1984$), or $249 per month.
b Adjusted from 1984 to 1996 dollars using the medical care component of the Consumer Price Index (1984:1996=2.14).
c Five years of maintenance care were assumed and a mortality rate of 50 percent was assumed (i.e., the terminal care costs were multiplied by .5). See text for discussion.
d These costs can be updated to the current year using inflation factors accessible by clicking below.

Link to inflation factors

II.1.H.6. Application to Specific Cancers

II.I.H.6.1 Method

A more precise approach can be taken for specific cancers, if necessary, when sufficient statistics are available. The typical costs per treatment phase discussed above are used, with the maintenance phase and terminal care evaluated in more detail. The following components were used:

1) initial care — all patients receive initial care, so there are no modifications made to this phase's costs.

2) maintenance care — the length of the maintenance phase was estimated based on the survival probability of people of the average age of diagnosis. This duration of care was used to estimate costs for this phase.

Two specific cancers were evaluated, bone and liver cancer, in response to specific requirements of the Agency for an upcoming rule requiring benefits evaluations. The rule required only the direct medical costs for *survivors* of bone and liver cancer because the value of a statistical life (VSL) was to be used for nonsurvivors. The percentage of survivors and nonsurvivors for these cancer are discussed in Section II.I.H.6.4 below. Cost estimations were made using steps above. Two different approaches to estimating maintenance costs were used to illustrate alternative methods.

As noted above, the initial care costs shown in Table II.1-4 were used without modification for the costs of this phase. To determine the estimated cost for the maintenance period care for survivors, the length of the maintenance period was evaluated using two statistics:

1) the average ages at diagnosis for the two cancers were determined using the National Cancer Institute's SEER database, as described in Section II.1.G.2 above. The percent of all patients diagnosed in each age group was used to calculate the mean age at diagnosis (this is illustrated graphically in the stomach cancer chapter).

Link to Chapter II.2
Link to Chapter II.1.G.2

The average age at diagnosis for bone and liver cancer were determined to be 69 and 66 years, respectively.

2) The life expectancy of an average individual in the general population was determined for the two ages of diagnosis listed above from vital statistics data (accessed in 1998 from National Center for Health Statistics web site). They were determined to be 14.8 years (rounded to 15 years) for a 69-year-old bone cancer patient, and 16.7 years (rounded to 17 years) for a 66-year-old liver cancer patient. It was assumed that the life expectancy of survivors is the same as that of the general population. In reality, the treatments for cancer, including radiation, antineoplastic drugs, etc., have toxic effects that may shorten the lives of cancer patients. There are not sufficient data on these effects to quantitatively determine the impact.

II.I.H.6.2 Approach I.

The full term of care was assumed to be ten years. This duration is reasonable because nonsurvivors were not included, and the life expectancy at the average ages of diagnosis (66 and 69 years) is considerable (15 to 17 years). Additional care associated with cancer may not be required over the full remaining life of the individual. The first-year costs consisted of initial care costs ($21,064) and nine months of maintenance care ($753,12 × 9 = $6,769). (See Table II.1-4 for incremental costs for each phase of care.) The remaining nine years of maintenance care were added to initial costs to obtain the total estimated lifetime direct medical costs.

II.I.H.6.3 Approach II.

The maintenance phase was assumed to be equal to the life expectancy of the general population at the average age of diagnosis, minus three months of initial care. As in Approach I, the first year costs consisted of initial care costs and nine months of maintenance care. The remaining years of life (i.e., life expectancy at the average age at diagnosis minus the first year of

services) were multiplied by the annual maintenance care cost and added to initial costs to obtain the total estimated lifetime direct medical cost (i.e., 14 years for bone cancer and 16 years for liver cancer). This approach is reasonable because patients may require maintenance care over their remaining lifetime due to the drastic nature of most cancers, and the likely concurrent effects induced by surgery, radiation, and chemotherapy.

In the absence of accurate long-term treatment information for survivors, either approach may be used. They are both offered to provide a range of options for economists and to illustrate the impact of altering assumptions regarding care on medical cost estimates.

The results obtained using both approaches are shown in Table II.1-5 using discount rates of 0, 3, 5, and 7 percent. Bone cancer lifetime medical cost estimates for survivors range from $109,052 to $154,189 (undiscounted). Liver cancer lifetime medical cost for survivors range from $109,052 to $172,240 (undiscounted).

As the results indicate, maintenance care costs are a major portion of total medical costs for survivors. Differing assumptions regarding the duration of time over which these costs will occur lead to differences in overall lifetime cost estimates that are not trivial ($87,000 versus $151,000, undiscounted). These differences are relatively small, however, when contrasted with costs associated with the value of a statistical life (approximately $5,000,000). Although it is important to obtain medical cost estimates that are as precise as possible, in the case of fatal cancers (where the VSL is used for some patients) the differences between Approach I and Approach II do not substantially alter the final results of a benefits assessment.

As noted above, these costs are for survivors of the diseases only. It is relatively simple to calculate the costs for nonsurvivors if data are located on the timing of death. Terminal care costs are listed in Table II.1-4 and can be used, with the appropriate maintenance care costs, to estimate direct medical costs for nonsurvivors. Note that the maintenance costs estimated for survivors should not be used because they are likely to have a much longer duration of care than do nonsurvivors.

Table II.1-5 Estimated Incremental Direct Medical Costs for Bone and Liver Cancer Survivors[a] (1996 dollars)[b]											
Type of Cancer and Approach [a]	**Age at Diagnosis**	**Life Expect-ancy**	**Initial Care Costs**	**Maintenance Care Costs**				**Total Lifetime Costs**			
				Discount Rates: 0	3	5	7	Discount Rates: 0	3	5	7
Bone	69	15	$21,064								
Approach I				87,988	77,042	70,920	65,572	$109,052	98,106	91,988	86,636
Approach II				133,125	108,721	96,108	85,700	$154,189	129,785	117,172	106,764
Liver	66	17	21,064								
Approach I				87,988	77,042	70,920	65,572	$109,052	98,106	91,988	86,636
Approach II				151,176	120,138	104,584	92,029	$172,240	141,202	125,648	113,093

a. See text for discussion of approaches.
b. These costs can be updated to the current year using inflation factors accessible by clicking below.

Link to inflation factors

II.1.H.6.4 Liver and Bone Cancer Survival Estimates

Because the VSL is sometimes used for nonsurvivors of bone and liver cancer, it is important to estimate the survival and mortality rates for these cancer patients. This was done using the RSR data from NCI as discussed in Section II.1.G.2 and presented in detail in Chapter II.2. Because the cost estimates for these two cancers are not precise (the costs for a "typical" cancer case were used, as described above), it was determined that the RSRs provided a reasonable approximation of the survival rate.

Link to Section II.1.G.2 and Chapter II.2

Ideally, one would determine the lifetime mortality impacts of these cancers on patients, which would require a lifetime follow-up. These data are not available. NCI provides a twenty-one year database (1973-1993) of the survival experience of liver cancer patients. That database was used in this analysis and provides a lower-bound estimate of mortality impacts. (It may slightly underestimate mortality because increased deaths may occur beyond the twenty-first year post-diagnosis. This increase, however, is not likely to be substantial.)

Bone cancer, which is rarer and less well studied, is included in the NCI grouping "bone and joint cancers." Consequently, the survival estimates are less precise for bone cancer. In addition, the RSR was available only for five years post-diagnosis for this group of cancers. The actual mortality rate is very likely to be greater than that observed at five years because mortality is typically elevated for more than five years post-diagnosis. Mortality will therefore be underestimated. Unfortunately, the dynamics of survival and relapse differ considerably among cancers, so it is not possible to estimate the longer-term survival for bone cancer based on mortality patterns for other cancers.

The NCI RSR data indicate that the survival rate for liver cancer is approximately 2.6 percent, indicating a 97.4 percent mortality rate (after 21 years). The bone and joint cancer survival rate is estimated to be 64.3 percent, indicating a 35.7 percent mortality rate (after five years).

II.1.H.7 Conclusions Regarding Typical Cancer Cost Estimates

There is clearly uncertainty when a "typical" cancer approach is used. As Table II.1-3 shows, however, there are relatively small differences among the medical costs of various cancers when contrasted with the uncertainty in risk estimations, changes in medical care and survival, and uncertainty associated with other parameters in a benefits assessment. The value in Table II.1-4 and approaches described above provide a means to obtain an estimate of cancer medical costs that may be useful in a benefits evaluation when limited data are available to support a full and detailed analysis of medical costs.

II.1.I Issues and Uncertainty in Cancer Medical Cost Estimation

Chapter I.1 contains a detailed discussion of numerous sources of uncertainty in medical cost estimation. Most issues related to estimating medical costs of specific types of cancer are discussed in the individual chapters, which also contain a detailed presentation of the methodologies used to estimate costs. Some issues are common to all cancers and are briefly discussed in this section. This section also contains the estimated lifetime medical costs for a "typical" cancer case. In addition, there are some uncertainties and issues that are particularly problematic for cancer cost estimation. These issues, discussed below, include new treatments that are developed (with attendant changes in cost) and concurrent effects associated with either the occurrence of the cancer or medical treatments for cancer.

Link to I.1.F: Limitations

II.1.I.1 New Treatments

The costs of new treatments are of particular concern in cancer therapy, because they may be very expensive, and because what is considered experimental at one time may soon become the treatment norm. For example, advances have been made very rapidly during the 1990s in the treatment of advanced stages of breast cancer. In the past, the prognosis was poor for advanced stages and the treatments limited. Consequently, economic valuations might include a value of life estimate rather than a medical cost estimate as the predominating cost factor. In recent years, however, more expensive and effective treatments, such as bone marrow transplants and new pharmaceuticals, have shifted the balance for this disease somewhat toward improved survival with a corresponding increase in medical costs. As a result of this dynamic, it is appropriate for an economic evaluation to include a review of recent literature to determine whether new treatment approaches with substantially different costs are being employed for a specific disease.

II.1.I.2 Concurrent Effects

As noted in Section II.1.B. above, concurrent effects are of particular concern for certain types of illnesses, including cancer and developmental effects (discussed in the next section). Cancer has a unique ability to metasticize, leading to multiple types of cancer in an individual. Cancer may also interfere with the functioning of various organs in the body, requiring medical attention above and beyond the cancer-limiting treatments. Finally, the treatments themselves, which often include ionizing radiation and highly toxic chemotherapeutics, may cause serious illnesses, including cancers at other sites in the body, impairment of the immune system, disabilities, and damage to the nervous system or other organs.

When data are not available on concurrent effects, and the chapter indicates that they are likely to occur (as is the case for all cancers), the medical cost estimates provided will underestimate total medical costs. This discrepancy should be noted when the costs are used.

All of these concurrent effects may occur during or significantly after the cancer occurrence. It is beyond the scope of this handbook to include a discussion of the multiple associated diseases that can arise from a specific cancer. This information may be important, however, to a comprehensive economic analysis. Where data are available regarding concurrent effects, they are described briefly in the cancer chapters. In addition, readers are urged to consult with the medical and toxicological sources providing the basic health risk information, in order to obtain additional data on likely concurrent effects arising from the diseases or their treatment.

Some cancer cost evaluations, such as those based on Baker et al. (i.e., lung, breast, liver, kidney, bladder, colorectal, and the "typical" cancer costs estimated in this chapter in the previous section) include all estimates of the incremental medical costs associated with a cancer diagnosis. These values are calculated by summing all medical costs and subtracting the background costs to obtain incremental costs. Using this approach, costs are included that may be cancer-related, but not specifically designed to address cancer. For example, immune-suppressed patients who are receiving radiation therapy may have greater costs associated with infectious diseases. The additional required services are due to cancer, but are not specifically designed to mitigate the cancer. Including these costs provides a more comprehensive and realistic estimate of the total medical cost of the disease.

CHAPTER II.2. COST OF STOMACH CANCER

Clicking on the sections below will take you to the relevant text.

CHAPTER II.2. COST OF STOMACH CANCER

II.2.A. Background

This chapter contains a discussion of the methods used to estimate the direct medical costs incurred by stomach cancer patients, and the results of the analysis for these two cost elements. It does not include information on elements such as indirect medical costs, pain and suffering, lost time of patients and unpaid caregivers, etc.[1] The reader is referred to Chapter I.1 for a discussion of the general methods and cost elements that are relevant to all benefits estimates and for a discussion of the limitations of estimating medical costs. In addition, Chapter II.1 contains information regarding the special characteristics of cost estimates for cancer.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and II.1
Link to inflation factors

II.2.A.1 Description

Stomach cancer, also called gastric cancer, refers in most cases to adenocarcinoma, which comprises 90 to 95 percent of all gastric malignancies. Other types of stomach cancer include lymphoma, leiomyosarcoma, carcinoid, adenocanthoma, and squamous cell carcinoma. Stomach cancer can occur in various anatomical sections of the stomach and may be limited to the mucosa of the stomach or include large portions of the stomach and other organs. In addition to these distinctions, there are two common classification systems, Lauren and Borrmanns, which provide additional definition to the description of stomach cancers (Gunderson et al., 1995). This Chapter will consider stomach cancer to cover all of the above types, in keeping with the recent oncology texts and the majority of information reviewed for this analysis.

There are approximately 24,000 cases of stomach cancer diagnosed per year in the United States. Stomach cancer is fatal in over 80 percent of all cases. It occurs with declining frequency in the United States. The

[1] Some of these cost elements, especially pain and suffering may comprise a very large portion of the cost of cancer. However, it was not feasible to estimate this cost component for this chapter.

incidence in 1994 was 7.2 cases per 100,000 total population, down from 28.8 in 1973 (incidence represents newly diagnosed cases in a year).

Stomach cancer occurs with much greater frequency among the elderly, which is typical of most cancers. The average age at diagnosis is approximately 70 years. Only one percent of stomach cancers are diagnosed before the age of 35, and the 5th percentile of age at diagnosis is approximately 45 years. The 95th percentile is over 84 years of age (NCI, 1998). The age corresponding to the 95th percentile cannot be determined precisely because the National Cancer Institute (NCI) aggregates all occurrences over the age of 85, and 12 percent of stomach cancers are diagnosed among people age 85 or greater.

The distribution of the age at diagnosis (onset) of stomach cancer is shown in Figure II.2-1. The steep incline in the probability of stomach cancer diagnosis is clear in this diagram, with a peak around 70 years of age. The data used to generate this figure, as well as the cumulative percents of stomach cancer in each five-year increment of life are shown in Table II.2-1. The age-specific incidence data were used in Section B medical cost calculations. Data on incidence and age at diagnosis were obtained from NCI's Surveillance, Epidemiology, and End Results (SEER) reports and tables. These were obtained on line through the NCI web site at: http://www-seer.ims.nci.nih.gov in January, 1998.

II.2.A.2. Concurrent Effects

As with all cancers, stomach cancer may spread to other organs. In approximately 30 percent of patients, stomach cancer has spread to the liver at the initial diagnosis (Gunderson et al., 1995). No data were located indicating that concurrent effects unrelated to stomach cancer or its treatment were likely to occur with this disease. As noted in Chapter II.1, secondary cancers and other adverse health effects may occur due to treatment and therapy. These can induce added medical costs not considered in this chapter.

Link to II.1.B

Figure II.2-1. Age-specific Incidence of Stomach Cancer
Based on NCI, 1998

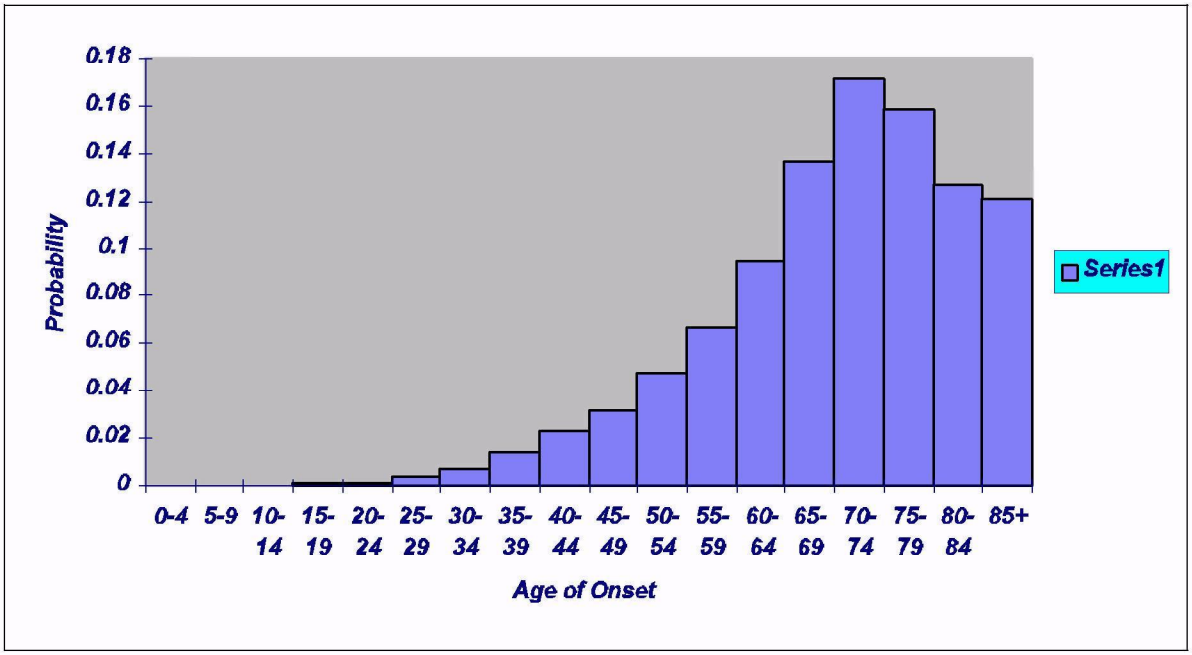

Table II.2-1. Age-specific Incidence of Stomach Cancer			
Age Group	Age-specific Rate of Diagnosis Per 100,000	Percent of All Stomach Cancer Occurring in Age Group	Cumulative Percent of Stomach Cancer
0 - 14	0	0	0
15 - 34	0.3	1	1
35 - 39	1.5	1	2
40 - 44	2.7	2	4
45 - 49	4.4	3	7
50 - 54	8.3	5	12
55 - 59	14.1	7	19
60 - 64	21.7	9	28
65 - 69	31.8	14	42
70 - 74	45.6	17	59
75 - 79	55.9	16	75
80 - 84	67.5	13	88
85+	79.4	12	100
Based on NCI, 1998			

II.2.A.3. Causality and Special Susceptibilities

Some environmental pollutants are associated with stomach cancer. Radon is of particular concern because it has been associated with stomach cancer in numerous studies of occupationally-exposed workers (summary provided in BEIR VI, 1998). Occupational studies also indicate possible relationships between stomach cancer and coal mining and rubber and asbestos manufacturing (Gunderson, et al., 1995).

Table II.1-1 in Chapter II.1 contains a list of chemicals known or suspected of causing cancer (as reported in the EPA databases IRIS, HEAST, and HSDB). Most chemicals in the table were carcinogenic in animal studies. These studies do not provide organ-specific data because it is not generally assumed that cancer induction will always occur at the same site in humans as in animals. Consequently, the chemicals listed in Table II-1 may cause stomach cancer and/or other types of cancer. Evaluation of the likelihood of this occurrence would require additional research (risk assessment).

Link to Table II.1-1

Stomach cancer has been associated with dietary factors in some populations. It occurs at a much higher rate in Japan and some other countries than in the U.S. This difference is thought to be due to dietary differences. Studies in the U.S. have shown that people with pernicious anemia and some types of ulcers and polyps are at greater risk (Gunderson et al., 1995). Very recent reports (1998) indicate an association between the bacteria responsible for ulcers and stomach cancer, probably with ulcers as an intermediate condition. This association is plausible based on current knowledge of cellular proliferation and its role in cancer induction.

NCI provides age-, sex-, and race-specific data regarding diagnosis of stomach cancer for the diagnosis years 1990 to 1994. Some statistics from this data compilation illustrate the higher rates of stomach cancer among males and African-Americans. The rate among males has been consistently higher than in females over the years (10.8 versus 4.4 per 100,000 respectively in 1994). It is also consistently higher among African-Americans than among whites (12.0 versus 6.1 per 100,000 respectively in 1994) (NCI, 1998), and is particularly high among African-American males (NCI, 1998).[2] For example, in the oldest age group of 85 years and up the general population rate was 79.4 per 100,000, whereas among African-American males it was 225.2 per 100,000.

The disproportionate occurrence of stomach cancer in males and African-Americans may be an important consideration when environmental equity

[2] The National Cancer Institute (NCI) data presented in this chapter are based on invasive cancer, which comprises greater than 99 percent of stomach cancers (NCI, 1998).

issues are evaluated. As noted above, the cause of the increased rate of stomach cancer among men and African-Americans is not known. It may be due to dietary, environmental, genetic, or other factors. In the absence of causal data, it is reasonable to assume that the cause could be genetic and that the increase in risk would be reflected in higher than average medical costs and lives lost among males and African-Americans exposed to a pollutant that causes stomach cancer. Issues related to susceptible subgroups in benefits assessments are discussed in the Chapter I.1 section titled "Susceptible Subgroups."

Link to Chapter I.1

The number of stomach cancer patients in the U.S. is relatively small and the NCI cohort was also relatively small. Consequently the rates in the younger age ranges (where the numbers are exceedingly small) are somewhat erratic due to the high variability of estimates based on small sample sizes. However, the data show a clear progression of increased incidence over the ages and a consistent pattern of higher risk among African-Americans than whites and males than females.

Section II.2.D.2 presents the results of a sensitivity analysis for stomach cancer among African-American males. The analysis uses the higher incidence rates observed among African-American males to estimate the medical costs for this subgroup. The analysis raises complicated issues in evaluating high-risk subgroups. In addition, this analysis evaluates costs per stomach cancer patient and so does not reflect the additional costs to society of the likely higher risks that would be incurred in an African-American versus non-African-American population. These issues must be dealt with by risk assessors in calculating the number of cases. It may also be important to evaluate the disproportionate impact of environmental stomach cancer risk factors on this population subgroup and the benefits that would result for them from reducing pollution exposures.

II.2.A.4 Treatment and Services

Initial diagnosis may include gastrointestinal (GI) imaging, blood tests, endoscopy, biopsy, computed tomography (CT) scans and laparoscopy. Treatment includes surgery, chemotherapy, irradiation, and other general medical services. Terminal care is eventually provided to most stomach cancer patients due to the high mortality rate for this cancer. This care may include a variety of services, including palliative surgery, drug therapy, home visits, psychological counseling, and other medical care (Gunderson et al., 1995).

II.2.A.5 Prognosis

II.2.A.5.1 Background

The overall prognosis for stomach cancer patients is poor, with approximately 80 to 85 percent of patients dying of the disease within ten years. Most deaths (over 90 percent) occur in the first four years, and approximately half of all patients die during the first year (NCI, 1998). Factors such as tumor size and location, histology, involvement of nodes, and the spread of cancer to other tissues affect outcome. Numerous new biochemical and immunological tests are used to provide additional information on the likely outcome. The importance of early detection and a confined tumor is evidenced by the greater than 90 percent survival rate among patients with a tumor confined to the mucosa or submucosa (Gunderson, 1995). However, few patients in the U.S. are diagnosed with stomach cancer at this early stage.

II.2.A.5.2 Relative Survival Rates (RSRs)

The NCI SEER data reports were accessed online to obtain information regarding mortality and survival probabilities and the duration after diagnosis until death (NCI, 1998). [3] These data are presented in this section because they relate to prognosis. Methods used to convert the NCI statistics to survival probabilities for stomach cancer patients, used in Section B to calculate medical costs, are discussed below.

The RSR is the number of observed survivors among patients, divided by the number of "expected" survivors among persons with the same age and gender in the general population (observed/expected). The RSR takes into account that there are competing causes of death that increase with age. The RSR for stomach cancer patients during the first year post-diagnosis is 46 percent. This value indicates that a person with stomach cancer would have, on average, a one-year survival probability that is 46 percent of someone of the same age and gender in the general population.

The RSRs provided by NCI for each year post-diagnosis are averages over all ages at diagnosis. RSRs are also provided for different ages at diagnosis, with five-year RSRs ranging from 19.0 to 21.8 percent (based on 1986-1993 data, NCI, 1998). (Five-year RSRs are the only form in which NCI provides RSRs that are specific to age at diagnosis.) Because RSRs are very similar across the ages at diagnosis for stomach cancer, relative survival rates are discussed without reference to the age at diagnosis.

An evaluation of the RSRs over the past 20 years indicates that they have increased overall through 1988, when they stabilized at approximately the same level through 1993 (the most recent year for which there are data).

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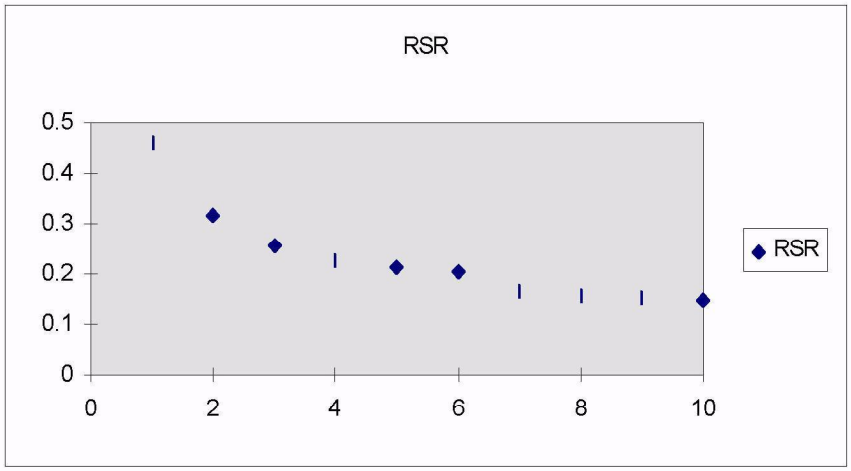
[33] The Website is http://www-seer.ims.mci.hin.gov

Based on this observation, the rates for 1988 through 1993 for the first through fifth years post-diagnosis were used in this analysis. It was necessary to use pre-1988 data to estimate survival beyond the fifth year. These longer-term survival data are from a period when RSRs were slightly lower. A very low rate of loss from stomach cancer exists after the first four years (generally less than two percent for the fifth and sixth years post-diagnosis, and less than one percent thereafter), so differences in survival in recent years will not have a substantial impact on costs. Ten years of data were used to estimate survival for the sixth through tenth years post-diagnosis to increase reliability because the number of stomach cancer deaths is very small during that period post-diagnosis.

II.2.A.5.3 Derivation of Survival and Mortality: Probabilities for Stomach Cancer Patients

The RSRs reported by NCI for each year post-diagnosis are based on a cohort followed over time. They are therefore *estimates* of the underlying population RSRs (i.e., the RSRs for the entire population of stomach cancer patients in the United States). A plot of the average RSRs for n years post-diagnosis (n = 1, 2, ..., 10) described above (Figure II.2-2) shows that the estimated RSRs follow a general exponential decay trend.

Figure II.2-2. Average Relative Survival Rates (RSR) for n Years Post-Diagnosis



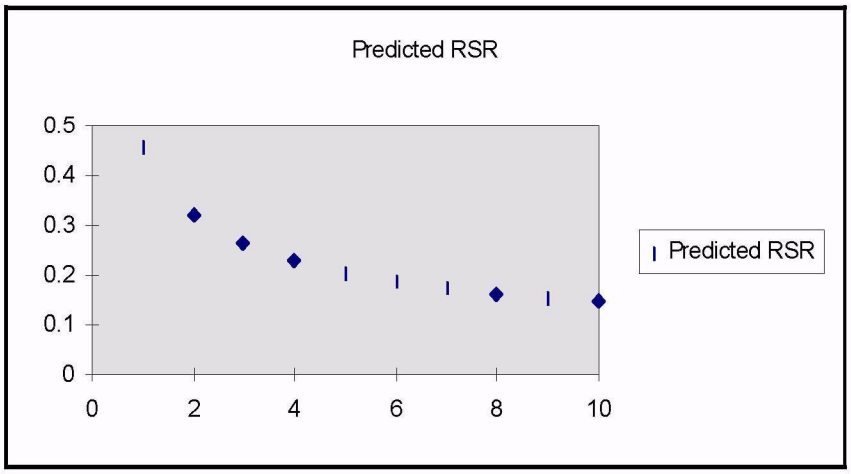
Rather than use these average estimated RSRs from NCI, which display some of the "bumpiness" that data often contain, the trend described by these RSRs was estimated by regression. The model that fit the data best was of the form:

$$\ln(RSR) = a + b \times \ln(Years\ Post\text{-}Diagnosis) \quad .$$

The intercept (a) was estimated to be -0.78613 and the slope (b) was estimated to be -0.49508. The fit was excellent, with an R^2 of 0.985. Exponentiating the predicted natural logarithms of RSR yielded the predicted RSRs shown in Table II.2-2. A plot of the adjusted RSRs against years post-diagnosis (Figure II.2-3) shows the generally smooth trend.

Table II.2-2. Average RSRs* and Predicted (Adjusted) RSRs		
Years Post-Diagnosis (n)	Average RSR for n Years Post-Diagnosis	Adjusted (Predicted) RSR for n Years Post-Diagnosis
1	0.46	0.456
2	0.32	0.323
3	0.26	0.264
4	0.23	0.229
5	0.22	0.205
6	0.21	0.188
7	0.16	0.174
8	0.16	0.163
9	0.15	0.154
10	0.15	0.146
*The average RSR for n years post-diagnosis is the average of a set of RSRs reported by NCI (1998) for n years post-diagnosis as described in the text above.		

Figure II.2-3. Adjusted Relative Survival Rates (RSR) for n Years Post-Diagnosis



The adjusted RSRs shown in Table II.2-2 were used to derive survival probabilities for stomach cancer patients for each of the first ten years post-diagnosis. The RSR, which expresses the survival of patients in relation to the survival of the general population, can be converted to a survival probability for stomach cancer patients by using the population survival rate in the RSR equation:

$$RSR = \frac{observed\ survival\ rate\ among\ stomach\ cancer\ patients}{survival\ rate\ among\ age-\ and\ sex-matched\ cohort\ in\ the\ general\ population}$$

The RSR is designed to enable the analyst to derive the probability of dying specifically of the cancer of interest; this probability, however, is conditional on having not already died of something else. Using the definition of the RSR, it can be shown that 1 – RSR is the number in the cohort who were expected to survive but died (and are therefore presumed to have died of stomach cancer), divided by the number who were expected to survive. This value effectively takes the original cohort of stomach cancer patients and first subtracts those who die of other causes, then calculates the proportion of the remaining subset who die of stomach cancer specifically. This result is slightly different than the probability of dying of stomach cancer, given that one is diagnosed with it. This latter probability has the same numerator, but has as its denominator the entire original cohort of stomach cancer patients.

To obtain an estimate of the survival rate for stomach cancer patients to one-year post-diagnosis, the RSR for one-year post-diagnosis and the background survival rate for one year were used in the above equation. The survival rate for the general population at the average age at diagnosis (70 years) during their 70th year (from age 70 to 71) is 0.97326. The survival rate for stomach cancer patients to one-year post-diagnosis can be calculated using this value and the RSR of 46.15 for the first year post-diagnosis reported by NCI (1998) as follows:

$$46.15 = \frac{X}{0.97326}$$

$$(RSR) \quad (background\ rate)$$

$$X = 44.91\ (45\ percent)$$

This equation converts the RSR to a survival probability for stomach cancer patients. It tells us that among all persons diagnosed with stomach cancer, approximately 45 percent will survive the first year and 55 percent will die.

Although most stomach cancer patients die of the disease, some die of other causes. The probability of a stomach cancer patient dying of other causes is not the same as the probability of someone in the general population dying of other causes, particularly in the first few years post-diagnosis, when a stomach cancer patient's probability of dying of stomach cancer is quite high.[4] The probability of a stomach cancer patient dying of

[4] This becomes clear in the extreme case in which the probability of dying of an illness is extremely high. Suppose, for example, that the probability of dying of all causes except for illness X is 0.025 in the general population. Suppose that in a cohort of patients diagnosed with illness X the probability of dying

stomach cancer and the probability of a stomach cancer patient dying of some cause other than stomach cancer in the *n*th year post-diagnosis, given survival to the *n*th year, were each derived from two known probabilities:

1) the probability of a stomach cancer patient surviving through the *n*th year post-diagnosis, given survival to the *n*th year, and

(2) the probability of dying of causes other than stomach cancer in a matched cohort in the general population.

The derivation is explained in detail in Appendix II.2-A at the end of this chapter.

Link to Appendix II.2-A

Each of the known probabilities depends on the number of years post-diagnosis and (minimally) on age at diagnosis. Consequently, separate probabilities were calculated for each year post-diagnosis and for each age at diagnosis considered in the analysis. They are shown for years one through ten post-diagnosis for someone diagnosed with stomach cancer at age 70 (the average age at diagnosis for stomach cancer) in Table II.2-3.

Using the probabilities in Table II.2-3, a hypothetical cohort of 100,000 stomach cancer patients diagnosed at age 70 was followed for ten years after diagnosis. For each year post-diagnosis, the analysis calculated the number of stomach cancer patients who:

1) survive through the year,
2) die of stomach cancer during the year, and
3) die of some other cause during the year.

---

from illness X in the first year post-diagnosis is 0.99. If the probability of dying of other causes in this cohort were the same as in the general population (0.025), then their probability of dying would be greater than 1.0.

Table II.2-3. Probabilities of Survival and Mortality for a Stomach Cancer Patient Diagnosed at Age 70

	A Matched Cohort in the General Population		A Cohort of 100,000 Stomach Cancer Patients					
Years post-diagnosis (n)	Probability of surviving n years	Probability of dying in *n*th year of causes other than stomach cancer, given survival to the *n*th year[a]	(Adjusted) Relative Survival Rate[b]	Probability of surviving n years post-diagnosis ((2)*(4))	Number surviving through the *n*th year (100,000*(5))	Probability of surviving through the *n*th year, given survival to the *n*th year ($(6)_n/(6)_{n-1}$)	Probability of dying of stomach cancer in the *n*th year, given survival to the *n*th year[b]	Probability of dying of other causes in the *n*th year, given survival to the *n*th year[c]
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0	1.000	---	---	---	100,000	---	---	---
1	0.973	0.026	0.456	0.4434	44,342	0.4434	0.5373	0.0193
2	0.945	0.029	0.323	0.3055	30,551	0.6890	0.2865	0.0245
3	0.915	0.031	0.264	0.2421	24,210	0.7925	0.1793	0.0283
4	0.884	0.034	0.229	0.2028	20,282	0.8378	0.1307	0.0315
5	0.852	0.037	0.205	0.1749	17,490	0.8624	0.1029	0.0347
6	0.817	0.040	0.188	0.1534	15,340	0.8771	0.0849	0.0380
7	0.782	0.043	0.174	0.1359	13,594	0.8862	0.0722	0.0416
8	0.745	0.047	0.163	0.1212	12,122	0.8917	0.0628	0.0455
9	0.707	0.051	0.154	0.1085	10,846	0.8948	0.0555	0.0497
10	0.667	0.056	0.146	0.0972	9,717	0.8959	0.0497	0.0544

[a]The probabilities in the general population of dying from stomach cancer are 0.000256 in the 70-74 year age group, and 0.000348 in the 75-79 year age group. The probabilities in column (3) were derived by subtracting these probabilities from the corresponding probabilities of dying from any cause in the *n*th year given survival to the *n*th year.

[b] From Table II.2-2.

[C] See Appendix to this chapter for derivation of these probabilities.

From these numbers, the probabilities of:

1) surviving through the *n*th year,
2) dying of stomach cancer during the *n*th year, and
3) dying of other causes during the *n*th year

were derived. The probability of dying of stomach cancer in the *n*th year post-diagnosis, for example, is calculated as the number of stomach cancer patients who die of stomach cancer in the *n*th year post-diagnosis divided by the original number in the cohort (100,000). The analysis is shown in Table II.2-4. The probabilities of a stomach cancer patient (age 70 at diagnosis) surviving through each year post-diagnosis, dying of stomach cancer during each year, and dying of other causes during each year are given in columns (7), (8) , and (9), respectively, of Table II.2-4. The probabilities in columns (7), (8), and (9) of Table II.2-4 are used in Section II.2.B to calculate the expected medical costs of stomach cancer patients diagnosed at age 70.

Table II.2-4. Following a Cohort of 100,000 Stomach Cancer Patients (Diagnosed at Age 70) Over Ten Years: Derivation of Probabilities of Survival and Mortality

						Probabilities		
Years Post-Diagnosis (n)	Probability of Surviving n years post-diagnosis (column (5) of Table II.2-3)	Number Surviving through *n*th year (100,000*(2))	Number Dying in *n*th year $((3)_{n-1} - (3)_n)$	Number dying of stomach cancer in the *n*th year $((3)_{n-1}*(8)_n$ of Table II.2-3)	Number dying of other causes in the *n*th year $((3)_{n-1}*(9)_n$ of Table II.2-3)	Probability of surviving through the *n*th year $((2)_n)$	Probability of dying of stomach cancer in the *n*th year ((5)/100,000)	Probability of dying of other causes in the *n*th year ((6)/100,000)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0	---	100,000	---	---	---	---		
1	0.4434	44,342	55,658	53,730	1,928	0.4434	0.5373	0.0193
2	0.3055	30,551	13,792	12,704	1,088	0.3055	0.1270	0.0109
3	0.2421	24,210	6,341	5,476	864	0.2421	0.0548	0.0086
4	0.2028	20,282	3,928	3,165	763	0.2028	0.0317	0.0076
5	0.1749	17,490	2,792	2,087	705	0.1749	0.0209	0.0071
6	0.1534	15,340	2,150	1,485	665	0.1534	0.0149	0.0067
7	0.1359	13,594	1,746	1,108	638	0.1359	0.0111	0.0064
8	0.1212	12,122	1,472	854	618	0.1212	0.0085	0.0062
9	0.1085	10,846	1,276	673	602	0.1085	0.0067	0.0060
10	0.0972	9,717	1,129	540	590	0.0972	0.0054	0.0059

II.2.B Costs of Medical Treatment and Services for Stomach Cancer Patients

II.2.B.1 Methodology

II.2.B.1.1 Overview

Treatment of stomach cancer may occur over a brief or extended period of time, and costs may be limited or substantial. There is no typical case because of individual differences in the stage of cancer at diagnosis, multiple treatment options, patient health and age, and other factors; however, average costs can be calculated. Stomach cancer has a relatively high mortality rate, as discussed in Section A. Approximately 82 percent of people with stomach cancer eventually die of the disease. As discussed in Chapter I.1 of this handbook, the medical costs of those who die of the disease are usually very different than for those who survive. Therefore, although the focus of this chapter is on the costs incurred by the average stomach cancer patient, survivors and nonsurvivors of stomach cancer are considered as separate groups for purposes of this analysis.

Link to I.1.D.2

A data search was conducted for information regarding medical costs associated with stomach cancer. In addition to a literature search, most federal agencies dealing with cancer and medical costs were contacted for information and the various federal databases were discussed with senior staff at these agencies. Very recent cost data were not located. However, current (1994) cancer data were obtained regarding incidence and survival, which were used in the cost calculations described below. The cost estimates presented in this are based primarily on the work of Baker et al. (1989) and on two sources of statistical data: the National Cancer Institute (1998) and Vital Statistics of the United States, 1993 (NCHS, 1997). These data were evaluated and used to calculate appropriate estimates of the direct medical costs due to stomach cancer.

II.2.B.1.2 Medical Cost Data

II.2.B.1.2.1 Sources

Medical cost data would ideally be obtained on current medical expenditures for a specific illness. Although data files are maintained by public and private sector sources, they are not readily available. In addition, to obtain reliable cost estimates it is necessary to evaluate very large databases of charges from a variety of sources, a method impractical for the development of this chapter. A review of the medical economics literature in 1997 did not identify very recent sources of cost estimates for stomach cancer. Baker et al. (1989) was previously used for other chapters of this handbook and has been used as the basis for the cost estimates in this chapter. Based on the 1997 review of the literature

carried out for the development of this chapter, there do not appear to be new treatment methods for stomach cancer that substantially alter either the medical costs or the survival rates. Consequently, the cost estimates presented in this chapter may be considered appropriate under most circumstances (e.g., regional costs may vary).

II.2.B.1.2.2 Baker et al.'s Cost Estimation Method

Baker et al. (1989) used the Continuous Medicare History Sample File (CMHSF) to estimate the per-patient average lifetime medical cost of treating stomach cancer based on data files from 1974 to 1981. They chose CMHSF because:

1) it is a nationally representative sample of the Medicare population (five percent), covering over 1.6 million patients;
2) it is longitudinal, dating from 1974 to 1981; and
3) it captures the majority of medical expenses for each beneficiary.

Five Medicare files are included in the CMHSF, which cover:

1) inpatient hospital stays,
2) skilled nursing facility stays,
3) home health agency charges,
4) physicians' services, and
5) outpatient and other medical services.[5]

Costs that were not included are outpatient prescription medications and nursing home care below the skilled level.

Because CMHSF provides no indication of initial diagnosis, Baker et al. assumed that disease onset occurred when a diagnosis of stomach cancer was listed on a hospitalization record following a minimum of one year without a stomach cancer diagnosis. This assumption is reasonable due to the high frequency of hospitalization associated with the disease (i.e. individuals diagnosed with stomach cancer would be hospitalized). Only patients with an initial diagnosis during the years covered by the database (1974-1981) were included.

Costs associated with stomach cancer were assigned to three post-diagnostic time periods:

- initial treatment, during the first three months following diagnosis;
- maintenance care, between initial and terminal treatment; and
- terminal treatment during the final six months prior to death.

[5] See Baker et al. (1989 and 1991) for further details. Baker et al. (1991) contains additional descriptive data regarding the database and methods used for the cost analysis; however, it does not contain cost data for stomach cancer.

As noted in Chapter I.1, the amount paid for service may differ from the actual medical costs because many insurers and federal programs either 1) pay only a portion of total costs or 2) pay more than actual costs to underwrite the care providers' losses due to underpayment from other sources. Baker et al. used provider charges, rather than Medicare reimbursements (which represent only a portion of most total charges), thus providing a more accurate cost estimate.

Link to Chapter I.1

To improve the accuracy of the cost estimates, Baker et al. included cost data on coinsurance, deductibles, and other cost components. They made four adjustments to the cost estimates calculated from the CMHSF. First, charges were added for skilled nursing facilities (SNFs) not covered by Medicare by multiplying the "length of stay" at an SNF (computed from admission and discharge dates) by the average daily SNF charge. Second, the annual Medicare Part B deductible of $60 was added to the reimbursed charges in the database. Third, since Medicare pays only 80 percent of physicians' charges, Baker et al. scaled these reimbursements to 100 percent of physicians' charges to better reflect social costs. Finally, they inflated all dollar values to 1984 dollars using the Medical Care component of the Consumer Price Index.

II.2.B.1.2.3 Cost Estimates by Treatment Period

Medical costs associated with the initial, maintenance, and terminal cancer care treatment periods were itemized in Baker et al., 1989 and are shown in Table II.2-5. To estimate the incremental costs, a co-morbidity cost of $2,988 per year from Baker et al. (1991) was used in this analysis. To account for costs of other medical services anticipated to occur while the patient was receiving cancer treatment (i.e., co-morbidity/background costs), the co-morbidity cost was pro-rated for this analysis using the specified durations for the initial (three-month) and terminal (six-month) treatment periods. These costs are listed in Table II.2-5 with the incremental costs calculated for the three treatment periods. Total costs are reported for the initial and terminal care periods. Annual costs for the maintenance period are shown and are further discussed in the "Lifetime Costs" section below. Using the Medical Care component of the Consumer Price Index (CPI-U), all costs are inflated to 1996 dollars (1984:1996 = 2.14).

Table II.2-5. Average Per Patient Costs for the Three Periods of Treatment for Stomach Cancer in 1996 dollars			
Treatment Period	**Cost[a]**	**Co-morbidity Charge[b]**	**Incremental Cancer Treatment Cost**
Initial (3 months)	$30,908	$1,599	$29,309
Maintenance (per year)	$16,949	$6,394	$10,554
Terminal (6 months)	$34,522	$3,197	$31,325

a. From Baker et al. (1989 and 1991) adjusted using the Medical Care component of the Consumer Price Index (CPI-U) 1984:1996 = 2.14.
b. Annual co-morbidity charges are $6,394 and were pro-rated for the duration of the treatment period.

II.2.B.1.3 Calculation of Lifetime Cost Estimates for Stomach Cancer Patients

Although Baker et al. provide useful cost estimates for the three treatment periods, they do not provide information on two critical aspects of medical costs:

1) costs for survivors versus nonsurvivors of stomach cancer. These may differ substantially. For example, survivors would not have terminal care costs and may receive maintenance services for an extended time period.

2) estimates of the duration of the maintenance periods.

Data regarding age at diagnosis of stomach cancer were obtained from NCI (1998). Survival and mortality probabilities for each year post-diagnosis were derived from relative survival rates obtained from NCI (1998), as discussed in Section II.2.A.5.3. This information was used to address many time-related medical cost issues. For some aspects of the analysis, however, detailed information was not available, and average values have been used as a reasonable approximation (e.g., a ten-year maintenance period was assumed for survivors of stomach cancer). When average values or other assumptions are used in this analysis, they are so noted.

Link to Section II.2.A.5.3

As previously noted, there are not substantial differences in survival related to age at diagnosis, and NCI does not provide age-specific relative survival rates for each year post-diagnosis. Consequently, it was assumed for this analysis that the relative survival rates for stomach cancer were the same for all ages. The survival and mortality probabilities for stomach cancer patients, which are incorporated into calculations of expected medical costs, are based on this assumption.

There is also a lack of information on age-specific medical costs incurred by stomach cancer patients during the three treatment periods defined by Baker et al. Because of this, any differences in expected medical costs for stomach cancer patients diagnosed at different ages, based on current information, would differ only because of differences in survival and mortality probabilities. The discussion here focuses on the costs incurred by stomach cancer patients diagnosed at age 70 (the average age at diagnosis); a summary table of expected medical costs for patients diagnosed at several different ages is presented in the "Results" section for comparison.

The analysis assumes that death always occurs midyear. All stomach cancer patients are therefore assumed to incur the costs of initial treatment during the first three months of the illness. The costs incurred after that during the first year depend on whether the patient (1) survives through the year, (2) dies of stomach cancer during the year, or (3) dies of some other cause during the year. Patients who survive through the year incur the costs of initial treatment ($29,309) during the first three months, and then incur nine months' worth of maintenance care costs (0.75 × $10,554 = $7,916) during the remainder of the year. The total cost incurred during the first year by those patients who survive the year is therefore $29,309 + $7,916 = $37,225. Stomach cancer patients who die of stomach cancer during the first year incur the initial treatment cost and then incur terminal care costs for the remaining three months of their lives (because those who die are assumed to die midyear). Total costs during the first year post-diagnosis in this case are therefore $29,309 + 0.5 × $31,325 = $44,972.

Finally, the small percentage of stomach cancer patients who die of causes other than stomach cancer during the first year post-diagnosis incur the initial treatment costs and then incur three months' worth of maintenance care costs. Total first-year costs for these patients are therefore $29,309 + 0.25 × $10,554 = $31,948.

The expected medical costs for stomach cancer patients during the first year post-diagnosis, then, may be expressed as:

> **<u>Expected First-Year Cost:</u> initial treatment costs + [maintenance care costs for nine months × probability of survival through first year + terminal care costs for three months × probability of dying of stomach cancer during first year + maintenance care costs for three months × probability of dying of other causes during the first year]**

For each subsequent year, costs consist entirely of maintenance care costs for those who survive the year. For those who do not survive the year, costs depend on whether death was due to stomach cancer or other causes. For those who die of stomach cancer during the *n*th year, costs incurred

that year consist of six months of terminal care costs, or $31,325. For those who die of other causes during the *n*th year, there are six months of maintenance care costs, or 0.5 × $10,554 = $5,277.

The expected medical costs for stomach cancer patients during the *n*th year post-diagnosis, for *n*>1, then, may be expressed as:

> **Expected *n*th Year (*n*>1) Cost: [maintenance care cost for one year × probability of survival through *n*th year + terminal care cost for six months × probability of dying of stomach cancer during the *n*th year + maintenance care cost for six months × probability of dying of other causes during the *n*th year]**

Expected Lifetime cost =

> **Expected First-Year cost + the sum of the (discounted) expected subsequent-year costs**

The first year of treatment is calculated differently from other years because the first three months of that year are spent in "initial" treatment and the costs for that period of intensive medical care and surgery are calculated separately. The mathematical equation for the expected lifetime medical costs incurred by a stomach cancer patient over a ten-year period is:

$$\$29{,}309 + (\$10{,}554 \times 0.75 \times ps_1) + (\$10{,}554 \times 0.25 \times pm_1^{o}) + (\$31{,}325 \times 0.5 \times pm_1^{sc})$$

$$+\sum_{y=2}^{10} \left[(ps_y \times \frac{\$10{,}554}{(1+r)^{y-1}}) + (pm_y^{o} \times \frac{\$5{,}277}{(1+r)^{y-1}}) + (pm_y^{sc} \times \frac{\$31{,}325}{(1+r)^{(y-1)}}) \right]$$

where: y = the year post-diagnosis
ps = the probability of surviving through the year,
pm^{sc} = the probability of dying of stomach cancer during the year
pm^{o} = the probability of dying from other causes during the year,
r = the discount rate

Example: Expected first-year medical costs of a stomach cancer patient diagnosed at age 70

As noted above, all stomach cancer patients incur an initial treatment cost of $29,309. Those who survive through the year (44.3 percent of those

diagnosed at age 70) also incur maintenance care costs for the remaining three quarters of the year. The total first-year costs of those who survive the year are:

Initial treatment:	$29,309
Maintenance treatment:	$7,916 (.75 × $10,554)
Total First-Year Cost	$37,225

More than half of stomach cancer patients (53.7 percent of those diagnosed at age 70) will die of stomach cancer during the first year. Those who do will incur the initial treatment costs plus half of the terminal care costs. The total first year costs of those who die of stomach cancer during the year are:

Initial treatment:	$ 29,309
Terminal care:	$15,663 (.50 × $31,325)
Total First-Year Cost	$44,972

Finally, a few stomach cancer patients (1.9 percent of those diagnosed at age 70) will die of competing illnesses during the first year. Because those who die of causes other than stomach cancer are assumed to die at the midpoint of the year, costs during the first half of the year are assumed to consist of the initial treatment costs for three months, plus three months of maintenance care costs as follows:

Initial treatment:	$29,309
Maintenance treatment:	$2,639 (.25 × $10,554)
Total First-Year Cost	$31,948

The expected first year medical cost incurred by a stomach cancer patient diagnosed at age 70 is just a weighted average of the costs of those who survive the first year, those who die of stomach cancer during the first year, and those who die of other causes during the first year, where the weights are the probabilities of each of these occurrences (see Table II.2-4):

$$\$37,225 \times 0.443 + \$44,972 \times 0.537 + \$31,948 \times 0.019 = \$41,286$$

The weighted average medical cost calculations were carried out for ten years and expected costs were summed over all years from diagnosis to year ten. This was assumed to be a reasonable period over which additional medical costs associated with stomach cancer (i.e. maintenance care costs) would be incurred by stomach cancer patients. In reality, there may be follow-up care and continued testing over a longer period;

however, no data were available regarding those costs. They would certainly be less than $10,554 per year.

II.2.B.2 Results

II.2.B.2.1 Lifetime Cost Estimates for Survivors and Nonsurvivors Combined

The cost estimates for each year post-diagnosis and the estimate of expected total cost for a ten-year period are shown in Table II.2-6 for stomach cancer patients whose age of onset is 70 (the average age at diagnosis for this cancer). The discounted results are shown in the "Results" section which follows. The survival and mortality probabilities necessary for the calculations are shown in columns (2), (3) and (4) (and were taken from Table II.2-4). The cost components used in the calculations are shown in columns (5), (6), and (7).

II.2.B.2.2 Lifetime Cost Estimates for Stomach Cancer Survivors and Nonsurvivors Separately

II.2B.2.2.1 Overview

There are differences in medical services provided to stomach cancer patients who survive the disease (survivors) versus those who die of the disease (nonsurvivors). Based on cost estimates by Baker et al. (1989), terminal care is provided for approximately six months to terminally ill cancer patients. The costs to nonsurvivors for this care ($31,325) is considerably higher than costs for survivors who receive maintenance care for the same period of time ($5,277).[6] EPA may use the value of a statistical life for nonsurvivors, and thus separate costs for survivors and nonsurvivors were calculated. The method to calculate costs for all patients described in Section II.2.B.1.3 uses the unconditional probabilities of survival and mortality given in Table II.2-4. The method used to calculate costs for survivors and nonsurvivors separately requires the conditional probabilities of survival and mortality in each group — that is, the probabilities conditional on being a stomach cancer survivor or being a stomach cancer nonsurvivor.

[6] Nonsurvivors include only those who die of stomach cancer and do NOT include those who die of any other causes.

Table II.2-6. Expected Costs of Medical Services (in 1996$) for Stomach Cancer Patients (Age of Onset = 70)							
	Probabilities[a]:			Medical Costs in the *n*th Year (undiscounted)			
Years Post-Diagnosis (n) (1)	of surviving through the *n*th year (2)	of dying of stomach cancer in the *n*th year (3)	of dying of other causes in the *n*th year (4)	if survive through the *n*th year (5)	if die of stomach cancer in the *n*th year (6)	if die of other causes in the *n*th year (7)	Expected Medical Costs for the *n*th Year Post-Diagnosis ((2)×(5)+(3)×(6)+(4)×(7))
1[b]	0.4434	0.5373	0.0193	$37,225	$44,972	$31,948	$41,286
2	0.3055	0.1270	0.0109	$10,554	$31,325	$5,277	$7,261
3	0.2421	0.0548	0.0086	$10,554	$31,325	$5,277	$4,316
4	0.2028	0.0317	0.0076	$10,554	$31,325	$5,277	$3,172
5	0.1749	0.0209	0.0071	$10,554	$31,325	$5,277	$2,537
6	0.1534	0.0149	0.0067	$10,554	$31,325	$5,277	$2,119
7	0.1359	0.0111	0.0064	$10,554	$31,325	$5,277	$1,815
8	0.1212	0.0085	0.0062	$10,554	$31,325	$5,277	$1,579
9	0.1085	0.0067	0.0060	$10,554	$31,325	$5,277	$1,387
10	0.0972	0.0054	0.0059	$10,554	$31,325	$5,277	$1,226
Expected Total Cost Through the 10th Year Post-Diagnosis for a Stomach Cancer Patient Diagnosed at Age 70:							$66,700

a. The probabilities listed in this table are from Table II.2-4. The costs are listed in Table II.2-5.
b. First year costs include the charge for "initial" therapy ($29,309). The duration of maintenance care is adjusted accordingly (see text for discussion).

Probabilities of survival were calculated using data shown in Table II.2-4. Summing the entries in column (5) of Table II.2-4, 81,822 of the 100,000 stomach cancer patients diagnosed at age 70 (or about 82 percent) die of stomach cancer within ten years. The remainder (100,000 - 81,822 = 18,178) are survivors of stomach cancer. The probabilities of a stomach cancer patient diagnosed at age 70 surviving stomach cancer and dying of stomach cancer are therefore estimated to be 0.182 and 0.818 (about 0.18 and 0.82), respectively.

Link to Table II.2-4

The conditional probability of a stomach cancer nonsurvivor dying in the *n*th year is just the number of stomach cancer patients who die of stomach cancer during the *n*th year (from column (5) of Table II.2-4) divided by the total number of stomach cancer nonsurvivors. For example, the conditional probability of a stomach cancer nonsurvivor dying during the first year post-diagnosis is 53,730/81,822 = 0.657. Similarly, the conditional probability of a stomach cancer survivor dying (of other causes) in the *n*th year is just the number of stomach cancer patients who die of other causes during the *n*th year (from column (6) of Table II.2-4) divided by the total number of stomach cancer survivors. For example, the conditional probability of a stomach cancer survivor dying of some other cause during the first year post-diagnosis is 1,928/18,178 = 0.106. The conditional probabilities of survival and mortality for survivors and nonsurvivors of stomach cancer are given in Table II.2-7.

Table II.2-7. Conditional Probabilities of Survival and Mortality for Survivors and Nonsurvivors of Stomach Cancer (Age of Onset = 70)

	Stomach Cancer Survivors		Stomach Cancer Nonsurvivors	
	Conditional probability of:		Conditional probability of:	
Years Post-Diagnosis (n)	Surviving through the *n*th year	Dying of some other cause during the *n*th year	Surviving through the *n*th year	Dying of stomach cancer during the *n*th year
1	0.894	0.106	0.343	0.657
2	0.834	0.060	0.188	0.155
3	0.787	0.048	0.121	0.067
4	0.745	0.042	0.082	0.039
5	0.706	0.039	0.057	0.026
6	0.669	0.037	0.039	0.018
7	0.634	0.035	0.025	0.014
8	0.600	0.034	0.015	0.010
9	0.567	0.033	0.007	0.008
10	0.535	0.032	0.000	0.007

II.2.B.2.2.2. Lifetime Cost Estimates for Stomach Cancer Survivors

As shown in Table II.2-5, all stomach cancer patients will incur initial treatment costs ($29,309) during the first three months of the first year post-diagnosis. If they survive the first year, they will also incur nine months worth of maintenance care costs (0.75 × $10,554 = $7,916) that first year. The total cost incurred during the first year by those stomach cancer survivors who survive the first year is therefore $29,309 + $7,916 = $37,225.

Link to Table II.2-5

Stomach cancer survivors who die of some other cause during the first year incur the initial treatment costs during the first three months and then incur three months (25 percent) of maintenance care costs (because they are assumed to die midyear), for a total cost of $29,309 + 0.25 × $10,554 = $31,948.

The expected medical costs for stomach cancer survivors during the first year post-diagnosis may therefore be expressed as:

> **Expected First-Year Cost: initial treatment costs + [maintenance care costs for nine months × probability of survival through first year + maintenance care costs for three months × probability of dying of other causes during the first year]**

For each subsequent year, costs consist entirely of maintenance care costs for those who survive the year. For those who die of other causes during the year, there are six months of maintenance care costs, or 0.5 × $10,554 = $5,277.

The expected medical costs for stomach cancer survivors during the *n*th year post-diagnosis, for $n>1$, then, may be expressed as:

> **Expected *n*th Year ($n>1$) Cost: [maintenance care cost for one year × probability of survival through *n*th year + maintenance care cost for six months × probability of dying of other causes during the *n*th year]**

Expected Lifetime cost =

> **Expected first year cost + the sum of the (discounted) expected subsequent-year costs**

The calculations above use the conditional probabilities of patients who do not die of stomach cancer, shown in Table II.2-7.

Using the initial, maintenance, and terminal care costs from Table II.2-5, the mathematical equation for the lifetime costs incurred by stomach cancer survivors is:

$$\$29{,}309 + pm_1^s \times 0.25\ (\$10{,}554) + ps_1^s \times .75 \times \$10{,}554 + \sum_{y=2}^{10} \left[ps_y^s \frac{\$10{,}554}{(1+r)^{y-1}} + pm_y^s \frac{\$5{,}277}{(1+r)^{y-1}} \right]$$

where: y = the year post-diagnosis
ps^s = the conditional probability of survival for that year, conditional on being a survivor of stomach cancer
pm^s = the conditional probability of mortality for that year, conditional on being a survivor of stomach cancer
r = the discount rate.

The expected medical costs for stomach cancer survivors for each year post-diagnosis, as well as the expected total medical costs over ten years post-diagnosis are shown in Table II.2-8.

II.2.B.2.2.3 Lifetime Cost Estimates for Stomach Cancer Nonsurvivors

Nonsurvivors of stomach cancer will incur initial, maintenance, and terminal costs. Their lifetime medical costs associated with the disease can be calculated from the costs per treatment period shown in Table II.2-5 and the conditional probabilities for nonsurvivors of stomach cancer shown in Table II.2-7.

Link to Table II.2-5 and II.2-7

As Table II.2-7 indicates, most stomach cancer patients who die of stomach cancer die in the first few years post-diagnosis. About 80 percent die in the first two years. Deaths from stomach cancer after the first four years are minimal. As with stomach cancer survivors, medical costs for nonsurvivors each year post-diagnosis were calculated as a weighted average of the costs incurred by those who survive the year and those who die (of stomach cancer) during the year.

Table II.2-8. Expected Costs of Medical Services (in 1996$) for Survivors of Stomach Cancer (Age of Onset = 70)

Years Post-Diagnosis (n)	Medical Costs Through the 10th Year Post-diagnosis[a] (undiscounted)				
	Medical Cost if Survive Through the *n*th Year (1)	Conditional Probability of Survival Through the *n*th Year[b] (2)	Medical Cost if Die of other Causes in the *n*th Year (3)	Conditional Probability of Mortality in the *n*th Year[b] (4)	Total Cost Based on Weighted Average[c] = (1)×(2) + (3)×(4)
1[d]	$37,225	0.894	$31,948	0.106	$36,666
2	$10,554	0.834	$5,277	0.060	$9,119
3	$10,554	0.787	$5,277	0.048	$8,553
4	$10,554	0.745	$5,277	0.042	$8,080
5	$10,554	0.700	$5,277	0.039	$7,654
6	$10,554	0.669	$5,277	0.037	$7,257
7	$10,554	0.634	$5,277	0.035	$6,878
8	$10,554	0.600	$5,277	0.034	$6,514
9	$10,554	0.567	$5,277	0.033	$6,159
10	$10,554	0.535	$5,277	0.032	$5,813
Expected Total (Undiscounted) Cost Through the 10th Year Post-Diagnosis:					**$102,693**

a. Costs are based on data reported in Table II.2-5, adapted from Baker et al., 1989.
b. Probabilities of survival and mortality, taken from Table II.2-7, are conditional on surviving stomach cancer.
c. Weighted average of the costs incurred by survivors who survive the year and the costs incurred by survivors who die of other causes during the year. Weighting is based on the conditional probabilities listed.
d. Costs during the first year include a charge for "initial" therapy ($29,309), and the duration of maintenance or terminal care is adjusted accordingly. See text for discussion.

It was assumed that those who die during a year receive six months of care (as was done for the survivors above). It was also assumed that terminal care lasting six months would be provided to all nonsurvivors. Therefore, unless death occurred during the first year, when initial care was assumed to occur, the care costs which were assigned to the last year of life were terminal costs. If death occurred during the first year post-diagnosis, it was assumed that initial care and three months (half of the total) of terminal care were provided.

The general description of medical costs for nonsurvivors may be expressed as:

Expected cost for each year post-diagnosis =

> **Expected First-Year Cost: [initial costs + half the terminal costs] × probability of mortality during the first year + [initial costs + maintenance care costs for nine months] × probability of survival for first year**
>
> **Expected *n*th Year (*n*>1) Cost: maintenance care cost for one year × probability of survival through *n*th year + terminal costs× probability of mortality in *n*th year**

Expected Lifetime cost =

> **Expected First-Year cost + the sum of the (discounted) expected subsequent-year costs**

As with the cost calculations for stomach cancer survivors, the probabilities used in these cost calculations are the conditional probabilities given in Table II.2-7, which are conditional on dying of stomach cancer.

Using the initial, maintenance, and terminal care costs from Table II.2-5, the mathematical equation for the expected lifetime costs incurred by nonsurvivors is:

$$\$29{,}309 + pm_1^{ns} \times 0.5\ (\$31{,}325) + ps_1^{ns} \times .75 \times \$10{,}554$$
$$+ \sum_{y=2}^{10} \left[ps_y^{ns} \frac{\$10{,}554}{(1+r)^{y-1}} + pm_y^{ns} \frac{\$31{,}325}{(1+r)^{y-1}} \right]$$

where: y = the year post-diagnosis

ps^{ns} = the conditional probability of survival for that year, conditional on being a nonsurvivor of stomach cancer

pm^{ns} = the conditional probability of mortality for that year, conditional on being a nonsurvivor of stomach cancer

r = the discount rate.

The costs are summed over all years from diagnosis to death. Maintenance care costs are not added in the last year of life because during the six months that are assumed to constitute this period the patient is assumed to receive terminal care. (The discounted results are shown in the "Results" section that follows.)

Example: Nonsurvivors Year One

During the first year post-diagnosis, nonsurvivors of stomach cancer who survive the year (34.3 percent) will, on average, incur the following costs:

Initial treatment:	$29,309
Maintenance treatment:	$7,916 (.75 × $10,554)
Total Cost	$37,225

However, 65.7 percent of stomach cancer nonsurvivors will die during the first year. Those individuals are assumed to die at the midpoint of the year (to obtain an average survival for the time period and average costs). That group will incur the initial costs for three months, plus three months of terminal care as follows:

Initial treatment:	$29,309
Terminal care:	$15,663 (.5 × $31,325)
Total Costs:	$44,972

A weighted average of the first-year costs incurred by stomach cancer nonsurvivors who do and do not die during the first year was calculated as follows:

$$\$37,225 \times 0.343 + \$44,972 \times 0.657 = \$42,312$$

During the second and subsequent years up to but not including the year of death, the medical costs of nonsurvivors will include the costs of maintenance care. As noted above, the last year of life is composed of

terminal care costs only, since all patients are assumed to receive six months of terminal care. For example, if someone died during the third year post-diagnosis, he would receive three months of initial care and nine months of maintenance care during the first year; he would receive 12 months of maintenance care during the second year; and he would receive terminal care for the six months that he is assumed to have survived during the third year (as noted previously, all patients are assumed to die mid-year to obtain average cost estimates for a year).

When the costs for each year are summed over a period of ten years post-diagnosis, during which essentially all patients who will die of stomach cancer have done so, the total cost per nonsurvivor is obtained. These costs are shown in Table II.2-9.

II.2.B.2.3 A Comparison of the Expected Medical Costs of Stomach Cancer Patients, Using Two Approaches

Section II.2B.1.3 discusses calculation of the average direct medical costs for all patients (average costs) and Section II.2.B.1.4 provides separate cost estimates for survivors and nonsurvivors of stomach cancer. The average patient cost can be calculated, however, from the results in II.2B.1.4 using the weighted average of the expected costs of stomach cancer survivors and nonsurvivors, where the weights are the probabilities of surviving stomach cancer and not surviving it, respectively.

As shown in Table II.2-6, the expected medical cost for ten years post-diagnosis for a stomach cancer patient diagnosed at age 70 is $66,700. The expected medical costs calculated separately for survivors and nonsurvivors of stomach cancer (for those diagnosed at age 70) are $102,693 and $58,704, respectively. The probability of being a stomach cancer survivor when onset occurs at age 70 is 0.18178; the probability of being a stomach cancer nonsurvivor is 0.81822. The expected cost incurred by a stomach cancer patient, calculated as a weighted average of the costs of those who survive stomach cancer and those who die from it, is therefore

$$\$102{,}693 \times 0.18178 \; + \; \$58{,}704 \times 0.81822 = \$66{,}700.$$

Link to Table II.2-6

This is the same value that was calculated by following a cohort of stomach cancer patients over the ten-year period, using their (unconditional) probabilities of survival, death from stomach cancer, and death from other causes for each year (shown in Table II.2-6).

Table II.2-9. Expected Costs of Medical Services (in 1996$) for Nonsurvivors of Stomach Cancer (Age of Onset = 70)					
	Medical Costs Through the 10th Year Post-diagnosis[a] (undiscounted)				
Years Post-Diag-nosis (n)	Medical Cost if Survive Through the *n*th Year (1)	Conditional Probability of Survival Through the *n*th Year[b] (2)	Medical Cost if Die in the *n*th Year (3)	Conditional Probability of Mortality in the *n*th Year[b] (4)	Total Cost Based on Weighted Average[c] = (1)×(2) + (3)×(4)
1[d]	$37,225	0.343	$44,972	0.657	$42,312
2	$10,554	0.188	$31,325	0.155	$6,849
3	$10,554	0.121	$31,325	0.067	$3,375
4	$10,554	0.082	$31,325	0.039	$2,082
5	$10,554	0.057	$31,325	0.026	$1,400
6	$10,554	0.039	$31,325	0.018	$978
7	$10,554	0.025	$31,325	0.014	$691
8	$10,554	0.015	$31,325	0.010	$483
9	$10,554	0.007	$31,325	0.008	$327
10	$10,554	0.000	$31,325	0.007	$207
Expected Total (Undiscounted) Cost Through the 10th Year Post-Diagnosis:					$58,704

a. Costs are based on data reported in Table II.2-6, adapted from Baker et al., 1989.
b. Probabilities of survival and mortality, taken from Table II.2-7, are conditional on dying of stomach cancer within ten years post-diagnosis.
c. Weighted average of the costs incurred by nonsurvivors who survive the year and the costs incurred by nonsurvivors who die during the year. Weighting is based on the conditional probabilities listed.
d. Costs during the first year include an additional charge for "Initial" therapy ($29,309), and the duration of maintenance or terminal care is adjusted accordingly. See text for discussion.

II.2.B.2.4 Discounted Medical Costs for All Patients, Survivors, and Nonsurvivors

The per patient lifetime direct medical costs were calculated for stomach cancer patients (as shown in Table II.2-6), stomach cancer survivors (as shown in Table II.2-8) and stomach cancer nonsurvivors (as shown in Table II.2-9) diagnosed at age 70, undiscounted as well as using discount rates of three, five, and seven percent. The discounted costs for each year were discounted back to year one (time of diagnosis). This procedure was carried out for ten years following diagnosis (which, for nonsurvivors, comprises the full duration of treatment time because virtually all patients that are going to die of stomach cancer do so within ten years) and comprises the assumed full duration of maintenance care for survivors. The results are shown in Table II.2-10.

Table II.2-10. Costs of Medical Services (in 1996$) for Stomach Cancer Patients, Survivors, and Nonsurvivors (Diagnosed at Age 70) Undiscounted and Discounted at 3, 5, and 7 Percent

	Discount Rate			
Patient Group	**Undiscounted**	**3**	**5**	**7**
Survivors	$102,693 ($102,700)	$94,229 ($94,200)	$89,749 ($89,700)	$85,654 ($85,700)
Nonsurvivors	$58,704 ($58,700)	$57,524 ($57,500)	$56,826 ($56,800)	$56,190 ($56,200)
Average Patient	$66,700 ($66,700)	$64,229 ($64,200)	$62,811 ($62,800)	$61,546 ($61,500)

* The costs in parenthesis have been rounded to the nearest hundred dollars.

II.2.C. Sensitivity Analyses

The calculation of expected medical costs incurred by a stomach cancer patient depends on several input factors, including treatment methods, survival percentages and durations, and the age of diagnosis. To illustrate the sensitivity of medical costs to key demographic characteristics, sensitivity analyses were carried out for age at diagnosis and for a sex and race combination. Age at diagnosis was selected because environmental pollutants may cause cancer to occur at earlier ages than the ages at which these cancers typically occur. Many chemicals studied in controlled animal cancer evaluations cause cancer at earlier ages than the ages at which cancer "spontaneously" occurs in the animals. This same dynamic has been observed among occupationally-exposed workers whose cancer results from exposures to chemicals and radiation. For example, many studies of radon and lung cancer indicate that radon-associated lung cancer occurs at

younger ages than would be expected in the general population. A sensitivity analysis of African-American males was conducted because this is a large high-risk group in the United States.

II.2.C.1 The Effect of Age at Diagnosis on Medical Costs

Expected medical costs incurred by stomach cancer patients, stomach cancer survivors, and stomach cancer nonsurvivors were calculated for ages at diagnosis of 22, 42, 52, 62, 70, and 82. For each age at diagnosis, the methods used to calculate expected medical costs were the same as those used when age at diagnosis is 70. These methods are discussed in Section II.2.B and are illustrated using:

- age at diagnosis equal to 70 in Table II.2-6 for expected medical costs incurred by stomach cancer patients;
- Tables II.2-8 and II.2-9 for expected medical costs incurred by survivors and nonsurvivors, respectively;

Link To Tables II.2-6 ,8 ,9

There is no information on age-specific medical costs comprising initial treatment, maintenance care, or terminal care (the three treatment phases delineated by Baker et al. (1989)); however, costs would not be expected to vary substantially by age. In addition, the relative survival rates obtained from NCI (1998) are not age-specific. Consequently, differences in expected medical costs across different ages at diagnosis are based solely on differences in age-specific survival and mortality probabilities in the general population. The results of the age-specific analysis are shown in Table II.2-11.

Table II.2-11. Summary Table of Expected Medical Costs Incurred by Stomach Cancer Patients, Survivors, and Nonsurvivors, by Age at Diagnosis

Age at Diagnosis	(Undiscounted) Expected Medical Costs for 10 Years Incurred by a Stomach Cancer:		
	Patient	Survivor	Non-survivor
22	$70,482	$130,789	$60,077
42	$70,227	$128,522	$59,987
52	$69,721	$124,298	$59,804
62	$68,479	$114,569	$59,360
70*	**$66,700**	**$102,693**	**$58,704**
82	$61,581	$77,086	$56,798

* This is the average age used in the main analysis and is included as a point of reference for this sensitivity analysis.

As can be seen in Table II.2-11, differences in expected medical costs across ages at diagnosis are greater among survivors than nonsurvivors. This may be an artifact of several characteristics of the analysis, in which medical costs and relative survival rates were not age-specific and a survivor's cost of surviving through the year is twice what it is if death from some other cause occurs during the year. Younger stomach cancer survivors have a greater chance of not dying of other causes during each year than older stomach cancer survivors, based simply on age-specific general population survival rates. Stomach cancer survivors who survive through a year incur twice the cost of those who die of other causes during the year (a full year's worth of maintenance care cost versus half a year's worth of maintenance care cost). Because of this, younger survivors, whose survival probabilities are greater than older survivors, incur substantially more costs.

II.2.C.2 The Effect of Race on Medical Costs: An Analysis of African-American Males

II.2.C.2.1 Incidence of Stomach Cancer

Of the four gender-race categories for which NCI (1998) provides information related to stomach cancer (white males, white females, African-American males, African-American females), the group with the highest rates of stomach cancer is African-American males. A comparison of incidence rates at the different ages at diagnosis for the general U.S. population versus African-American males is given in Table II.2-12.

Table II.2-12. Stomach Cancer Incidence Rates for the General U.S. Population Versus African-American Males

Age at Diagnosis	Incidence per 100,000		Ratio of Incidence Rates (general population/African-American Males)
	General U.S. Population	African-American Males	
0-4	0.0	0.0	----
5-9	0.0	0.0	----
10-14	0.0	0.0	----
15-19	0.1	0.0	0.00
20-24	0.1	0.7	7.00
25-29	0.4	0.2	0.50
30-34	0.7	1.7	2.43
35-39	1.5	3.5	2.33
40-44	2.7	8.1	3.00
45-49	4.4	10.0	2.27
50-54	8.3	22.5	2.71
55-59	14.1	38.8	2.75
60-64	21.7	55.9	2.58
65-69	31.8	83.9	2.64

Table II.2-12. Stomach Cancer Incidence Rates for the General U.S. Population Versus African-American Males			
Age at Diagnosis	Incidence per 100,000		Ratio of Incidence Rates (general population/African-American Males)
	General U.S. Population	African-American Males	
70-74	45.6	127.8	2.80
75-79	55.9	111.6	2.00
80-84	67.5	135.8	2.01
85+	79.4	225.2	2.84

Incidence rates for the earliest ages at diagnosis are probably unreliable because they are based on very small samples. Starting from about age 30, however, African-American males have an incidence rate of stomach cancer that is two to three times that of the general U.S. population. The cause of the increased rate of stomach cancer among African-Americans males is not known. It may be due to dietary, environmental, genetic, or other factors. Issues related to susceptible subgroups in benefits assessments are discussed in the Chapter I.1 section titled "Susceptible Subgroups."

Link to Chapter I.1

II.2.C.2.2 Risk Versus Per Capita Costs

Incidence rates that are two to three times higher than those of the general population suggest that exposure to pollutants associated with stomach cancer may result in expected costs-of-illness for African-American males that are two to three times higher *per exposed African-American male* as compared with the expected costs incurred by the average exposed individual in the general population. Suppose, for example, that stomach cancer costs $50,000 per stomach cancer patient on average. Suppose also that the incidence rate among African-American males is 84 per 100,000 while the incidence rate in the general population is 32 per 100,000. If the cost per patient is the same among African-American males as among individuals in the general population, then the expected cost of stomach cancer *per exposed African-American male* is

$$\$50{,}000 \times 0.00084 = \$42.$$

The expected cost of stomach cancer *per exposed individual in the general U.S. population* is

$$\$50{,}000 \times 0.00032 = \$16.$$

II.2.C.2.3. Comparison of Per Capita Costs: African-American Males versus the General U.S. Population

The costs of illness analyzed in this handbook are not costs per exposed individual, but rather costs *per patient (per capita)*, unlike the analysis above. This chapter estimates the expected costs incurred by an individual who has been diagnosed with stomach cancer. Even though disproportionately more African-American males are diagnosed with stomach cancer than the general population, their medical costs per patient may or may not be higher than those of stomach cancer patients in the general population. To contrast the costs of these two groups, the analyses that were carried out for the general U.S. population were also carried out for African-American males.

Although the methodology used for this sensitivity analysis was the same as that used in the main analysis, the values of the following inputs to the analysis were altered to be specific to the population of African-American males in the U.S.:

- age-specific survival rates,
- age-specific life expectancies,
- age-specific probabilities of dying specifically of stomach cancer, and
- RSRs for each year post-diagnosis.

RSRs were not available for African-American males for each year post-diagnosis. These were therefore derived by multiplying the adjusted RSRs used in the main analysis (see Table II.2-2) by the ratio of the five-year RSR for African-American males, 1986-1993 (16.9), to the corresponding five-year RSR for the general population (20.6).

Link to Table II.2-2

Given values for these input parameters specific to African-American males in the U.S., the expected per capita medical costs incurred by African-American male stomach cancer patients were calculated. The resulting medical costs is shown, and compared with the corresponding medical costs of the average patient in the general population, in Tables II.2-13.

Table II.2-13. Expected Medical Costs Over 10 Years for a Stomach Cancer Patient, Survivor, and Nonsurvivor for Selected Ages at Diagnosis: A Comparison Between the General U.S. Population and African-American Males

Age at Diagnosis	General U.S. Population			African-American Males		
	Expected Medical Costs for 10 Years for a stomach cancer:			Expected Medical Costs for 10 Years for a stomach cancer:		
	Patient	Survivor	Non-survivor	Patient	Survivor	Non-survivor
22	$70,482	$130,789	$60,077	$65,629	$127,517	$56,898
42	$70,227	$128,522	$59,987	$65,014	$121,002	$56,678
52	$69,721	$124,298	$59,804	$64,205	$113,390	$56,383
62	$68,479	$114,569	$59,360	$62,669	$100,569	$55,829
82	$61,581	$77,086	$56,798	$56,026	$65,150	$53,296
Average age at diagnosis for African-American males: 66	-----	-----	-----	$61,779	$94,397	$55,489
Average age at diagnosis in the general U.S. population: 70	$66,700	$102,693	$58,704	-----	-----	-----

Expected per capita medical costs of African-American male stomach cancer patients are uniformly less than the corresponding per capita costs for stomach cancer patients in the general U.S. population at all ages at diagnosis considered. The patterns are similar for stomach cancer survivors and nonsurvivors. As noted in Section II.2.C.1, Baker et al. (1989) do not report costs for any of the three treatment periods separately by age at diagnosis or by any other demographic characteristic. Differences in expected medical costs between African-American male stomach cancer patients (or survivors or nonsurvivors of stomach cancer) and their counterparts in the general population are therefore, in this analysis, due solely to differences in survival and mortality probabilities.

II.2.C.2.3.1 Survivors' Medical Costs

Among survivors of stomach cancer, costs beyond the first year consist only of maintenance care costs. The greater the probability of survival (i.e., of not dying of some other cause), the longer the expected period of maintenance care, and the greater the expected costs incurred by survivors. African-American males have notably *lower* survival rates (death rates are higher from non-stomach cancer causes) than the general population at each age. Consequently, the expected costs incurred by an African-American male survivor of stomach cancer are *lower* than the corresponding costs of a stomach cancer survivor from the general population. That is, at each age there is a smaller proportion of African-American males surviving to incur the costs of maintenance care as compared with stomach cancer survivors in the general U.S. population.

II.2.C.2.3.2 Nonsurvivors' Medical Costs

Among nonsurvivors of stomach cancer, costs beyond the first year are three times as high for those who die of stomach cancer during the year ($31,325) as for those who survive the year ($10,554). In the first year post-diagnosis, the cost differential between those who survive the year and those who die of stomach cancer during the year is much less than in subsequent years. This is because those who die are assumed to die midyear, and during the first three months of the first year stomach cancer patients are assumed to undergo initial treatment, leaving only three months (as opposed to the full six months) of expensive terminal care in the first year. Because a substantially larger percentage of African-American male nonsurvivors die during the first year post-diagnosis as compared with general population nonsurvivors, the overall costs incurred by African-American male nonsurvivors are estimated to be less than those incurred by general population nonsurvivors. This is to some extent due to the assumption that, if the patient dies of stomach cancer during the first year post-diagnosis, there are only three months of terminal care costs incurred.

II.2.D. Uncertainties and Limitations

As noted periodically in the above discussion, there is substantial uncertainty surrounding various aspects of cost in the analyses. Information concerning important inputs to the analysis was often limited to some degree and, in some cases, was highly limited. Although a complete uncertainty analysis is beyond the scope of this work, the significant sources of uncertainty are discussed below in Section II.2.D.1. The scope of the analysis had some limitations as well. These are discussed in Section II.2.D.2.

II.2.D.1. Uncertainties Surrounding Key Inputs to the Analysis

The cost estimates based on Baker et al. (1989, 1991) have a number of limitations, many of them noted by Baker et al. (1991) and Mor et al. (1990) and Mor (1993). Most of these limitations arise from the use of CMHSF. Medicare data has five limitations that decrease its value for calculating the average lifetime direct medical costs of treating stomach cancer. First, Medicare covers only medical services for most persons age 65 and over, disabled persons entitled to Social Security cash benefits for at least 24 months, and most persons with end-stage renal disease. All patients not covered by Medicare are excluded from the database, including all non-disabled women under 65, and women over 65 using private health insurance (Baker et al., 1991).

Given that diagnosis of stomach cancer occurs before age 65 in 28.7 percent of patients (NCI, 1998), the CMHSF excludes a significant number of younger patients. According to Mor et al., treatment for younger

women tends to be more intensive (and therefore more costly per unit time) than treatment for older women, though older women tend to have longer hospital stays. Because these differences counteract each other, the omission of younger women from the analysis is not expected to affect the results substantially. In addition, the majority of senior citizens are enrolled in Medicare (Ibid); differences in medical costs incurred by senior citizens not using Medicare should have little effect on overall cost estimates.[7]

Medicare also does not cover self-administered drugs, intermediate nursing care, long-term nursing care, and expensive, extraordinary treatments (such as bone marrow transplants). For some patients these may represent significant percentages of total treatment costs. Most direct medical costs, however, appear to be covered by the CMHSF database and are included in Baker et al.'s analysis.

Another drawback is that Baker et al. were not able to identify stomach cancer patients in CMHSF whose diagnosis and first course of therapy did not involve hospitalization. In an analysis of Rhode Island stomach cancer patients covered by Medicare, Mor et al. determined that approximately 13 percent of stomach cancer patients were initially diagnosed without hospitalization, and had substantially lower initial and subsequent treatment costs (Mor et al., 1990). This omission likely causes average treatment costs to be overestimated, though by relatively little, since 87 percent of stomach cancer patients on Medicare are initially diagnosed during hospitalization and therefore would be recorded in CMHSF.

A fourth drawback is that Baker et al. (1989) provides no information concerning the duration of the maintenance period for stomach cancer. The analysis in this chapter assumed that stomach cancer survivors incur maintenance care costs for ten years. If the average duration of maintenance care among survivors of stomach cancer is shorter (longer) than ten years, the estimates of the costs incurred by survivors would be biased upward (downward). This is less of an issue for nonsurvivors' costs because the great majority of stomach cancer nonsurvivors die within the first few years. Because most stomach cancer patients (about 82 percent) are ultimately nonsurvivors, the duration of the maintenance period is of somewhat less importance for stomach cancer patients than for the 18 percent who ultimately survive the illness.

A fifth drawback is that the data used by Baker are from the period 1974 to 1981. Increased early detection and treatment modifications for stomach cancer have increased the life expectancy of those diagnosed with the disease.

[7] This figure represents those enrolled in Medicare Part A; 95 percent of those enrolled in Medicare Part A choose also to enroll in Medicare Part B.

Finally, the reliability of the data contained in the database used by Baker et al. varies. An independent analysis of CMHSF performed in 1977 by the Institute of Medicine of the National Academy of Sciences found that the frequency of discrepancies in principal diagnoses varied among diseases (Baker et al., 1991). It is unclear whether the presence of misnamed diagnoses contained in CMHSF potentially increases or decreases the resultant cost estimates.

Overall, despite the limitations described above, Baker's analysis of the CMHSF data represents the most nationally-representative, per-patient lifetime estimate of the direct medical costs of treating stomach cancer to date. Their cost estimates are based on sound criteria. Some of the data limitations underestimate costs and others overestimate costs; the sum of the data limitations therefore decreases the magnitude of error. More of the uncertainties in their analysis appear to underestimate costs, however; the net result is a likely underestimation of actual direct medical costs.

Although some uncertainties are associated with the estimation of the survival and mortality probabilities used in the calculation of expected medical costs, these uncertainties are likely to be relatively small. As noted in the text, NCI RSRs used to estimate survival and mortality for this analysis are based on the survival experience of a large group of stomach cancer patients considered in relation to the survival experience of the general population. Although age-specific RSRs for each year post-diagnosis are not available, the age-specific five-year RSRs provided by NCI (1998) suggest that there is relatively little variation in RSRs across ages at diagnosis for stomach cancer patients.

An additional limitation of this analysis is that medical costs incurred as a result of stomach cancer, but not considered by Baker et al., may arise as a result of treatment for stomach cancer. Secondary cancers and other adverse health effects may occur due to radiation, chemotherapy treatment, and other therapies. These may occur substantially after stomach cancer treatment has been completed and can incur added medical costs not considered in this chapter.

Data have not yet been located regarding the average duration of maintenance care. For purposes of this analysis, ten years of follow-up care was assumed to be reasonable due to the severity of the disease and the consequences of stomach surgery. This assumption may be revised in the future if data are located.

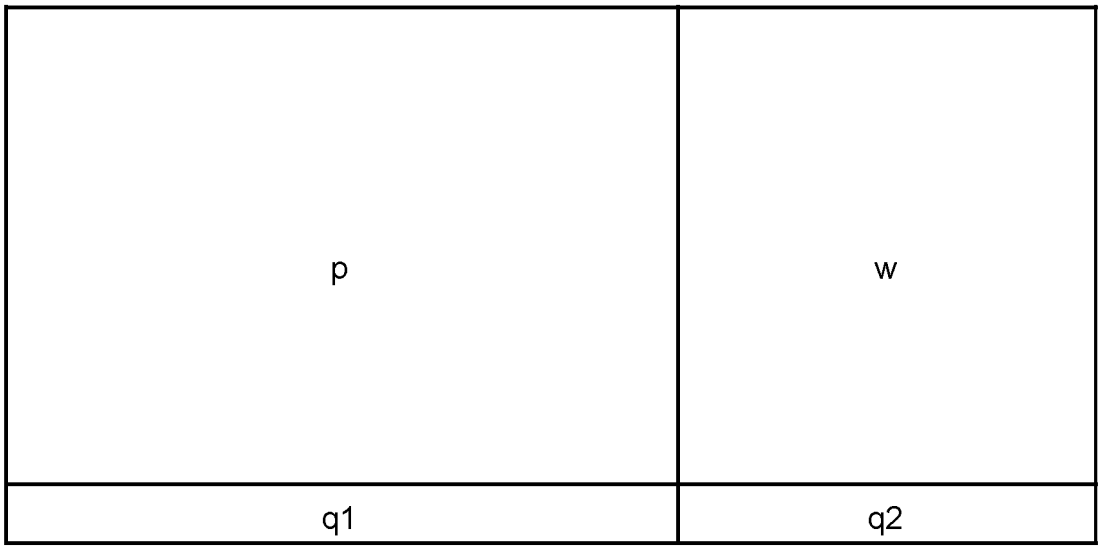
II.2.D.2. Scope of the Analysis

The analysis in this chapter was confined to direct medical costs by the patient. As noted in Chapter I.1, willingness-to-pay has many other cost elements. The analysis does not include time lost by the patient; their family and friends who provide care; pain and suffering on the part of the patient, family, and friends; changes in job status among previously employed patients, training for new job skills due to physical limitations; or medical costs incurred after the ten-year maintenance period. These cost elements may comprise a substantial portion of the total cost of stomach cancer.

Link to Chapter I.1

Appendix II.2-A Deriving the Probabilities of Dying of Stomach Cancer and Dying of Other Causes

This appendix contains a method to derive the probabilities of dying of stomach cancer and dying of other causes in the *n*th year in a cohort of stomach cancer patients who have survived to the *n*th year.



The diagram above represents the stomach cancer cohort remaining at the beginning of the *n*th year. The area of the entire box = the probability of having survived to the beginning of the *n*th year post-diagnosis = 1. That is, all probabilities described below are conditional on having survived to the beginning of the *n*th year post-diagnosis.

p = the proportion of the cohort who survive through the *n*th year (= the probability of surviving the *n*th year.)

q = the probability in the general population of dying of causes other than stomach cancer. We assume that the proportion of the stomach cancer cohort who *would* die of other causes if they were not a cohort of stomach cancer patients is also q.

q = q1 + q2 in the diagram.

z = the proportion of the cohort who *would* die of stomach cancer if there were no other causes of death.

z = w + q2 in the diagram.

q2 = the portion of the cohort who *would* die of other causes if they were not stomach cancer patients but who *could* die instead of stomach cancer (because they are in fact stomach cancer patients).

= the portion of those who *would* die of stomach cancer if there were no other causes of death who *could* die instead of other causes (because there are in fact other causes of death).

= the intersection of z and q.

We assume that, of those who could die of either stomach cancer or other causes (q2), half will die of stomach cancer and half will die of other causes. Because this is a very small portion of the cohort, even if the split is not exactly 50-50, this should affect the results only minimally.

Let:

a = the proportion of the cohort who actually die of stomach cancer (= the probability of dying of stomach cancer in the stomach cancer cohort), and
b = the proportion of the cohort who actually die of other causes (= the probability of dying of other causes in the stomach cancer cohort).

Then:

a = $w + 0.5 \times q2$, and
b = $q1 + 0.5 \times q2 = (q - q2) + 0.5 \times q2 = q - 0.5 \times q2$

Because:

w = $1 - p - q$ (see diagram), and
a = $1 - p - q + 0.5 \times q2$

To solve for q2 in terms of known quantities (p and q), we use the following (see the diagram):

$$\frac{q2}{q} = \frac{w}{(w + p)} \quad .$$

(Recall that $q = q1 + q2$). This implies that

$$q2 = q \times \frac{w}{(w + p)} \quad .$$

We also know that w = 1 - p - q (see diagram). Substituting this into the above equation, we get q2 as a function of p and q, both of which are known:

$$q2 = \left(\frac{q}{1-q}\right) \times (1 - p - q) \quad .$$

We can now derive a and b, given q2.

In summary,

$$q2 = \left(\frac{q}{1-q}\right) \times (1 - p - q) \quad .$$

where, recall, *a* is the probability of a stomach cancer patient dying of stomach cancer during the *n*th year and *b* is the probability of a stomach cancer patient dying of other causes during the *n*th year.

$$a = 1 - p - q + 0.5 \times q2$$

$$b = q - 0.5 \times q2$$

CHAPTER II.4. COST OF KIDNEY CANCER

Clicking on the sections below will take you to the relevant text.

CHAPTER II.4. COST OF KIDNEY CANCER

II.4.A Background

This chapter contains a discussion of the methods used and results of estimating the direct medical costs incurred by kidney cancer patients. It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter II.1 contains information regarding cancer causality, a list of known and suspected carcinogens, and information on cancer cost estimation.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and II.1
Link to inflation factors

II.4.A.1 Description

Kidney cancer is a malignancy within the kidneys and may be localized or have spread to multiple sites (Bennet and Plum 1996). It represents one to three percent of all adult cancers in the United States (Javadpour 1984, Klein et al., 1993). Kidney cancer occurs most frequently in individuals in their fifties through seventies, with two to three times as many males as females developing the disease (NCI 1994, Javadpour 1984, Klein et al., 1993, Montie et al., 1990). Approximately 25,300 new cases of kidney cancer were diagnosed in 1991 in the U.S. (NCI 1994).

According to the National Cancer Institute (NCI 1994), the incidence of kidney cancer in the U.S. has increased by over 30 percent over the past 20 years, from a rate of 6.7 per 100,000 in 1973 to 8.8 per 100,00 in 1991. Although this increase may be attributed in part to improved detection techniques, a concurrent rise in mortality due to kidney cancer indicates that there has been a real increase in disease incidence in the U.S. over time (McCredie 1994). Reported rates of kidney cancer incidence and mortality have increased worldwide in the past decades, particularly in more industrialized countries. According to McCredie (1994), kidney cancer is likely to become the most common urinary cancer in the coming decades, and one of the major cancers of affluent societies, unless its etiology can be better identified and addressed.

II.4.A.2 Concurrent Effects

No data were located indicating that concurrent effects unrelated to kidney cancer or its treatment were likely to occur with this disease. Secondary cancers and other adverse health effects may occur due to treatment and therapy. These can incur added medical costs not considered in this chapter.

II.4.A.3 Causality

Carcinogens suspected of causing renal cancer in human study groups include hormones, radiation, certain viruses, tobacco smoking, phenacetin-containing analgesics, paracetamol, obesity and hypertension (or drugs used for their treatment), asbestos, and renal injury (Javadpour 1984, McCredie 1994). Kidney cancer has been induced in experimental animals via exposure to chemical, physical, viral, and hormonal agents; radiation; and dietary deficiencies (Konishi et al., 1994, Javadpour 1984). Epidemiological data show significantly greater frequencies of kidney cancer in cigar smokers, smokers with occupational exposures to cadmium, petroleum industry workers, and possibly workers with occupational exposures to lead. Kidney toxins, such as unleaded gasoline, have demonstrated carcinogenic potential in chronic bioassays in animals (Konishi et al., 1994). Other risk factors appear to be linked to a more affluent lifestyle, including diet; and perhaps to increasing industrial exposure in some localities (McCredie 1994). As is often the case with cancers, however, it is difficult to prove causality. McCredie (1994), for example, hypothesizes that the general effect of changes in standard of living is a significant cause of the increased incidence of kidney cancer.

Table II.1-1 in Chapter II.1 contains a list of chemicals known to cause or suspected of causing cancer (as reported in the EPA databases IRIS, HEAST, and HSDB). Most chemicals in the table were carcinogenic in animal studies. These studies do not provide organ-specific data because it is not generally assumed that cancer induction will always occur at the same site in humans as in animals. Consequently, the chemicals listed in Table II-1 may cause kidney cancer and/or other types of cancer. Evaluation of the likelihood of this occurrence would require additional research (risk assessment).

Link to Table II.I-1

II.4.A.4 Treatments and Services

Kidney cancer is slow to develop, and may reach relatively advanced stages before detection. Symptoms may include fever, weight loss, generalized weakness, abdominal pain, abnormal increases in red blood cells or blood calcium levels, anemia, bloody urine, cardiac enlargement, or liver dysfunction without evidence of liver cancer. Advances in diagnostic techniques, such as bone scanning, chest tomography, computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI) have greatly improved the diagnosis of kidney cancer, though have not yet increased survival rates (Javadpour, 1984).

The only effective therapy for kidney cancer is surgical excision (often involving removal of the kidney, adrenal gland, associated fat, and regional lymph nodes) before it has a chance to spread to other organs or metastasize to distant sites in the body (Javadpour 1984, Klein et al., 1993). Chemotherapy, radiotherapy, and hormone therapy have all proven ineffective as a systemic treatment for kidney cancer. Immunotherapy (also known as biologic response modifier (BRM) therapy), though still experimental, may prove valuable in treating advanced kidney cancer (Klein et al., 1993, Montie et al., 1990).

II.4.A.5 Prognosis

Overall, the five-year survival rate in the U.S. for all kidney cancer patients is only about 54 percent (McCredie 1994) and the six-year survival is approximately 50 percent (NCI, 1998, based on patients diagnosed in 1987). Kidney cancer can and does metastasize to most areas of the body, most commonly the lymph nodes, lungs, liver, and bones (Montie et al., 1990). More than half of all new patients are diagnosed with regionally advanced or metastatic kidney cancer (Klein et al., 1993). Although kidney cancer can include spontaneous regressions and long survival in the presence of metastatic disease, there is currently no effective treatment of metastatic kidney cancer, and prognosis for these patients is very poor (Javadpour 1984, Montie et al., 1990). Patients with advanced kidney cancer face a median survival of ten months and a one to two percent chance of surviving five years or more (Klein et al., 1993).

II.4.B. Costs of Treatment and Services

II.4.B.1 Methodology

This chapter estimates the per-patient lifetime direct medical costs of treating kidney cancer based on the work of Baker et al. (1989 and 1991). Baker et al. used the Continuous Medicare History Sample File (CMHSF) to estimate average per-patient medical costs of treating kidney cancer. They chose CMHSF because: (1) it is a nationally representative sample of

the Medicare population (5 percent), covering over 1.6 million patients; (2) it is longitudinal, dating from 1974 to 1981; and (3) it captures the majority of medical expenses for each beneficiary.

Five Medicare files are included in the CMHSF, which cover:

1) inpatient hospital stays,
2) skilled nursing facility stays,
3) home health agency charges,
4) physician services, and
5) outpatient and other medical services.[1]

Baker et al. calculated the average medical costs of Medicare patients with kidney cancer, as well as the average medical costs of a randomly-selected sample of Medicare patients without cancer (i.e., baseline costs). To estimate costs attributable to kidney cancer, this report subtracts baseline costs from the costs of patients with kidney cancer. An alternative approach would have been to examine the medical services used by patients with kidney cancer and make judgments, based on the nature of each service, about whether its use was attributable to kidney cancer. This second method is more complicated and requires that the motivation for medical services be inferred.

Because CMHSF provides no indication of initial diagnosis, Baker et al. assumed that a kidney cancer diagnosis appearing on a hospitalization record after a minimum of one year without a kidney cancer diagnosis indicated disease onset. This assumption would seem to hold true for a majority of cases because of the high frequency of surgery and hospitalization associated with initial treatment of kidney cancer (Klein et al., 1993). Only patients with an initial diagnosis during the years covered by the database were included.

The number of Medicare beneficiaries included in the kidney cancer subset of the CMHSF, as defined by Baker et al., was 1,953. The random subset of non-cancer patients, called the "co-morbidity subset" by the authors, consisted of every 16th beneficiary contained in the CMHSF who had not been hospitalized for cancer. Given that the CMHSF database contains approximately 1.6 million accounts, the co-morbidity subset represents about 100,000 individuals.

Baker et al. estimated total costs associated with three phases of treatment:

[1] See Baker et al., 1991 for further details.

Initial: all costs appearing on a beneficiary's record for up to three months following diagnosis;

Terminal: all costs appearing on a beneficiary's record within six months of death; and

Maintenance (intermediate phase): all costs incurred between these two periods (calculated as an average monthly cost).

These periods differ significantly in intensity and cost of related medical care. Initial therapy generally includes intensive diagnostic testing and surgical removal of the tumor, incurring very high medical costs over the approximately three months following initial diagnosis. If this treatment is successful, a cancer patient will undergo a period of remission, during which little medical treatment is given apart from monitoring for potential cancer recurrence.

For the approximately fifty percent (NCI 1994) of patients who eventually die of kidney cancer, a third phase of intensive terminal care (involving further surgery, radiation, and/or other measures to alleviate symptoms) takes place over approximately the last six months of their lives, which again incurs substantial medical costs. According to Baker et al., the pattern of initial, maintenance, and terminal care treatment phases is apparently little affected by differences in total survival time of the patient; the major difference is in the length of the maintenance phase (Baker et al., 1991). Because Baker et al. (1989) calculated *monthly* maintenance phase costs but not the duration of the maintenance phase, this report calculates average *lifetime* maintenance phase costs based on survival rate data.

Baker et al. made four adjustments to the cost estimates calculated from the CMHSF. First, they added charges for skilled nursing facilities (SNFs) that were not covered by Medicare by multiplying the "length of stay" at an SNF (computed from admission and discharge dates) by the average daily SNF charge.[2] Second, they added the annual Medicare Part B deductible of $60 to the reimbursed charges in the database. Third, since Medicare only pays 80 percent of physicians' charges, they scaled these reimbursements up to 100 percent of physician charges to better reflect social costs. Finally, they inflated all dollar values to 1984 dollars using the Medical Care component of the Consumer Price Index.

[2] Where no discharge date was given, Dec 31, 1981 (the end of the file) was used as the discharge date. This likely underestimates SNF stays and therefore overall costs for some patients.

II.4.B.2 Results

II.4.B.2.1 Treatment Phase Costs

Costs were estimated for each treatment phase, using the methodology described above for Baker et al. Their cost estimates are given in 1984 dollars. Table II.4-1 shows average undiscounted total (non-incremental) charges incurred over the three phases of kidney cancer treatment. The comorbidity charges corresponding to the duration of each treatment period are also listed.

Table II.4-1
Average Patient Charges Per Treatment Phase of Kidney Cancer, in 1984 dollars

	Kidney cancer treatment charges	Co-morbidity charges[a]
Initial (Total Over 3 Months)	$12,608	$747
Maintenance (Average per Minth)	$670	$249
Terminal (Total Over 6 Months)	$19,302	$1,494

Source: Baker, et al., 1989 and 1991 (for background costs).
[a] From Baker et al. (1991) This is the average cost of medical care for patients not undergoing treatment for cancer.

Table II.4-1 also includes co-morbidity charges (i.e., baseline charges) from Baker et al. (1991). Co-morbidity charges for initial, maintenance, and terminal phase treatment are $747 total, $249/month, and $1,494 total, respectively.[3] These charges are subtracted from the charges associated with kidney cancer to yield net charges for the treatment of kidney cancer.

Baker et al. (1989) provides only summary charges for each of the treatment phases; cost associated with each of the treatment components (i.e., inpatient hospital stays, skilled nursing facility stays, home health agency charges, physician services, outpatient services, and other medical services) were not listed in the report.

[3] Co-morbidity charges of $249 per month were reported in Baker et al.'s analysis of breast and lung cancer (1991). The charges represent medical costs for a random sample of the Medicare population without cancer *with age distribution matching that of the breast and lung cancer subsets*. Co-morbidity charges for a sample matching the age distribution of the population with kidney cancer may vary slightly.

II.4.B.2.2 Lifetime Cost Estimates

Lifetime costs of treating kidney cancer were calculated using the following information:

1. the charges per phase (presented above),

2. an estimate of the average length of the maintenance phase of treatment, and

3. the percentage of patients who survive the disease.

Survival data from the National Cancer Institute (NCI) indicate that approximately 50 percent of the patients who die of kidney cancer do so within one year of diagnosis. The NCI data cover a diagnostic period from 1974 to 1981. Although survival rates have improved, the distribution of the occurrence of death is not expected to have changed substantially. This is supported by Klein et al (1993), who found that more than half of all new cases are diagnosed with regionally advanced or metastatic disease. The median survival for patients with metastatic disease is approximately ten months (Klein et al. 1993). The terminal charges are therefore assumed to occur within one year of diagnosis, on average.

It is more difficult to determine the average period of maintenance. NCI data indicate that the *average* relative survival rate is 49.8 percent at six years after diagnosis.[4] For the purposes of this analysis the average life span for a person diagnosed with kidney cancer was assumed to be six years post-diagnosis. Using this value, the average maintenance period was assumed to be 5.25 years, after adjusting for initial care and terminal care. Many patients will receive a longer or shorter period of maintenance care; however, this is a reasonable estimate based on available information. This approach is an approximation, and may be refined in the future. It is likely to underestimate medical costs due to the improved prognosis and survival duration of kidney cancer patients in recent years leading to longer periods of maintenance care.

To determine the average lifetime incremental medical costs associated with kidney cancer, the following calculations were used:

Initial phase costs attributable to kidney cancer were calculated using $12,608 in gross charges from Table II.4-1 minus $747 in co-morbidity charges to obtain a cost of $11,861.

[4] The relative survival rate (RSR) is an approximation of the survival rate, adjusted for background mortality. For a detailed discussion of RSR see Chapter II.2.

Link to Chapter II.2

Maintenance period charges were first calculated at $670/month from Table II.4-1 multiplied by 63 months or 5.25 years. Sixty-three months were estimated as the maintenance period based on a six-year average post-diagnosis survival, minus three months initial phase and six months terminal phase care. The average co-morbidity charges of $15,687 ($249/month multiplied by 63 months) for the maintenance phase were subtracted from the gross maintenance phase costs to obtain undiscounted annual maintenance phase charges attributable to kidney cancer of $26,523.

Terminal costs attributable to kidney cancer were estimated by subtracting co-morbidity charges of $1,494 from $19,302 (the gross charges for terminal care for kidney cancer patients) to obtain an incremental cost of $17,808. As noted previously, approximately 50 percent of patients with kidney cancer ultimately die of the disease. Therefore the terminal costs were multiplied by .5 to obtain an estimated average cost for this phase of $8,904.

Total Costs. Table II.4-2 shows Baker et al.'s values for the incremental medical costs for each phase. The total costs were modified by the comorbidity costs (as shown in Table II.4-1).

Table II.4-2
Average Incremental Per Patient Charges in 1984 dollars (undiscounted)

	Incremental Costs	Total cost
Initial (3 months care)	$11,861	
Maintenance (5.25 years care [a])	$26,523	
Terminal (6 months care[b])	$8,904	
	$11,861	$47,288

Source: Table II.4-2, modified per text to obtain incremental charges.
[a] Six-year assumed life span minus 3 months of initial treatment and 6 months of terminal treatment.
[b] Terminal costs are incurred by only 50 percent of patients and were adjusted accordingly.

The costs shown in Table II.4-2 were used to calculate the discounted incremental per capital direct medical costs in 1996 dollars (based on the Consumer Price Index ratio (CPI-U) for medical care, 1996:1984=2.14). Both initial phase and terminal phase charges are present values because they occur in the first year post-diagnosis. Those patients who will die of kidney cancer do so, on average, within ten months of diagnosis. As noted previously, terminal charges were adjusted to reflect the fact that approximately 50 percent of patients incur terminal charges. Maintenance care is assumed to be provided over a period of 5.25 years and is discounted accordingly. (This calculation may be modified in the future as

additional information is obtained on the duration of maintenance care.) Present value maintenance phase charges are:

$26,523 using a zero percent discount rate

$24,747 using a three percent discount rate

$23,682 using a five percent discount rate

$22,702 using a seven percent discount rate

The undiscounted initial and terminal costs were summed with the various discounted maintenance care charges to obtain the total incremental per capita medical costs, as shown in Table II.4-3.

Table II.4-3
Incremental Direct Medical Costs of Lifetime per Capita Treatment of Kidney Cancer in 1984 and 1996 Dollars with Various Discount Rates [a] (1996:1984 = 2.14)

	Present Value of Attributable Charges (Discount Rate %)			
	0	3	5	7
Lifetime Charges 1984 dollars	47,288	45,512	44,417	43,467
Lifetime Charges 1996 dollars[d]	96,916	97,396	95,117	93,019

[a] Treatment components are discounted based on when they occur in the course of treatment. See text for discussion.
The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

II.4.B.3 Limitations

There are many limitations in cancer cost estimation. Those common to most cancers are discussed in the introductory cancer chapter: II.2.

Link to Chapter II.2

There are a number of limitations to the use of the Baker et al. data, many of which the authors have noted. These limitations are primarily related to the use of CMHSF (Medicare) data. First, Medicare does not cover all potential kidney cancer patients; it covers only most persons 65 and over, disabled persons entitled to Social Security cash benefits for at least 24

months, and most persons with end-stage kidney disease (Baker et al. 1991). All patients not covered by Medicare are excluded from the database, including all non-disabled people under 65 and those over 65 using private health insurance. Given that approximately half of all kidney cancer patients are under 65 (NCI 1994), the CMHSF excludes a significant number of younger patients. Approximately 95 percent of Americans 65 and over, however, are enrolled in Medicare (Baker et al. 1991).[5] Differences in medical costs incurred by senior citizens not using Medicare, or using it for only a portion of their costs, could lead to an underestimate of medical costs.

Medicare also does not cover self-administered drugs, intermediate nursing care, long-term nursing care, and expensive, extraordinary treatments (such as bone marrow transplants). For some patients these may represent significant percentages of their total treatment costs. To the extent that 1) younger patients receive more aggressive (and therefore more expensive) medical treatment for kidney cancer and 2) Medicare beneficiaries use medical care not covered by Medicare, the values in the CMHSF database will underestimate medical costs.

A minor drawback of the Baker et al. data is due to the researchers' inability to identify cancer patients in CMHSF whose diagnosis and first course of therapy did not involve hospitalization. For most kidney cancer patients the first course of therapy involves major surgery. Consequently, the omission of non-hospitalized patients is likely to result in a negligible underestimate of medical costs.

The reliability of the data contained in the CMHSF database varies. An independent analysis of CMHSF performed in 1977 by the Institute of Medicine of the National Academy of Sciences found that the frequency of discrepancies in principal diagnoses varied among diseases (Baker et al., 1991). It is unclear whether the presence of misnamed diagnoses contained in CMHSF potentially increase or decrease the resultant cost estimates.

Since Baker et al. include only those costs *after* the initial diagnosis, they omit costs associated with prediagnostic tests and treatment. Although these costs could be significant, substantial medical treatment (e.g., tests requiring hospitalization) would also likely result in a diagnosis and thus be included in Baker et al.'s analysis. This omission likely causes the values generated by Baker et al. to somewhat underestimate direct medical costs from the treatment of kidney cancer.

Another limitation to using the Baker data is its age. The most recent data used by Baker is more than a decade old. Although many aspects of

[5] This figure represents those enrolled in Medicare Part A; 95 percent of those enrolled in Medicare Part A choose also to enroll in Medicare Part B.

treatment have remained constant, new diagnostic methods and treatments such as immunotherapy have potentially increased lifetime treatment costs. Improved diagnostic procedures such as CT scans, ultrasonography, and MRI (McCredie 1994) have led to earlier diagnoses and treatment. The lack of data on new treatment methods may cause costs to be underestimated.

Age of the data is also a problem with regard to survival statistics. NCI maintains current survival information, but the survival prospects for a patient diagnosed now are better than in previous decades. Since long-term survival can only be evaluated retrospectively, there is uncertainty in estimations of survival for current patients based on past survival patterns.

An additional limitation of this analysis is that medical costs incurred as a result of kidney cancer, but not considered by Baker et al., may arise as a result of treatment for kidney cancer. Secondary cancers and other adverse health effects may occur due to radiation, chemotherapy treatment, and other therapies. These effects may occur substantially after the cancer treatment has been completed and can incur added medical costs not considered in this chapter.

One limitation of the cost estimates that is directly related to the analytical method used in this chapter is the lack of a yearly sequential analysis of costs. A more precise method for estimating direct medical costs would include year-to-year information on treatment and survival, with costs determined using an estimate of the proportion of patients surviving each year and those who died due to natural causes or kidney cancer. When this chapter was developed, that method was not yet in use for this handbook. (See Chapter III.2 for a more complete discussion of the new method.) Average durations of treatment and survival were used in this analysis and are likely to provide a good approximation of the costs that would be obtained through a more detailed and complex analysis.

Link to Chapter II.2

II.4.C. Conclusions

Overall, despite the limitations described above, Baker's analysis of the CMHSF data represents the most nationally-representative per-patient lifetime estimate of the direct medical costs of treating kidney cancer available. Their cost estimates are based on sound criteria and reasonably current data, since the treatment of kidney cancer has not changed substantially since Baker et al.'s analysis. The authors have made adjustments for many of the factors that can be quantitatively modified (e.g., Medicare's underpayment for services).

Because more of the uncertainties in their analysis appear to underestimate costs (e.g., population covered, changes in treatment, and omission of pre-diagnostic costs), the net result is a likely underestimation of actual direct medical costs. This tendency toward underestimation can be noted when using the cost estimates in this chapter in a benefits assessment.

CHAPTER II.5: COST OF LUNG CANCER

Clicking on the sections below will take you to the relevant text.

CHAPTER II.5: COST OF LUNG CANCER

This chapter contains a discussion of the methods used and results of estimating the direct medical costs incurred by lung cancer patients. It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter II.1 contains information regarding cancer causality, a list of known and suspected carcinogens, and information on cancer cost estimation.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and II.1
Link to inflation factors

II.5.A Background

II.5.A.1 Description

Lung cancer is the most frequent cause of cancer death in men and women in the United States (Feld et al., 1995). There were approximately 173,000 cases of lung cancer diagnosed in 1994 in the United States and approximately 150,000 lung cancer deaths occurred in that year (NCI, 1998). The increase in overall deaths per year from 18,000 in 1950 and 125,000 in 1988 to the current level is due, in part, to a more than five-fold increase in lung cancer death rates (per 100,000) among women. This increase is likely to be due to increased smoking rates (Bennett and Plum, 1996). Lung cancer is fatal in over 88 percent of all cases (NCI, 1998).

Lung cancer is a malignancy within the lungs and may be localized or have spread to multiple sites (Bennet and Plum 1996). All types of lung cancer likely originate from a common pluripotent stem cell. There are four types of lung cancer: squamous (epidermoid), adenocarcinoma, large cell, and small cell (oat cell). The first three types are often grouped together as non-small cell lung cancer (NSCLC). These three types, which comprise 75 to 80 percent of all lung cancers, have different natural histories and respond differently than small cell lung cancer to therapies. There are also very rare types of lung cancer (with an approximate incidence of two percent) that include adenosquamous mixed tumor or mixed small cell and non-small cell histologies (Feld et al., 1995). Survival data from the National Cancer Institute (1998) and cost data from Baker et al. (1989) that are used in this chapter do not provide quantitative information for different types of lung cancer. Consequently, this chapter contains an

evaluation of all types of lung cancer in aggregate. In addition, most risk assessments that would be used in evaluating benefits do not specify the type of lung cancer. If a specific type of lung cancer is of concern, Feld et al. (1995) may be consulted for additional information regarding prognostic information and treatment; however, the quantitative data are limited.

New discoveries may, have an impact on the diagnosis and understanding of the causality of lung cancer in the future. Cytogenic abnormalities have been demonstrated in lung cancer cells including lesions in chromosome region 3p, which occurs as an early event in the biology of the tumor. Mutation of the p53 gene is the most frequently identified genetic change in human lung cancer. Activated proto-oncogenes are seen in lung cancer and may arise from point mutations in the level of expression. Some of the above changes may be used in the future for early detection of lung cancer. Screening programs in the past, using more traditional diagnostic measures, have not been successful in reducing lung cancer mortality among study participants (Feld et al., 1995). [1]

Lung cancer occurs with much greater frequency among the elderly, which is typical of most cancers. The average age at diagnosis is approximately 68 years. Less than two percent of lung cancers are diagnosed before the age of 40 and five percent are diagnosed over the age of 85 (NCI, 1998). The distribution of the age at diagnosis of lung cancer is shown in Figure II.5-1. The steep incline in the probability of lung cancer diagnosis is clear in this diagram, with a peak around 68 years of age. Approximately 50 percent of all lung cancer cases are diagnosed in the relatively small age interval of 60 to 75 years. The data used to generate Figure II.5-1 are shown in Table II.5-1. The cumulative percents of lung cancer at various ages were calculated using the population-weighted distribution of occurrence.

[1]The above information is not currently used in a manner that alters the survival or costs associated with lung cancer.

Figure II.5-1

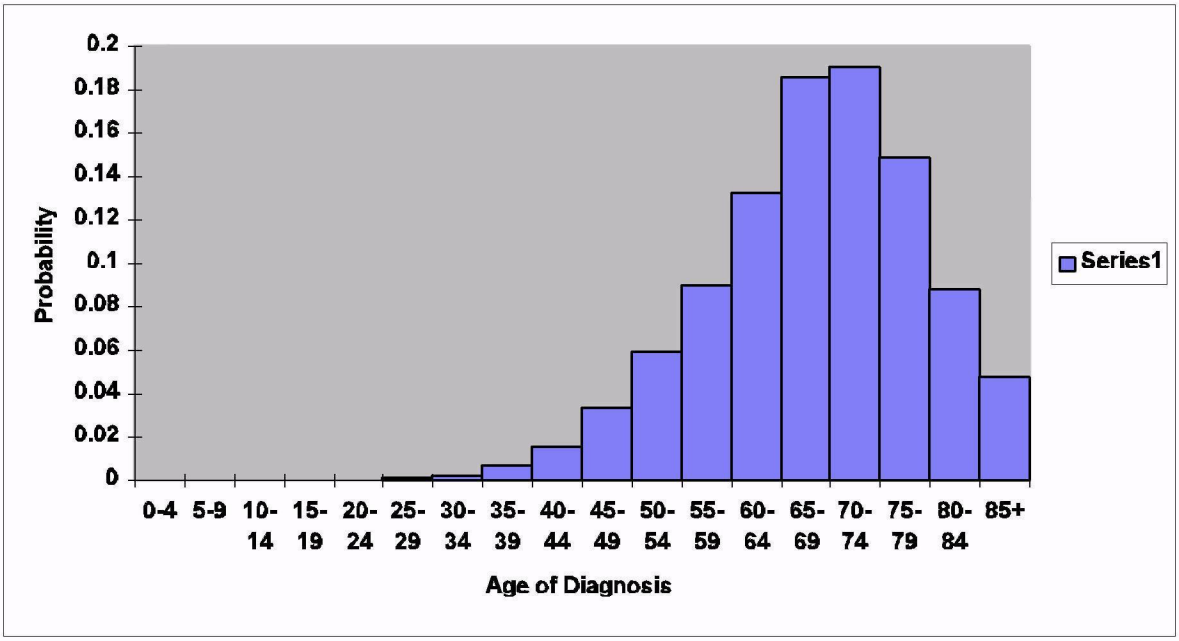


Table II.5-1. Age-specific Incidence of Lung Cancer			
Age Group	Age-specific Rate of Diagnosis Per 100,000	Percent of All Lung Cancer Occurring in Age Group	Cumulative Percent of Lung Cancer
0 - 14	0.0	0.0	0.0
15 - 34	2.8	0.30	0.34
35 - 39	5.2	0.7	1.0
40 - 44	13.0	1.5	2.5
45 - 49	34.5	3.3	5.8
50 - 54	77.7	5.9	11.8
55 - 59	141.0	8.9	20.7
60 - 64	226.7	13.2	33.9
65 - 69	321.5	18.6	52.5
70 - 74	375.2	19.0	71.5
75 - 79	391.1	14.9	86.4
80 - 84	349.3	8.8	95.2
85+	233.4	4.8	100.0
Based on NCI, 1998			

The age-specific incidence data were used in the Section B medical cost calculations. Data on incidence and age at diagnosis were obtained from NCI's Surveillance, Epidemiology, and End Results (SEER) reports and tables, obtained online in 1998 through the NCI Website at: http://www-seer.ims.nci.nih.gov.

II.5.A.2 Concurrent Effects

As with all cancers, lung cancer may spread to other organs. In addition, treatment of cancer, which usually includes chemotherapy, radiation, and surgery, has numerous adverse side effects and may, in itself, lead to death. For example, vinca alkaloids, used in lung chemotherapy, cause peripheral neuropathy in some patients. Radiation treatments of cancer have led to increased risks of other types of cancer, sterility, etc. Surgery, especially the removal of a lung, may cause long-term changes in health status, including reduced capacity or increased susceptibility to respiratory disease that may lead to death. These effects are associated with additional medical costs not considered in this chapter.

There is a strong link between lung cancer and smoking. Lung cancer patients are much more likely to have smoked than people who have not been diagnosed with lung cancer. Smoking is also associated with increased risks of many other diseases, including other cancers. There is no indication, however, that lung cancer *causes* these other diseases. The simultaneous or sequential occurrence of the diseases are likely due to their common causal link to smoking.

No data were located indicating that concurrent effects unrelated to lung cancer or its treatment were likely to occur as a result of this disease, although the same pollutants that cause lung cancer, especially respiratory irritants (e.g., silica, nickel), may cause other adverse effects. These effects can incur added medical costs not considered in this chapter. The risk assessment that serves as the basis for a benefits evaluation should include all adverse effects that are anticipated to result from exposure to the agent of interest.

II.5.A.3 Causality & Special Susceptibilities

As noted above, lung cancer is caused by exposure to tobacco smoke. It is also associated with certain air pollutants, such as radon and silica, and chemical pollutants. Table II-1 in Chapter II contains a list of chemicals known to cause or suspected of causing cancer (as reported in the EPA databases IRIS, HEAST, and HSDB). Most chemicals in the table were carcinogenic in animal studies. These studies do not provide organ-specific data because it is not generally assumed that cancer induction will necessarily occur at the same site in humans as in animals. Consequently, the chemicals listed in Table II-1 may cause lung cancer and/or other types of cancer. Evaluation of the likelihood of this occurrence would require additional research (risk assessment).

Link to Table II.1-1

NCI provides age-, sex-, and race-specific data regarding diagnosis of lung cancer from 1990 to 1994, which may be used to evaluate susceptibilities among population subgroups. The data must be used with care because diagnostic rates indicate occurrence only, and may, or may not indicate differences in susceptibility. See Chapter I.1 for a more detailed discussion of susceptibilities.

Link to Chapter I.1

NCI lung cancer diagnosis and mortality data show higher diagnosis and death rates among men than women. Lung cancer rates have been declining over the past 22 years among males under 65 years of age, however, while. lung cancer has been increasing in women. These dynamics have been attributed to a tapering off of smoking rates in males and a rapidly increasing rate of smoking among women in recent decades (NCI, 1998).

The rate of diagnosis among black males in 1994 was approximately 50 percent higher than among white males, which cannot be fully explained by smoking differences. The increased rate of lung cancer among black males may be due to exposure to pollutants in the workplace or ambient environment, exposure to carcinogens through other sources, or an inherently greater susceptibility to lung cancer among blacks (NCI, 1998). Some genetic factors have been identified that may increase the risk of lung cancer. Individuals who metabolize debrisoquine readily, as well as those lacking the MU phenotype of glutathione transferase, have an increased lung cancer risk. There is also evidence for Mendelian inheritance of lung cancer, indicating the importance of family history (Feld et al., 1995).

II.5.A.4 Treatments and Services

As noted above, lung cancer is usually treated with surgery, chemotherapy, and/or radiation, depending on the type of lung cancer, the stage of cancer at diagnosis, patient health, and other factors. The treatment of lung cancer can be defined more precisely by histologic type and specific location of the cancer in the lung. In this analysis, which is concerned with the average cost for all lung cancers, all histologic types and sub-sites are considered together.

Treatment is carried out in phases including initial diagnosis, initial treatment, follow-up and maintenance treatment, and, for those who do not survive, terminal treatment and palliative care. Some components of each treatment are unique to each phase, but most medical activities and services may occur more than once over the course of the disease from diagnosis to death or cure. For example, X-rays may be used in diagnosis, to provide ongoing status updates, to assist in determining initial and subsequent surgical and other treatment interventions, etc.

Initial diagnostic activities may include an evaluation of signs and symptoms, chest X-rays, computed tomography (CT) of the chest, magnetic resonance imaging (MRI) of the chest, sputum cytological analysis, percutaneous aspiration of pulmonary nodules, bronchoscopy, mediastinoscopy, thorascopy, thoracotomy, and other procedures. Staging of the disease occurs during this phase and is critical to determination of subsequent medical actions (Feld et al., 1995). Surgery is usually performed, and is associated with a relatively low mortality rate. Radiation and/or chemotherapy may be done with or without surgery. In many patients cancer has spread to the central nervous system, abdomen, bone marrow, and other areas, requiring additional treatment strategies (Feld et al., 1995).

Due to its poor prognosis, most patients receive terminal care. This care may include a variety of medical services, long-term care in a nursing facility, palliative care, family counseling, etc.

II.5.A.5 Prognosis

II.5.A.5.1 Background

As noted above, the overall prognosis for lung cancer patients is poor, with an average of 88 percent of patients dying of the disease within 10 years. Most deaths from lung cancer occur in the first four years, and approximately 60 percent of all patients die during the first year (NCI, 1998). Patients with early stages (I and II) of the disease have a 40 to 85 percent five-year survival rate (Bennet and Plum, 1996). Unfortunately, most diagnoses occur at later stages of the disease. Factors such as tumor size and location, histology, involvement of nodes, and the spread of cancer to other tissues affect outcome. Numerous new biochemical and immunological tests are used to provide additional information on the likely outcome (Feld et al., 1995).

II.5.A.5.2 Relative Survival Rates (RSRs)

The NCI SEER data reports were accessed online to obtain information regarding mortality and survival probabilities and the duration after diagnosis until death (NCI, 1998). Basic survival statistics on lung cancer are provided in this section because they relate to prognosis. Methods used to convert the NCI statistics to survival probabilities are discussed briefly in this section and in detail in Chapter II.2 on stomach cancer.

Link to Chapter II.2

NCI provides the RSR for each year post-diagnosis. The RSR is the number of observed survivors among these patients, divided by the number

of "expected" survivors among persons with the same age and gender in the general population (observed/expected). The equation for this is:

$$RSR = \frac{observed\ survival\ rate\ among\ cancer\ patients}{survival\ rate\ among\ age-\ and\ sex-matched\ cohort\ in\ the\ general\ population}$$

The RSR takes into account that there are competing causes of death that increase with age. The RSR for lung cancer patients during the first year post-diagnosis is 41 percent (NCI, 1998). A person with lung cancer would therefore have, on average, a one-year survival probability that is 41 percent of someone of the same age and gender in the general population. The RSRs provided by NCI for each year post-diagnosis are averages over all ages at diagnosis. An evaluation of the RSRs over the past 20 years indicates that they have increased by about 33 percent, with most of the progress occurring in the early 1970s (NCI, 1998). The most current information, the rates for 1988 through 1993, was used for the first through fifth years post-diagnosis Ten years of data were used to estimate survival for the sixth through tenth years post-diagnosis due to the need for a longer time span. Table II.5-2 lists the average RSRs for lung cancer for the first ten years post-diagnosis. The RSRs shown in Table II.5-2 were used to derive survival probabilities for lung cancer patients for each of the first ten years post-diagnosis.[2]

Table II.5-2. Average RSRs* for Lung Cancer for the First 10 Years Post Diagnosis

Years Post-Diagnosis (n)	Average RSR for n Years Post-Diagnosis
1	0.41
2	0.24
3	0.18
4	0.15
5	0.14
6	0.12
7	0.12
8	0.11
9	0.10
10	0.10

*The average RSR for each year post-diagnosis is the average of a set of RSRs reported by NCI (1998) as described in the text above.

[2] All vital statistic data in this document applicable to the general population were obtained from the National Center for Health Statistics (NCHS) Vital Statistics in the United States (NCHS, 1993).

Although most lung cancer patients will die of lung cancer, some may die of other causes. The probability of a lung cancer patient dying of causes other than lung cancer cannot be assumed to be the same as the probability of someone in the general population dying of other causes, particularly in the first few years post-diagnosis, when a lung cancer patient's probability of dying of lung cancer is quite high.[3]

The probability of a lung cancer patient dying of lung cancer and the probability of a lung cancer patient dying of some cause other than lung cancer in the *n*th year post-diagnosis, given survival to the *n*th year, were each derived from two known probabilities:

1) the probability of a lung cancer patient surviving through the *n*th year post-diagnosis, given survival to the *n*th year, and

2) the probability of a lung cancer patient dying of causes other than lung cancer in a matched cohort in the general population.

The derivation is explained in detail in the Appendix to Chapter II.2.

Link to Chapter II.2, Appendix II.2-A

Because each of the known probabilities depends on the number of years post-diagnosis and (minimally) on age at diagnosis, the derived probabilities were calculated for each of the ten years post-diagnosis and for the average age at diagnosis (68 years).[4] The following probabilities are shown in Table II.5-3:

1) survival through the *n*th year,
2) dying of lung cancer during the *n*th year, and
3) dying of some other cause during the *n*th year.

Probabilities of survival and dying of all causes among all members of the general population aged 68 were obtained from the National Center for Health Statistics (NCHS) Vital Statistics in the United States (NCHS,

[3] This difference becomes clear in the extreme case in which the probability of dying of an illness is extremely high. Suppose, for example, that the probability of dying of all causes except for illness X is 0.025 in the general population. Suppose that in a cohort of patients diagnosed with illness X, the probability of dying from illness X in the first year post-diagnosis is 0.99. If the probability of dying of other causes in this cohort equaled that in the general population (0.025), then the probability of someone in the cohort dying would be greater than 1.0.

[4] Ten years is a generous follow-up period during which most individuals who will die of lung cancer have done so. It is also used as a reasonable maximum duration of maintenance care and treatment for those who do not die of lung cancer.

1993). These probabilities are also shown in Table II.5-3. The values in this table are used in Section II.5.B to calculate the expected medical costs of lung cancer patients.

Table II.5-3. Probabilities of Survival and Mortality for Lung Cancer Patient Diagnosed at Age 68[a]

Years post-diagnosis (n)	A Cohort in the General Population (Matched)		A Cohort of Lung Cancer Patients			
	Probability of surviving n years	Probability of dying in *n*th year of causes other than lung cancer, given survival to the *n*th year[b]	Relative Survival Rate[c]	Probability of surviving through the *n*th year post-diagnosis[d]	Probability of dying of lung cancer in the *n*th year post-diagnosis[e]	Probability of dying of other causes in the *n*th year post-diagnosis[f]
0	1.000	---	---	1.0	---	---
1	.977	.023	.41	.401	.586	.014
2	.953	.025	.24	.229	.165	.007
3	.928	.027	.18	.167	.057	.005
4	.901	.029	.15	.135	.028	.004
5	.872	.031	.14	.122	.009	.004
6	.843	.034	.12	.101	.018	.003
7	.812	.037	.12	.097	.000	.003
8	.779	.040	.11	.086	.008	.003
9	.745	.044	.10	.075	.008	.003
10	.710	.047	.10	.071	.000	.003

a. The survival and mortality probabilities for lung cancer patients presented here are derived from the RSRs obtained from NCI and the survival probabilities for a matched cohort in the general population. They are therefore only *estimates* of the underlying population survival and mortality probabilities for lung cancer patients. Whereas the underlying population probabilities are likely to follow a smooth trend (over years post-diagnosis), the estimates exhibit some of the "bumpiness" around that trend that typically results from normal sampling variability. This variability will also be true of any other probabilities (such as the conditional probabilities discussed below) that are derived from the estimated probabilities shown here.
b. The probabilities in the general population of dying from lung cancer are 0.000256 in the 70-74 year age group, and 0.000348 in the 75-79 year age group. The probabilities in column (3) were derived by subtracting these probabilities from the corresponding probabilities of dying from any cause in the *n*th year, given survival to the *n*th year.
c. From Table II.5-2.
d. See Chapter II.2 for an explanation of the derivation of these probabilities.

II.5.B Costs of Treatment and Services

II.5.B.1 Methodology

II.5.B.1.1 Overview

There is no single typical case or treatment pattern for lung cancer because of individual differences in the stage of cancer at diagnosis, multiple treatment options, patient health and age, and other factors; however, average costs can be calculated. Treatment of lung cancer may occur over a brief or extended period of time, and costs may be limited or substantial. Lung cancer has a relatively high mortality rate of 88 percent, as discussed in Section A. The medical costs of those who die of the disease are usually very different than for those who survive (this is discussed in more detail in Chapter I.1). This chapter therefore provides costs for the "average" lung cancer patient, as well as for survivors and nonsurvivors as separate patient groups.

Link to Chapter I.1

II.5.B.1.2 Medical Cost Data

II.5.B.1.2.1 Sources

Medical cost data would ideally be obtained on current medical expenditures. Although data files are maintained by public and private sector sources, they are not readily available. In addition, to obtain reliable cost estimates it is necessary to evaluate very large databases of charges from a variety of sources. This activity was not practical for the development of this chapter. A data search was conducted to locate information in the medical economics literature regarding medical costs associated with lung cancer. In addition to a literature search, most federal agencies dealing with cancer, disabilities, medical costs and their management, and related issues were contacted for information and the various federal databases were discussed with senior staff at these agencies.

Very recent cost data were not located.[5] Current (1994) cancer data were obtained regarding incidence and survival (as reported in Section II.5.A, above), and were used with cost data from the 1980s described below. The cost estimates presented in this section are based primarily on the work of Baker et al. (1989) and Hartunian et al. (1981) and on two sources of statistical data: the National Cancer Institute (1998) and Vital Statistics of the United States, 1993 (NCHS, 1997). These data were evaluated and cost elements were used to calculate lifetime estimates of the direct medical costs due to lung cancer.

[5] Studies were located that used more recent cost data than the data used in this analysis. Serious limitations existed, however (data were incomplete), and so the studies were not used. They are reported in the "Other Studies" section at the end of Section B.

Based on the 1997 review of the medical literature carried out for the development of this chapter, there do not appear to be widely-adopted new treatment methods for lung cancer that substantially alter either the medical costs or the survival rates for most patients. Consequently, the cost estimates presented in this chapter may be considered appropriate under most circumstances (e.g., regional costs may vary).

II.5.B.1.2.2 Baker et al.'s Cost Estimation Method

Baker et al. (1989) used the Continuous Medicare History Sample File (CMHSF) to estimate the per-patient average lifetime medical cost of treating lung cancer based on data files from 1974 to 1981. They chose CMHSF because:

1) it is a nationally representative sample of the Medicare population (five percent), covering over 1.6 million patients;
2) it is longitudinal, dating from 1974 to 1981; and
3) it captures the majority of medical expenses for each beneficiary.

Five Medicare files are included in the CMHSF, which cover:

1) inpatient hospital stays,
2) skilled nursing facility stays,
3) home health agency charges,
4) physicians' services, and
5) outpatient and other medical services.[6]

Costs that were not included are outpatient prescription medications and nursing home care below the skilled level.

Because CMHSF provides no indication of initial diagnosis, Baker et al. assumed that disease onset occurred when a diagnosis of lung cancer was listed on a hospitalization record following a minimum of one year without a lung cancer diagnosis. This assumption is reasonable due to the high frequency of hospitalization associated with the disease (i.e., individuals diagnosed with lung cancer would be hospitalized). Only patients with an initial diagnosis during the years covered by the database (1974-1981) were included.

[6] See Baker et al. (1989 and 1991) for further details. Baker et al. (1991) contains additional descriptive data regarding the database and methods used for the cost analysis; however, it does not contain cost data for lung cancer.

Costs associated with lung cancer were assigned to three post-diagnostic time periods:

- initial treatment, during the first three months following diagnosis;
- maintenance care, between initial and terminal treatment; and
- terminal treatment during the final six months prior to death.

As noted in Chapter I.1, the amount paid for service may differ from the actual medical costs because many insurers and federal programs either 1) pay only a portion of total costs or 2) pay more than actual costs to underwrite the care providers' losses due to underpayment from other sources.

Link to Chapter I.1

Baker et al. used provider charges, rather than Medicare reimbursements (which represent only a portion of most total charges), thus providing a more accurate cost estimate. To improve the accuracy of the cost estimates, Baker et al. included cost data on coinsurance, deductibles, and other cost components. They made four adjustments to the cost estimates calculated from the CMHSF. First, charges were added for skilled nursing facilities (SNFs) not covered by Medicare by multiplying the "length of stay" at an SNF (computed from admission and discharge dates) by the average daily SNF charge. Second, the annual Medicare Part B deductible of $60 was added to the reimbursed charges in the database. Third, since Medicare pays only 80 percent of physicians' charges, Baker et al. scaled these reimbursements to 100 percent of physicians' charges to better reflect social costs. Finally, they inflated all dollar values to 1984 dollars using the Medical Care component of the Consumer Price Index.

II.5.B.1.2.3 Cost Estimates by Treatment Period

Medical costs associated with the initial, maintenance, and terminal cancer care treatment periods were itemized in Baker et al. (1989) and are shown in Table II.5-4. The 1989 paper did not report incremental costs or the costs of other medical services that would be anticipated to occur while the patient was receiving cancer treatment (i.e., co-morbidity/background costs). In order to estimate the incremental costs, a co-morbidity cost of $2,988 per year (1984 dollars) from Baker et al. (1991) was used in this analysis. (This is equivalent to $6,394 in 1996 dollars using the CPI multiplier of 2.14 for 1984 to 1996.) The co-morbidity cost was pro-rated for this analysis using the specified durations for the initial (three-month) and terminal (six-month) treatment periods.

Table II.5-4 lists the incremental costs calculated for the three treatment periods. Total costs are reported for the initial and terminal care periods. Annual costs for the maintenance period are shown and are further discussed in the "Lifetime Costs" section below. Using the Medical Care

component of the Consumer Price Index (CPI-U), all costs are inflated to 1996 dollars for purposes of this handbook. (The adjustment factor for 1984 to 1996 is 2.14; Bureau of Labor Statistics.)

Table II.5-4. Average Per Patient Costs for the Three Periods of Treatment for Lung Cancer in 1996 dollars
Costs adjusted for inflation using the Medical Care component of the Consumer Price Index (CPI-U) 1996:1984 = 2.14 (Bureau of Labor)

Treatment Period	Incremental Cancer Treatment Cost
Initial (3 months)	$26,042
Maintenance (per year)	$11,325
Terminal (6 months)	$30,112

(Based on Baker et al., 1989, with comorbidity charges from Baker et al., 1991.

II.5.B.1.3 Calculation of Lifetime Cost Estimates for the "Average" Lung Cancer Patient

This section contains a discussion of the calculation of lifetime medical costs for the "average" lung cancer patient. Sections that follow discuss methods and results of calculations for estimating costs for survivors and nonsurvivors of lung cancer separately. These separate approaches were used to address specific requirements of different activities that EPA carries out using direct medical cost data. Although Baker et al. (1989) provide useful cost estimates for the three treatment periods, they do not provide information on two critical aspects of medical costs:

1) costs for survivors versus nonsurvivors of lung cancer. These values may differ substantially. For example, survivors would not have terminal care costs and may receive maintenance services for an extended time period; and

2) estimates of the duration of the maintenance periods.

Data regarding age at diagnosis of lung cancer were obtained from NCI (1998). Survival and mortality probabilities for each year post-diagnosis were derived from relative survival rates obtained from NCI (1998), as discussed in Section II.5.A.5.2.

Link to Section II.5.A.5.2

This information was used to address many time-related medical cost issues. For some aspects of the analysis, however, detailed information

was not available and average values have been used as a reasonable approximation (e.g., a ten-year maintenance period was assumed for survivors of lung cancer). When average values or other assumptions are used in this analysis, they are so noted.

As previously noted, there are not substantial differences in survival related to age at diagnosis, and NCI does not provide age-specific RSRs for each year post-diagnosis. Consequently, it was assumed for this analysis that the relative survival rates for lung cancer were the same for all ages. The survival and mortality probabilities for lung cancer patients, which are incorporated into calculations of expected medical costs as discussed below, are based on this assumption.

The analysis assumes that death always occurs midyear. All lung cancer patients are therefore assumed to incur the costs of initial treatment during the first three months of the illness. The costs incurred after that during the first year depend on whether the patient:

(1) survives through the year,
(2) dies of lung cancer during the year, or
(3) dies of some other cause during the year.

Patients who survive through the year incur the costs of initial treatment ($26,042) during the first three months, and then incur nine months' worth of maintenance care costs ($0.75 \times \$11,325 = \$8,494$) during the remainder of the year. The total cost incurred during the first year by those patients who survive the year is therefore $\$26,042 + \$8,493 = \$34,535$.

Lung cancer patients who die of lung cancer during the first year incur the initial treatment cost and then incur terminal care costs for the remaining three months of their lives (because those who die are assumed to die midyear). Total costs during the first year post-diagnosis in this case are therefore $\$26,042 + (0.5 \times \$30,112) = \$41,098$.

Finally, the small percentage of lung cancer patients who die of causes other than lung cancer during the first year post-diagnosis incur the initial treatment costs and then incur three months' worth of maintenance care costs. Total first-year costs for these patients are therefore $\$26,042 + 0.25 \times \$11,325 = \$34,536$.

The expected medical costs for lung cancer patients during the first year post-diagnosis, then, may be expressed as:

Expected First-Year Cost: **initial treatment costs + [maintenance care costs for nine months × probability of survival through first year + terminal care costs for three months × probability of dying of lung cancer during first year + maintenance care costs for three months × probability of dying of other causes during the first year]**

Example: Expected first-year medical costs of a lung cancer patient diagnosed at age 68

As noted above, all lung cancer patients incur an initial treatment cost of $26,042. Those who survive through the year also incur maintenance care costs for the remaining three quarters of the year. The total first-year costs of those who survive the year are:

Initial treatment:	$26,042
Maintenance treatment:	$8,493 (.75 × $11,325)
Total First-Year Cost	$34,535

More than half of lung cancer patients die of lung cancer during the first year. Those who do will incur the initial treatment costs plus half of the terminal care costs. The total first-year costs of those who die of lung cancer during the year are:

Initial treatment:	$ 26,042
Terminal care:	$15,056 (.50 × $30,112)
Total First-Year Cost	$41,098

Finally, a small percentage of patients will die of competing illnesses during the first year. Because those who die of causes other than lung cancer are assumed to die at the midpoint of the year, costs during the first half of the year are assumed to consist of the initial treatment costs for three months, plus three months of maintenance care costs as follows:

Initial treatment:	$26,042
Maintenance treatment:	$2,831 (.25 × $11,325)
Total First-Year Cost	$28,873

For each subsequent year, costs consist entirely of maintenance care costs for those who survive the year. For those who do not survive the year, costs depend on whether death was due to lung cancer or other causes. For those who die of lung cancer during the *n*th year, costs incurred that year consist of six months of terminal care costs, or $30,112. For those

who die of other causes during the *n*th year, there are six months of maintenance care costs, or 0.5 × $11,325 = $5663.

The expected first-year medical cost incurred by the "average" lung cancer patient diagnosed at age 68 is a weighted average of the costs of those who survive the first year, those who die of lung cancer during the first year, and those who die of other causes during the first year, where the weights are the probabilities of each of these occurrences. The weighted average medical cost were calculated for ten years post diagnosis, and expected costs were summed over the ten years. This was assumed to be a reasonable period over which additional medical costs associated with lung cancer (i.e., maintenance care costs) would be incurred by lung cancer patients. In reality, there may be follow-up care and continued testing over a longer period; however, no data were available regarding those costs. They would certainly be less than $11,325 per year.

The expected medical costs for lung cancer patients during the *n*th year post-diagnosis, for *n*>1, then, may be expressed as:

> **<u>Expected *n*th Year (*n*>1) Cost:</u> [maintenance care cost for one year × probability of survival through *n*th year + terminal care cost for six months × probability of dying of lung cancer during the *n*th year + maintenance care cost for six months× probability of dying of other causes during the *n*th year]**
>
> **<u>Expected Lifetime Cost</u> = Expected first-year cost + the sum of the (discounted) expected subsequent-year costs**

The first year of treatment is calculated differently from other years because the first three months of that year are spent in "initial" treatment, and the costs for that period of intensive medical care and surgery are calculated separately.

The mathematical equation for the expected lifetime medical costs incurred by the "average" lung cancer patient over a ten-year period is:

$$\$26{,}042 + (\$11{,}325 \times 0.75 \times ps_1) + (\$11{,}325 \times 0.25 \times pm_1{}^{o}) + (\$30{,}112 \times 0.5 \times pm_1{}^{sc})$$

$$+\sum_{y=2}^{10}\left[(ps_y \times \frac{\$11{,}325}{(1+r)^{y-1}}) + (pm_y{}^{o} \times \frac{\$5{,}663}{(1+r)^{y-1}}) + (pm_y{}^{sc} \times \frac{\$30{,}112}{(1+r)^{(y-1)}})\right]$$

Where:

y	=	the year post-diagnosis,
ps	=	the probability of surviving through the year,
pm^{sc}	=	the probability of dying of lung cancer during the year

pm^o	=	the probability of dying from other causes during the year,
r	=	the discount rate

The cost estimates for each year post-diagnosis and the estimate of undiscounted expected total cost for a ten year period are shown in Table II.5-5 for the "average" lung cancer patients diagnosed at age 68. The survival and mortality probabilities necessary for the calculations of costs are shown in Table II.5-3.

Link to Table II.5-3

II.5.B.1.4 Calculation of Lifetime Cost Estimates Separately for Lung Cancer Survivors and Nonsurvivors

II.5.B.1.4.1 Survivors and Nonsurvivors

As noted above, there are differences in medical services provided to lung cancer patients who survive the disease (survivors) versus those who die of the disease (nonsurvivors). Based on cost estimates by Baker et al. (1989), terminal care is provided for approximately six months to terminally ill cancer patients. The costs to nonsurvivors for this care ($30,112) is considerably higher than costs for survivors who receive maintenance care for the same period of time ($5,662).[7]

EPA may use the value of a statistical life (VSL) for nonsurvivors, and thus separate costs for survivors and nonsurvivors were calculated. The method shown above to calculate costs for the "average" patient uses the unconditional probabilities of survival and mortality listed in Table II.5-3. The method used to calculate costs for survivors and nonsurvivors separately requires the probabilities that are conditional on being either a survivor or nonsurvivor of lung cancer.

[7] Nonsurvivors include only those who die of lung cancer and do NOT include those who die of any other causes.

Table II.5-5. Expected Costs of Medical Services (in 1996$) for Lung Cancer Patients (Age of Onset = 68)				
	Medical Costs in the *n*th Year (undiscounted)			
Years Post-Diagnosis (n)	if survive through the *n*th year	if die of lung cancer in the *n*th year	if die of other causes in the *n*th year	Expected Medical Costs for the *n*th Year Post-Diagnosis (Discounted)
1[b]	34,535	41,098	28,873	38,300
2	11,325	30,112	5.662	7,601
3	11,325	30,112	5,662	3,636
4	11,325	30,112	5,662	2,393
5	11,325	30,112	5,662	1,684
6	11,325	30,112	5,662	1,694
7	11,325	30,112	5,662	1,133
8	11,325	30,112	5,662	1,239
9	11,325	30,112	5,662	1,101
10	11,325	30,112	5.662	831
Expected Total Cost Through the 10th Year Post-Diagnosis for a Lung Cancer Patient Diagnosed at Age 68				59,612

a. The probabilities listed in this table are from Table II.5-3. The costs are listed in Table II.5-4.
b. First-year costs include the charge for "initial" therapy ($26,042). The duration of maintenance care is adjusted accordingly (see text for discussion).
c. Calculated using the probabilities in Table II.5-3 and the costs in Columns (5), (6), and (7) of this table.

The conditional probability of a lung cancer nonsurvivor dying in the *n*th year is the number of nonsurviving lung cancer patients who die of lung cancer during the *n*th year divided by the total number of lung cancer nonsurvivors. Likewise, the conditional probability of a lung cancer survivor dying in the *n*th year is the number of surviving lung cancer patients who die of lung cancer during the *n*th year divided by the total number of lung cancer survivors. A detailed explanation of the derivation of these values is provided in Chapter II.2. The conditional probabilities of survival and mortality for survivors and nonsurvivors of lung cancer are given in Table II.5-6.

Link to Chapter II.2

Table II.5-6. Conditional Probabilities of Survival and Mortality for Survivors and Nonsurvivors of Lung Cancer (Age of Onset = 68) a				
	Lung Cancer Survivors		Lung Cancer Nonsurvivors	
	Conditional probability of:		Conditional probability of:	
Years Post-Diagnosis (n)	Surviving through the *n*th year	Dying of some other cause during the *n*th year	Surviving through the *n*th year	Dying of lung cancer during the *n*th year
1	.886	.114	.334	.666
2	.829	.056	.146	.188
3	.791	.039	.081	.065
4	.758	.033	.050	.032
5	.727	.030	.039	.011
6	.699	.029	.019	.020
7	.671	.028	.019	.000
8	.643	.028	.009	.009
9	.616	.027	.00	.009
10	.589	.027	.00	.000

a. As noted for Table II.5-3, the survival and mortality probabilities for lung cancer patients presented here are derived from the relative survival rates obtained from NCI and the survival probabilities for a matched cohort in the general population. They are therefore only *estimates* of the underlying population survival and mortality probabilities for lung cancer patients. Whereas the underlying population probabilities are likely to follow a smooth trend (over years post-diagnosis), the estimates exhibit some of the "bumpiness" around that trend that typically results from normal sampling variability. This variability will also be true of any other probabilities (such as the conditional probabilities discussed below) that are derived from the estimated probabilities shown here.

II.5.B.1.4.2 Calculation of Lifetime Cost Estimates for Lung Cancer Survivors

As shown in the example portion of Section II.5.B.1.3, cost estimates are calculated by summing the costs of the different treatment phases over the lifetime of the lung cancer patient. The expected medical costs for lung cancer survivors during the first year post-diagnosis may therefore be expressed as:

<u>Expected First-Year Cost:</u> initial treatment costs + [maintenance care costs for nine months × probability of survival through first year + maintenance care costs for three months × probability of dying of other causes during the first year]

The expected medical costs for lung cancer survivors during the *n*th year post-diagnosis, for $n>1$, then, may be expressed as:

> **<u>Expected *n*th Year (*n*>1) Cost:</u> [maintenance care cost for 1 year × probability of survival through *n*th year + maintenance care cost for six months × probability of dying of other causes during the *n*th year]**
>
> **<u>Expected Lifetime Cost</u> = Expected first-year cost + the sum of the (discounted) expected subsequent-year costs**

Note that the probabilities used in these calculations are the conditional probabilities given in Table II.5-6. They are conditional on the lung cancer patient not dying of lung cancer.

Using the initial, maintenance, and terminal care costs from Table II.5-6, the mathematical equation for the lifetime costs incurred by lung cancer survivors is:

$$\$26{,}042 + pm_1^{\,s} \times 0.25\ (\$11{,}325) + ps_1^{\,s} \times .75 \times \$11{,}325 + \sum_{y=2}^{10} \left[ps_y^{\,s} \frac{\$11{,}325}{(1+r)^{y-1}} + pm_y^{\,s} \frac{\$5{,}662}{(1+r)^{y-1}} \right]$$

where: y = the year post-diagnosis
ps^s = the conditional probability of survival for that year, conditional on being a survivor of lung cancer
pm^s = the conditional probability of mortality for that year, conditional on being a survivor of lung cancer
r = the discount rate.

The expected medical costs for lung cancer survivors for each year post-diagnosis, as well as the expected total medical costs over ten years post-diagnosis, are shown in Table II.5-7.

Table II.5-7. Expected Undiscounted Costs of Medical Services (in 1996$) for Survivors of Lung Cancer (Age of Onset = 68)			
Years Post-Diagnosis (n)	Medical Costs Through the 10th Year Post-diagnosis[a] (undiscounted)		
	Medical Cost if Survive Through the *n*th Year	Medical Cost if Die of other Causes in the *n*th Year	Total Cost Based on Weighted Average[c]
1[d]	34,535	28,873	33,889
2	11,325	5,662	9,713
3	11,325	5,662	9,173
4	11,325	5,662	8,768
5	11,325	5,662	8,411
6	11,325	5,662	8,077
7	11,325	5,662	7,756
8	11,325	5,662	7,438
9	11,325	5,662	7,124
10	11,325	5,662	6,818
Expected Total (Undiscounted) Cost Through the 10th Year Post-Diagnosis:			**107,167**

a. Costs are based on data reported in Table II.5-4, adapted from Baker et al., 1989.
b. Probabilities of survival and mortality, taken from Table II.5-6, are conditional on surviving lung cancer.
c. Weighted average of the costs incurred by survivors who survive the year and the costs incurred by survivors who die of other causes during the year. Weighting is based on the conditional probabilities provided in Table II.5-6.
d. Costs during the first year include a charge for "initial" therapy ($26,042), and the duration of maintenance or terminal care is adjusted accordingly. See text for discussion.

II.5.B.1.4.3 Calculation of Lifetime Cost Estimates for Lung Cancer Nonsurvivors

Nonsurvivors of lung cancer will incur initial, maintenance, and terminal costs. Their lifetime medical costs associated with the disease can be calculated from the costs per treatment period shown in Table II.5-4 and the conditional probabilities for nonsurvivors of lung cancer shown in Table II.5-6.

As Table II.5-6 indicates, most lung cancer patients who will ultimately die of lung cancer do so in the first few years post-diagnosis. About 85 percent die in the first two years. Deaths from lung cancer after the first four years are minimal. As with lung cancer survivors, medical costs for nonsurvivors each year post-diagnosis were calculated as a weighted average of the costs incurred by those who survive the year and those who die (of lung cancer) during the year.

It was assumed that those who die during a year receive six months of care (as was done for the survivors above). It was also assumed that terminal care lasting six months would be provided to all nonsurvivors. Therefore, unless death occurred during the first year, when initial care was assumed to occur, the care costs which were assigned to the last year of life were terminal costs. If death occurred during the first year post-diagnosis, it was assumed that initial care and three months (one-half of the total) of terminal care were provided.

The general description of medical costs for nonsurvivors may be expressed as:

> **Expected First-Year Cost: [initial costs + one-half terminal costs] × probability of mortality during the first year + [initial costs + maintenance care costs for nine months] × probability of survival for first year**
>
> **Expected *n*th Year (*n*>1) Cost: maintenance care cost for 1 year × probability of survival through *n*th year + terminal costs × probability of mortality in *n*th year**
>
> **Expected Lifetime Cost = Expected first-year cost + the sum of the (discounted) expected subsequent year costs**

As with the cost calculations for lung cancer survivors, the probabilities used in these cost calculations are the conditional probabilities given in Table II.5-6: in this case, conditional on dying of lung cancer.

Using the initial, maintenance, and terminal care costs from Table II.5-6, the mathematical equation for the expected lifetime costs incurred by nonsurvivors is:

$$\$26{,}042 + pm_1^{ns} \times 0.5\ (\$30{,}112) + ps_1^{ns} \times .75 \times \$11{,}325 + \sum_{y=2}^{10} \left[ps_y^{ns} \frac{\$11{,}325}{(1+r)^{y-1}} + pm_y^{ns} \frac{\$30{,}112}{(1+r)^{y-1}} \right]$$

where: y = the year post-diagnosis
ps^{ns} = the conditional probability of survival for that year, conditional on being a nonsurvivor of lung cancer
pm^{ns} = the conditional probability of mortality for that year, conditional on being a nonsurvivor of lung cancer
r = the discount rate.

The costs are summed over all years from diagnosis to death. Maintenance care costs are not added in the last year of life because during the six months that are assumed to constitute this period the patient is assumed to receive terminal care. (The discounted results are shown in the "Results" section that follows.) The approach is the same as that shown in the example in Section II.5.B.1.3 When the costs for each year are summed over a period of ten years post-diagnosis, during which essentially all patients who will die of lung cancer have done so, the total cost per nonsurvivor is obtained. These costs are shown in Table II.5-8.

Link to Section II.5.B.1.3

The results shown above can be used to calculated costs for an "average" lung cancer patient, from the costs calculated for survivors and nonsurvivors. The expected medical costs of a lung cancer patient can be calculated as a weighted average of the expected costs of survivors and nonsurvivors of lung cancer. This approach, which was not used to calculated costs for the "average" patient in this chapter, yields the same results as the approach shown in Section II.5.B.1.3. A discussion of why these to approaches yield the same results is provided in Chapter II.2 (Section II.2.B.2.3). In brief, the approach used in this chapter for the average patient uses cost data for all patients, weighted by their average utilization of services. If the survivor and nonsurvivor data were used, which incorporates utilization of services, cost results obtained through separate calculations for the two subgroups are simply re-aggregated based on each group's proportional contribution to the cost.

Link to Chapter II.2.B.2.3

Table II.5-8. Expected Undiscounted Costs of Medical Services (in 1996$) for Nonsurvivors of Lung Cancer (Age of Onset = 68)			
Years Post-Diagnosis (n)	Medical Costs Through the 10th Year Post-diagnosis[a] (undiscounted)		
	Medical Cost if Survive Through the *n*th Year	Medical Cost if Die in the *n*th Year	Total Cost Based on Weighted Average[c]
1[d]	34,535	41,098	38,905
2	11,325	30,112	7,311
3	11,325	30,112	2,877
4	11,325	30,112	1,519
5	11,325	30,112	761
6	11,325	30,112	818
7	11,325	30,112	224
8	11,325	30,112	389
9	11,325	30,112	274
10	11,325	30,112	9
Expected Total (Undiscounted) Cost Through the 10th Year Post-Diagnosis:			53,088

a. Costs are based on data reported in Table II.5-5, adapted from Baker et al., 1989.
b. Probabilities of survival and mortality, taken from Table II.5-6, are conditional on dying of lung cancer within 10 years post-diagnosis.
c. Weighted average of costs incurred by nonsurvivors who survive the year and those who die during the year. Weighting is based on the conditional probabilities shown in Table II.5-6.
d. Costs during the first year include "Initial" therapy ($26,042) , and pro-rated maintenance or terminal care. See text for discussion.

II.5.B.2 Results of Medical Cost Analysis

The per patient lifetime direct medical costs calculated for the "average" lung cancer patient (as shown in Table II.5-5), lung cancer survivors (as shown in Table II.5-7) and lung cancer nonsurvivors (as shown in Table II.5-8) diagnosed at age 68 are listed in Table II.5-9. Undiscounted costs and costs discounted at three, five, and seven percent back to year one (time of diagnosis) are shown. Discounting was carried out for ten years following diagnosis (which, for nonsurvivors, comprises the full duration of treatment time because virtually all patients that are going to die of lung cancer do so within ten years) and comprises the assumed full duration of maintenance care for survivors.

Table II.5-9. Incremental Per-capita Medical Costs for the Average Lung Cancer Patient, Survivors, and Nonsurvivors (Diagnosed at Age 68) Undiscounted and Discounted at 3, 5, and 7 Percent ($1996)

Patient Group	Discount Rate			
	Undiscounted	3%	5%	7%
Survivors	$107,167	$97,822	$92,572	$87,966
Nonsurvivors	$53,088	$52,215	$51,692	$51,211
Average Patient	$59,612	$57,716	$56,624	$55,645

See text for a definitions of patient groups.

The results show much higher costs for survivors than nonsurvivors, due primarily to their ongoing maintenance care. It is noted that although a ten-year maintenance period for lung cancer survivors is assumed (with adjustment for background mortality that reduces utilization), the actual average period of maintenance is not known and is likely to vary considerably among individuals, depending on age, health status, access to care, and other factors. Most lung cancer patients (88 percent) die of the disease, and their costs are the major cost element in determining the "average" patient costs. The uncertainty surrounding the period of maintenance care for survivors therefore does not have a substantial impact on the cost estimates for the "average" patient.

II.5.B.3 Other Studies

The results of these studies are examined: Mor et al. (Draft 1990), Hartunian et al. (1981), Oster et al. (1984), Riley et al., (1995). The Baker et al. study has a combination of characteristics of study design and data quality that makes it preferable to the other studies, as discussed below.

II.5.B.3.1 Mor et al.

The Mor et al. (1990) study tracked prospectively eligible Medicare beneficiaries in Rhode Island from 1984-1986 by "examining pathology reports in nine Rhode Island hospitals." The medical records were linked to Medicare inpatient and outpatient claims data. Medicare claims files were reviewed, and the charges associated with lung cancer were aggregated for the first year post-diagnosis. The study has three limitations that make it less appropriate for use than the Baker et al. study:

1) the study was limited to Medicare beneficiaries in Rhode Island;
2) the study has not yet been submitted to a refereed journal;
3) the study covers only one year of treatment;
4) costs are only those reimbursed by Medicare, rather than all costs.

The study does, however, use more recent data than those used by Baker et al. Mor et al.'s estimates for the cost of lung cancer in the first year after diagnosis (i.e., lifetime cost, since the majority of lung cancer patients survive less than one year) is $40,051 (inflated from 1986 to 1996 dollars using the CPI-U for Medical Care). This value agrees closely with the results of Baker et al.'s work.

II.5.B.3.2 Hartunian et al.

Hartunian et al.'s (1981) method of estimating the costs of illness has been discussed in Chapter I.1. The authors defined expected treatment on a yearly basis, developed annual costs of the treatment, and combined the cost data with survival data. Using this method, they estimated the costs of cancer at eight sites, including cancer of the respiratory system.

Link to Chapter I.1

Hartunian et al. estimated the costs of inpatient stays for respiratory cancer using a 1976 study by Scotto and Chazze, in which 6,332 newly diagnosed cancer patients were followed over a two-year period to establish hospitalization and payment patterns. For other costs, the authors relied on a questionnaire, called the Patient Interview Book (PIB), delivered as part of the Third National Cancer Survey. Using the PIB, about 8,500 cancer patients or surviving relatives were interviewed regarding the costs of non-hospital medical services. The PIB presents the proportional distribution of total medical expenditures between hospital and non-hospital charges. Applying these proportions to the hospital costs from Scotto and Chiazze, Hartunian et al. estimated non-hospital costs. Hartunian et al. presented their estimates of the present value of total direct costs of respiratory cancers in 1975 dollars, discounted by six percent, by the age of onset for males and females. Inflated to 1996 dollars using the CPI-U for Medical Care (Bureau of Labor Statistics), their cost estimates, which approximate Baker et al.'s estimates are:

Males	
Age 65-74	$37,201
Age 75+	$34,821

Females	
Age 65-74	$36,838
Age 75+	$34,508

The Hartunian data are quite old (over 20 years) and both survival and treatment methods have changed since that time.

II.5.B.3.3 Oster et al.

Oster et al. (1984) estimated the cost of lung cancer as part of an analysis of the cost of smoking. Their methodology followed that laid out by Hartunian et al. Annual cost estimates were multiplied by survival rates and discount factors and summed to arrive at a present value of the direct costs of treating lung cancer. Oster et al.'s cost estimates were presented in 1980 dollars for all ages. Using the CPI-U for Medical Care (Bureau of Labor Statistics), these prices are inflated to 1996 dollars. The resulting cost estimates (using a discount rate of three percent) are:

Males $57,861

Females $60,047

Although these estimates are substantially higher than the Baker et al., estimate, Oster et al.'s estimate of the cost of a lung cancer patient who survives between zero and one year past disease onset is $45,013 in 1996 dollars. This cost estimate is similar to that developed based on Baker et al. A potential explanation for the remaining difference in the cost estimates is that Oster et al. assume that all patients incur the same costs in their first year of disease regardless of their survival period. This cost scheme may be realistic, but it is also possible that patients with relatively long survival periods were diagnosed with less advanced cancer cases. These cancer cases may require less extensive treatment and may therefore be associated with lower first-year costs.

II.5.B.3.4 Riley et al

A study of medicare payments from diagnosis to death in elderly cancer patients was carried out by Riley et al. (1995). The cost estimates are based on Medicare payments only, which do not include: most nursing home care, home health care, pharmaceuticals unless supplied for inpatients, out-of-pocket expenses, deductibles, charges in excess of Medicare paid by other sources (e.g., coinsurance), and other related medical services that are not covered by Medicare.

Medicare patients younger than 65 were not included, and the average age at diagnosis of the lung cancer cohort was 73.6 years, in contrast with the 68-year national average. Riley et al. note that patients diagnosed at younger ages have higher costs. In addition, those diagnosed at earlier stages have a better prognosis, but may have higher medical costs (due to longer continuing care).

Medical costs are reported for all patients who were diagnosed with lung cancer, regardless of other diseases or their ultimate causes of death. Due to the link between lung cancer, smoking, and numerous other diseases, this method is especially problematic because costs associated with other illnesses may be commingled with the lung cancer costs.

The background cost per year for medical services was estimated by Riley et al. to be $2,250 ($3,154 in 1996 dollars), based on the experience of all people over the age of 65 who received Medicare-compensated care. The study excluded those costs that occur during the last year of a person's life. Consequently, the estimated background value may underestimate background costs, especially as age and associated mortality risks increase over the age of 65.

Riley et al. estimated that the total average Medicare payment from diagnosis to death for persons diagnosed with lung cancer was $29,184 in 1990 dollars ($40,908 in 1996 dollars). This value is considerably lower than the estimates obtained from Baker et al. The difference is most likely due to the exclusion of many costs that are not covered by Medicare and the various other factors described above. Due to these limitations, the Riley et al. study is not recommended for a benefits evaluation.

II.5.C Uncertainties and Limitations

As noted periodically in the above discussion, there is uncertainty surrounding various aspects of the analysis. Information concerning some inputs to the analysis was often limited. Although a complete uncertainty analysis is beyond the scope of this work, the significant sources of uncertainty are discussed. Limitations of the scope of the analysis are also discussed.

II.5.C.1 Uncertainties Surrounding Key Inputs to the Analysis

II.5.C.1.1. Analysis of Medical Costs

The cost estimates based on Baker et al. (1989, 1991) have a number of limitations, many of them noted by Baker et al. (1991) and Mor et al. (1990) and Mor (1993). Most of these limitations arise from the use of CMHSF. Medicare data have five limitations that decrease its value for calculating the average lifetime direct medical costs of treating lung cancer. First, Medicare covers medical services for only most persons age 65 and over, disabled persons entitled to Social Security cash benefits for at least 24 months, and most persons with end-stage renal disease. All patients not covered by Medicare are excluded from the database, including all non-disabled women under 65, and women over 65 using private health insurance (Baker et al. 1991).

Given that diagnosis of lung cancer occurs before age 65 in 34 percent of patients (NCI, 1998), the CMHSF excludes a significant number of younger patients. According to Mor et al., treatment for younger women tends to be more intensive (and therefore more costly per unit time) than treatment for older women, though older women tend to have longer hospital stays. Because these differences counteract each other, the

omission of younger women from the analysis is not expected to affect the results substantially. In addition, the majority of senior citizens are enrolled in Medicare (Ibid); differences in medical costs incurred by senior citizens not using Medicare should have little effect on overall cost estimates.[8]

Medicare also does not cover self-administered drugs, intermediate nursing care, long-term nursing care, and some expensive new treatments (such as bone marrow transplants). For some patients these may represent significant percentages of total treatment costs. Most direct medical costs, however, appear to be covered by the CMHSF database and are included in Baker et al.'s analysis. In addition, Baker et al. made adjustments for some cost elements not covered by Medicare (see Section B).

Another drawback is that Baker et al. were not able to identify lung cancer patients in CMHSF whose diagnosis and first course of therapy did not involve hospitalization. In an analysis of Rhode Island lung cancer patients covered by Medicare, Mor et al. determined that a small percentage of lung cancer patients were initially diagnosed without hospitalization, and had substantially lower initial and subsequent treatment costs (Mor et al. 1990). This omission likely causes average treatment costs to be overestimated, though by relatively little.

A fourth drawback is that Baker et al. (1989) provides no information concerning the duration of the maintenance period for lung cancer. The analysis in this chapter assumed that lung cancer survivors incur maintenance care costs for ten years. If the average duration of maintenance care among survivors of lung cancer is shorter (longer) than ten years, then the estimates of the costs incurred by survivors would be biased upward (downward). This bias is less of an issue for nonsurvivors' costs because the great majority of lung cancer nonsurvivors die within the first few years. Because most lung cancer patients (about 88 percent) are ultimately nonsurvivors, the duration of the maintenance period is of somewhat less importance for lung cancer patients than for the 12 percent who ultimately survive the illness.

A fifth drawback is that the data used by Baker are from the period 1974 to 1981. This limitation causes uncertainty regarding changes in treatment methods and costs.

Finally, the reliability of the data contained in the database used by Baker et al. varies. An independent analysis of CMHSF performed in 1977 by the Institute of Medicine of the National Academy of Sciences found that the frequency of discrepancies in principal diagnoses varied among diseases (Baker et al., 1991). It is unclear whether the presence of misnamed

[8] This figure represents those enrolled in Medicare Part A; 95 percent of those enrolled in Medicare Part A choose also to enroll in Medicare Part B.

diagnoses contained in CMHSF potentially increases or decreases the resultant cost estimates.

Overall, despite the limitations described above, Baker's analysis of the CMHSF data represents the most nationally-representative, per-patient lifetime estimate of the direct medical costs of treating lung cancer to date. Their cost estimates are based on sound criteria. Some data limitations underestimate costs and others overestimate costs; the sum of the data limitations therefore decrease the magnitude of error. More of the uncertainties in their analysis appear to underestimate costs, however; the net result is a likely underestimation of actual direct medical costs.

Although there are some uncertainties associated with the estimation of the survival and mortality probabilities used in the calculation of expected medical costs and lost time (discussed below), these uncertainties are likely to be relatively small. As noted in the text, NCI RSRs used to estimate survival and mortality for this analysis are based on the survival experience of a large group of lung cancer patients considered in relation to the survival experience of the general population. Although age-specific RSRs for each year post-diagnosis are not available, the age-specific five-year RSRs provided by NCI (1998) suggest that there is relatively little variation in RSRs across ages at diagnosis for lung cancer patients.

An additional limitation of this analysis is that medical costs incurred as a result of lung cancer, but not considered by Baker et al., may arise as a result of treatment for lung cancer. Secondary cancers and other adverse health effects may occur due to radiation, chemotherapy treatment, and other therapies. These effects may occur substantially after lung cancer treatment has been completed, and can incur added medical costs not considered in this chapter.

Data have not yet been located regarding the average duration of maintenance care. For purposes of this analysis, ten years of follow-up care was assumed to be reasonable due to the severity of the disease and the consequences of lung surgery. This assumption may be revised in the future if data are located.

II.5.C.2 Scope of the Analysis

The analysis in this chapter was confined to direct medical costs by the patient. As noted in Chapter I.1, willingness-to-pay has many other cost elements.

Link to Chapter I.1

The analysis does not include time lost by the patient and his or her family and friends who provide care, pain and suffering on the part of the patient and his or her family and friends, changes in job status among previously employed patients, training for new job skills due to physical limitations, or medical costs incurred after the ten-year maintenance period. These cost elements may comprise a substantial portion of the total cost of lung cancer.

CHAPTER II.7: COST OF COLORECTAL CANCER

Clicking on the sections below will take you to the relevant text.

CHAPTER II.7: COST OF COLORECTAL CANCER

This chapter contains a discussion of the methods used to estimate and the results of estimating the direct medical costs incurred by surviving colorectal cancer patients.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter II.1 contains information regarding cancer causality, a list of known and suspected carcinogens, and information on cancer cost estimation.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapter I.1 and II.1
Link to inflation factors

Survival data from the National Cancer Institute (NCI, 1998) and cost data from Baker et al (1989) that are used in this chapter do not provide quantitative information for different types of colorectal cancer. Consequently, this chapter contains an evaluation of all types in aggregate. In addition, most risk assessments used in evaluating benefits do not specify the type of colorectal cancer.

II.7.A. Background

II.7.A.1. Description

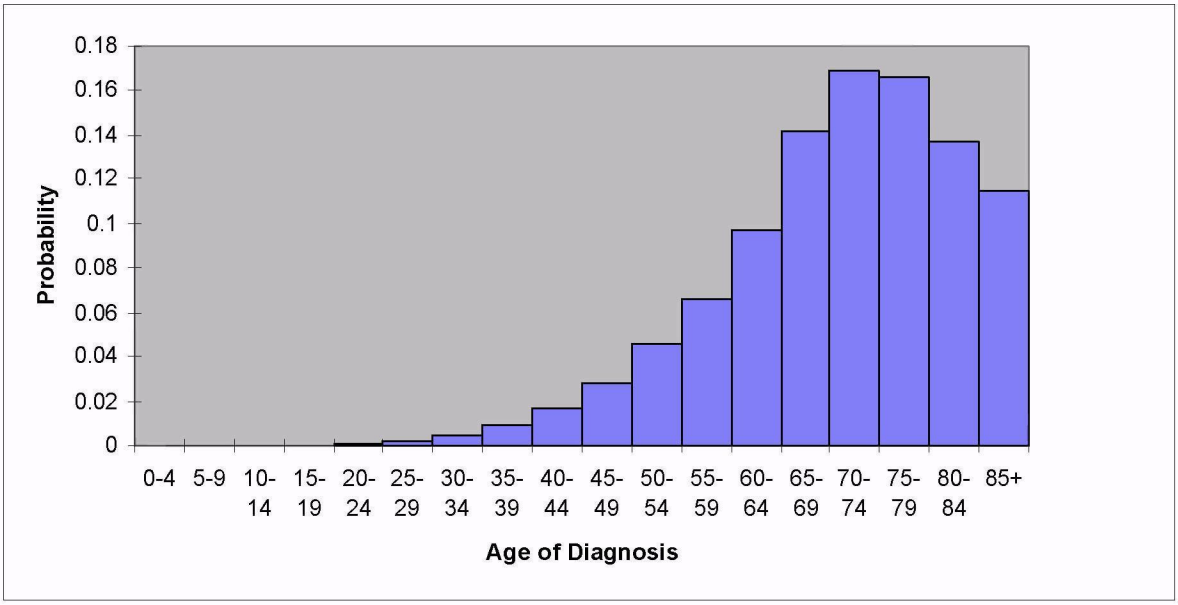
Colorectal cancers are malignancies of the colon or rectum. They are most often adenocarcinomas that are thought to develop through genetic alterations in the cells. Colorectal cancers can be differentiated, based on the site of the tumor(s). As noted above, however, they are considered as a single cancer type for this cost analysis.

Most cases of colorectal cancer occur among the elderly, which is typical of cancer. The average age at diagnosis is 70.4 years. Less than two percent of colorectal cancers are diagnosed before the age of 40, and 42 percent are diagnosed over the age of 75 (NCI, 1998). The age distribution at diagnosis of colorectal cancer is shown in Figure II.7-1. The

[1] Survivors are those who do not die of this specific disease. This chapter was prepared in response to EPA's specific requirement for a proposed rule. Because they were using the value of a statistical life (VSL) for those who die of the disease, they required only cost data for disease survivors. Sources provided in the chapter can be used to calculate medical costs for nonsurvivors, if required.

steep incline in the probability of diagnosis is clear in this diagram, with a peak around 70 years of age. The data used to generate Figure II.7-1 are shown in Table II.7-1. The cumulative percents of colorectal cancer at various ages were calculated using the population-weighted distribution of occurrence. These percents are also shown in Table II.7-1. Approximately 60 percent of all colorectal cancer cases are diagnosed in the relatively small age interval of 70 to 85 years.

Figure II.7-1



The age-specific incidence data were used in Section II.7.B medical cost calculations. Data on incidence and age at diagnosis were obtained from NCI's Surveillance, Epidemiology, and End Results (SEER) reports and tables, obtained on line through the NCI web site at: http://www-seer.ims.nci.nih.gov in 1998.

Table II.7-1. Age-specific Incidence of Colorectal Cancer			
Age Group	Age-specific Rate of Diagnosis Per 100,000	Percent of All Colorectal Cancer Occurring in Age Group	Cumulative Percent of Colorectal Cancer
0 - 14	0.1	0.0	0.0
15 - 34	5.5	0.8	0.8
35 - 39	6.4	1.0	1.8
40 - 44	12.7	1.7	3.5
45 - 49	24.7	2.8	6.3
50 - 54	49.9	4.5	10.8
55 - 59	88.4	6.6	17.5
60 - 64	140.3	9.7	27.2
65 - 69	206.4	14.1	41.3
70 - 74	281.5	16.9	58.3
75 - 79	367.8	16.6	74.9
80 - 84	457.5	13.7	88.6
85+	473.1	11.4	100.0
Based on NCI, 1998			

II.7.A.2. Concurrent Effects

As with all cancers, colorectal cancer may spread to other organs. Colorectal cancer often spreads to distant sites, involving regional lymph nodes, or to the liver or lung (Abeloff et al., 1995). In addition, treatment of cancer, which usually includes chemotherapy, radiation, and surgery, has numerous adverse side effects and may in itself lead to death. Radiation treatments of cancer have led to increased risks of other types of cancer, sterility, etc. Surgery may cause long-term changes in health status that may also lead to death. These effects are associated with additional medical costs not considered in this chapter.

The material herein was specifically developed for the U.S. EPA for use in the analysis of a particular Rule, and does not include information regarding additional medical costs incurred from concurrent effects of colorectal cancer or its treatment.

II.7.A.3. Causality & Special Susceptibilities

Dietary, environmental, and heriditary factors are important in colorectal cancer causality (Abeloff et al., 1995). Table II.1-1 in Chapter II.1 contains a list of chemicals known to cause or are suspected of causing cancer (as reported in the EPA databases IRIS, HEAST, and HSDB). Most chemicals in the table were carcinogenic in animal studies. These studies do not provide organ-specific data because it is not generally assumed that cancer induction will necessarily occur at the same site in humans as in animals. Consequently, the chemicals listed in Table II.1-1

may cause colorectal cancer and/or other types of cancer. Evaluation of the likelihood of this occurrence would require additional risk assessment research.

Link to Table II.1-1

Epidemiologic studies worldwide have documented a direct correlation between colorectal cancer mortality and per capita consumption of calories, meat protein, and dietary fat and oil (Mayer, 1998). Other risk factors include hereditary syndromes (as many as 25 percent of colorectal cancer patients have a family history of the disease), and inflammatory bowel disease (colorectal cancer risk is relatively small among this population during the first ten years of the disease, but it increases at a rate of approximately 0.5-1 percent per year) (Mayer, 1998). Various syndromes affecting the intestine are linked to a much higher risk of colorectal cancer, and both primary and secondary mutations are found in about 15 percent of cases. In addition to genetic alterations, abnormal DNA methylation is an important factor in colorectal cancer. There has been, and continues to be, intensive study of the genetic aspects of this disease (Abeloff et al., 1995).

Colorectal cancer generally affects the over-50-year-old population. Most colorectal cancers, regardless of etiology, are believed to arise from adenomatous polyps, which have been found in the colons of approximately 30 percent of middle-aged or elderly people. Less than one percent of these polyps, however, ever become malignant (Mayer, 1998) Other risk factors include prior history of breast, ovarian, endometrial, genital, colon, or bladder cancer.

NCI provides age-, sex-, and race-specific data regarding diagnosis of colorectal cancer from 1990 to 1994, which may be used to evaluate susceptibilities among population subgroups. The data must be used with care, however, because diagnostic rates indicate occurrence only, and may or may not indicate differences in susceptibility. See Chapter I.1 for a more detailed discussion of susceptibilities.

Link to Chapter I.1

NCI colorectal cancer diagnosis and mortality data show higher diagnosis and death rates among men than women. From the 1973 to 1994 time period, males generally had a 50 percent higher mortality rate than females. Over the time period of 1978-1994, black women consistently showed higher incidence rates than white women. The percent change from 1973 to 1994 were +14 percent and -11 percent, respectively.

The rate of diagnosis among black males from 1973-1994 was higher than that in the white male. Over the period 1973 to 1994, incidence rates among black men increased 34 percent, while it dropped five percent in

white men. A similar trend was also observed of mortality rates over that same time period.

II.7.A.4. Treatments and Services

Colorectal cancer is usually treated with surgery, chemotherapy, and/or radiation, depending on the type of colorectal cancer, the stage of cancer at diagnosis, patient health, and other factors. The treatment is defined more precisely by histologic type and specific location of the cancer. In this analysis, all histologic types and sub-sites are considered together. Most surgery involved en bloc resection, which entails removing large sections of the intestinal tract. This procedure may be modified if cancer has not spread to regional lymph nodes (Abeloff et al., 1995). Treatment for this type of cancer often requires permanent lifestyle changes due to the nature of the surgical intervention required.

Treatment is carried out in phases including initial diagnosis, initial treatment, follow-up and maintenance treatment, and, for those who do not survive, terminal treatment and palliative care. Although there are some components of each treatment that are unique to each phase, most medical activities and services may occur more than once over the course of the disease from diagnosis to death or cure. For example, X-rays may be used in diagnosis, to provide ongoing status updates, to assist in determining initial and subsequent surgical and other treatment interventions, etc.

Initial diagnostic activities may include an evaluation of signs and symptoms, X-rays and other types of imaging, laboratory tests, and other procedures. Staging of the disease occurs during this phase and is critical to determination of subsequent medical actions (Feld et al., 1995). Surgery is usually performed, as well as radiation and/or chemotherapy. In some patients, cancer has spread to other organs requiring additional treatment strategies. Colorectal cancer is fatal in approximatley 50 percent of patients. Consequently, most patients receive terminal care that may include a variety of medical services, long-term care in a nursing facility, palliative care, family counseling, etc.

II.7.A.5. Prognosis

Cancer of the large bowel is the second highest cause of cancer death in the U.S. Although approximately 70-80 percent of all patients survive colorectal cancer for three years following diagnosis (NCI, 1998),

approximately 47 percent of patients die of colorectal cancer within ten years of diagnosis (53 percent survive).[2] This value is used as a reasonable approximation of the lifetime mortality rate in later sections of this chapter.

Factors such as tumor size and location, histology, involvement of nodes, and the spread of cancer to other tissues affect outcome. As with other cancers, the prognosis of colorectal cancer is determined partially by the occurrence of cancer at other sites. When it has metasticized, the survival rate is poorer. As noted above, colorectal cancer generally spreads to distant sites, involving regional lymph nodes or the liver. The latter is reportedly the initial site of distant cancer spread in 33 percent of recurring colorectal cancer patients, and involved in over 66 percent of such patients at their time of death. In fact, colorectal cancer rarely disseminates to the lungs, bone, or brain without hepatic involvement first. The median survival duration for colorectal cancer-associated liver metastases ranges from 6-9 months to 24-30 months (Mayer, 1998).

The prognosis for this cancer has improved in recent decades. An estimated six to eight percent increase in survival over the past two decades has been reported (Abeloff et al., 1995). The change has been attributed to earlier detection and a decrease in treatment-related mortality. The mortality rates among African-American patients are typically higher than within other racial groups.

II.7.B. Costs of Treatment and Services

II.7.B.1. Methodology

II.7.B.1.1 Overview

As noted above, this chapter examines the direct medical cost for the "average" colorectal cancer survivor and does not include nonsurvivors of colorectal cancer.

II.7.B.1.2 Medical Cost Data

II.7.B.1.2.1 Sources

Medical cost data would ideally be obtained on current medical expenditures. Although data files are maintained by public and private sector sources, they are not readily available. In addition, it is necessary to evaluate very large databases of charges from a variety of sources to obtain

[2] The SEER data reports were accessed online to obtain information regarding mortality and survival probabilities (RSRs) (NCI, 1998). The RSR is the number of observed survivors among these patients, divided by the number of "expected" survivors among persons with the same age and gender in the general population (observed/expected). The RSR takes into account that there are competing causes of death that increase with age. Methods used to convert the NCI statistics to survival probabilities are described in detail in Chapter II.2.
Link to Chapter II.2

reliable cost estimates. That method was not practical for the development of this chapter. A data search was conducted to locate information in the medical economics literature regarding medical costs associated with colorectal cancer. In addition to a literature search, most federal agencies dealing with cancer, disabilities, medical costs and their management, and related issues were contacted for information; the various federal databases were discussed with senior staff at these agencies. Very recent cost data were not located.[3] Current (1994) cancer data were obtained regarding incidence and survival (as reported in Section II.7.A, above), and were used with cost data from the 1980s, described below.

The cost estimates presented in this section are based primarily on the work of Baker et al. (1989) and Hartunian et al. (1981) and on two sources of statistical data: the National Cancer Institute (1998) and Vital Statistics of the United States, 1995, Preprint of Volume II, Mortality, Part A Section 6 Life Tables (NCHS, 1998). These data were evaluated and cost and time elements were used to calculate lifetime estimates of the direct medical costs due to colorectal cancer. Based on a 1998 review of the literature, carried out for the development of this chapter, there do not appear to be new treatment methods for lung cancer that alter either the medical costs or the survival rates for most patients substantially. Consequently, the cost estimates presented in this chapter may be considered appropriate under most circumstances (e.g., regional costs may vary).

II.7.B.1.2.2 Baker et al.'s Cost Estimation Method

Baker et al. (1989) used the Continuous Medicare History Sample File (CMHSF) to estimate the per-patient average lifetime medical cost of treating lung cancer based on data files from 1974 to 1981. They chose CMHSF because:

1) it is a nationally representative sample of the Medicare population (five percent), covering more than 1.6 million patients;
2) it is longitudinal, dating from 1974 to 1981; and
3) it captures the majority of medical expenses for each beneficiary.

Five Medicare files are included in the CMHSF, which cover:

1) inpatient hospital stays,
2) skilled nursing facility stays,
3) home health agency charges,

[3]Studies were located that used more recent cost data than were used in this analysis. The studies were not used due to serious limitations (e.g., data were incomplete). The studies are reported in the "Other Studies" section at the end of Section II.7.B.

4) physicians' services, and
5) outpatient and other medical services.[4]

Costs that were not included are outpatient prescription medications and nursing home care below the skilled level.

Because CMHSF provides no indication of initial diagnosis, Baker et al. assumed that disease onset occurred when a diagnosis of colorectal cancer was listed on a hospitalization record following a minimum of one year without a colorectal cancer diagnosis. This assumption is reasonable due to the high frequency of hospitalization associated with the disease (i.e., individuals diagnosed with colorectal cancer would be hospitalized). Only patients with an initial diagnosis during the years covered by the database (1974-1981) were included.

Costs associated with colorectal cancer were assigned to three post-diagnostic time periods:

- initial treatment, during the first three months following diagnosis;
- maintenance care, between initial and terminal treatment; and
- terminal treatment, during the final six months prior to death.

As noted in Chapter I.1, the amount paid for service may differ from the actual medical costs because many insurers and federal programs either 1) pay only a portion of total costs or 2) pay more than actual costs to underwrite the care providers' losses due to underpayment from other sources. Baker et al. used provider charges, rather than Medicare reimbursements (which represent only a portion of most total charges), thus providing a more accurate cost estimate.
To improve the accuracy of the cost estimates, Baker et al. included cost data on coinsurance, deductibles, and other cost components. They made four adjustments to the cost estimates calculated from the CMHSF. First, charges were added for skilled nursing facilities (SNFs) not covered by Medicare by multiplying the "length of stay" at an SNF (computed from admission and discharge dates) by the average daily SNF charge. Second, the annual Medicare Part B deductible of $60 was added to the reimbursed charges in the database. Third, since Medicare pays only 80 percent of physicians' charges, Baker et al. scaled these reimbursements to 100 percent of physicians' charges to better reflect social costs. Finally, they inflated all dollar values to 1984 dollars using the Medical Care component of the Consumer Price Index.

[4] See Baker et al. (1989 and 1991) for further details. Baker et al. (1991) contains additional descriptive data regarding the database and methods used for the cost analysis; however, it does not contain cost data for lung cancer.

II.7.B.1.2.3 Cost Estimates by Treatment Period

Medical costs associated with the initial, maintenance, and terminal cancer care treatment periods were itemized in Baker et al., 1989. These figures are reported as incremental costs in Table II.7-2, because the 1989 paper did not specifically report incremental costs or the costs of other medical services anticipated to occur while the patient was receiving cancer treatment (i.e., co-morbidity/background costs). To estimate the incremental costs, a co-morbidity cost of $2,988 per year (1984 dollars) from Baker et al. (1991) was used in this analysis.

The total cost for the initial three-month treatment period is reported in Table II.7-2, which includes the pro-rated co-morbidity cost for that three-month time period. Annual costs for the maintenance period are also shown and are further discussed in the "Lifetime Cost Estimates" section below (see II.7.B.1.3). Note that only the initial and maintenance costs are relevant to this analysis on colorectal cancer survivor population. Nonsurvivors, and hence terminal treatment costs, are not further addressed herein.

Using the Medical Care component of the Consumer Price Index (CPI-U), all costs were inflated to 1996 dollars for purposes of this handbook. For example, the 1984 annual co-morbidity cost of $2,988 would be equivalent to $6,394 in 1996 dollars, using the CPI adjustment multiplier factor of 2.14 for the period 1984 to 1996.

Table II.7-2. Average Per Patient Costs for the Treatment Periods for Colorectal Cancer (in 1996$)
Costs adjusted for inflation using the Medical Care component of the Consumer Price Index (CPI-U) 1996:1984 = 2.14 (Bureau of Labor Statistics)

Treatment Period	Incremental Cancer Treatment Cost
Initial (3 months)	$28,768
Maintenance (per year)	$8,295
Terminal (6 months)	$30,563

(Based on Baker et al., 1989, with co-morbidity charges from Baker et al., 1991.

II.7.B.1.3 Calculation of Lifetime Cost Estimates for the "Average" Colorectal Cancer Survivor

This section contains a discussion of the calculation of lifetime medical costs for the "average" colorectal cancer patient, identified in this analysis as an individual diagnosed at age 70.4 (the average age of colorectal cancer diagnosis from SEER, NCI 1998), with a life expectancy period of 13.8 years beyond that age (as determined by linear interpolation of NCHS 1998

data for the years 70 and 71). The approach described below was used to address specific EPA rulemaking requirements of the direct medical cost data. It therefore focuses specifically on the lifetime costs of colorectal cancer survivors over the life expectancy period from the average age of diagnosis. As in the previous chapters of this handbook, lifetime costs for nonsurvivors or for other compounding illnesses will not be presented.

The analysis assumes that death may occur only after the full life expectancy period from the average age of diagnosis has elapsed. All patients are therefore assumed to incur initial treatment costs during the first three-month period of the illness as defined by Baker et al. (1989). The costs incurred during the remaining months of the first year of illness are calculated by pro-rating the annual maintenance costs. For example, in the first year, the average colorectal cancer survivor incurs the costs of initial treatment ($28,768) over the first three months, and then incurs nine months' worth of maintenance care costs ($8,295 × 0.75 = $6,221) (see Table II.7-2). The total cost of colorectal cancer incurred during the first year to survivors is therefore $28,768 + $6,221 = $34,989, representing the intensive medical care treatment a patient would initially receive.

The expected medical costs for colorectal cancer patients during the first year post-diagnosis, then, is defined as:

> **Expected First-Year Cost: initial treatment costs over a three-month period + maintenance care costs for nine months**

Example: Expected first-year medical costs of a colorectal cancer patient diagnosed at age 70.4

As noted above, all colorectal cancer patients incur an initial treatment cost of $28,768. Those who survive through the year also incur maintenance care costs for the remaining three quarters of the year. Recall from above that the total first-year costs of those who survive the year were:

Initial treatment:	$28,768
Maintenance treatment:	$6,221 ($8,295 × 0.75)
Total First-Year Cost	$34,989

For each subsequent year post-diagnosis, medical costs consist entirely of annual maintenance care costs.

In this analysis, each patient would incur 13.8 years of maintenance costs, assumed to be a reasonable average period over which additional medical costs associated with colorectal cancer would also be incurred.

The expected medical costs for lung cancer patients during the *n*th year post-diagnosis, for $n>1$, then, is defined as:

Expected *n*th Year ($n>1$) Cost: maintenance care cost for the year, pro-rated as necessary.

Maintenance care costs are not assumed at full value in the last year (i.e., in the fourteenth year) of life expectancy. The treatment costs must be pro-rated based on how long a colorectal cancer survivor is anticipated to live in the final year of expected life. As previously discussed, linear interpolation of life expectancy data between the ages of 70 and 71 resulted in a forecast of 13.8 years, which means that only 80 percent of the annual maintenance costs ($8,295 × 0.80) will be incurred by the patient, or $6,636.

The expected lifetime or total cost to a colorectal cancer survivor is subsequently derived by summing all the expected medical costs over the entire period from diagnosis to death.

Expected Lifetime Cost = Expected first-year cost + the sum of the (discounted) expected subsequent-year costs

Using the initial treatment and maintenance costs listed in Table II.7-2, the mathematical equation for the expected lifetime medical costs incurred by the "average" colorectal cancer survivor over a 13.8-year period may be expressed as:

$$\$28{,}768 + (\$8{,}295 \times 0.75) + \sum_{y=2}^{13} \left[\left(\frac{\$8{,}295}{(1 + r)^{y-1}} \right) \right] + (\$8{,}295 \times 0.8)$$

Where: y = the year post-diagnosis, and
r = the discount rate.

The cost estimates for each year post-diagnosis and the estimate of expected undiscounted and discounted (at three, five, and seven percent) total costs for a fourteen- year period are shown in Table II.7-3 for the "average" colorectal cancer survivor diagnosed at age 70.4.

Table II.7-3. Expected Costs of Medical Services (in 1996$) for Surviving Colorectal Cancer Patients (Age of Onset = 70.4) Over a Life Expectancy Period of 13.8 Years				
Years Post-Diagnosis (n)	**Expected Medical Costs in the *n*th Year Post-Diagnosis (Undiscounted)[a]**	**Expected Medical Costs in the *n*th Year Post-Diagnosis (Discounted 3%)**	**Expected Medical Costs in the *n*th Year Post-Diagnosis (Discounted 5%)**	**Expected Medical Costs in the *n*th Year Post-Diagnosis (Discounted 7%)**
1[b]	$34,989	$34,989	$34,989	$34,989
2	8,295	8,053	7,900	7,752
3	8,295	7,818	7,523	7,245
4	8,295	7,591	7,165	6,771
5	8,295	7,370	6,824	6,328
6	8,295	7,155	6,499	5,914
7	8,295	6,947	6,190	5,527
8	8,295	6,744	5,895	5,165
9	8,295	6,548	5,614	4,828
10	8,295	6,357	5,347	4,512
11	8,295	6,172	5,092	4,217
12	8,295	5,992	4,850	3,941
13	8,295	5,818	4,619	3,683
14[c]	6,636	4,519	3,519	2,754
Expected Total Cost[d]	$141,160	$122,072	$112,026	$103,624

a. The undiscounted initial and maintenance costs used in this table are from Table II.7-2, as adapted from Baker et al., 1989. *Link to Table II.7-2*
b. First-year costs include the charge for "initial" therapy ($28,768) and an adjusted maintenance cost pro-rated for the initial year (see text for discussion).
c. Final-year costs are pro-rated according to the average life expectancy (13.8 years) at the average age of diagnosis (70.4) (see text for discussion).
d. Sums may not equal reported totals due to rounding.

II.7.B.2. Results of Medical Cost Analysis

The per-patient lifetime direct medical costs calculated for the "average" colorectal cancer patient (as shown in Table II.7-3), diagnosed at age 70.4 are listed in Table II.7-4.

Undiscounted costs and costs discounted at three, five, and seven percent, are shown. Discounting was carried out for 14 years following diagnosis, which represents the full duration of treatment and maintenance care duration and the life expectancy at that age.

Table II.7-4. Summary of Total Costs of Medical Services (in 1996$) for Surviving Colorectal Cancer Patients

Undiscounted	Discount Rate		
	3	5	7
$141,160	$122,072	$112,026	$103,624

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

The actual average period of maintenance is not known and is likely to vary considerably among individuals, depending on age, health status, access to care, and other factors. For the EPA requirements under which this analysis was developed, however, this method is assumed to represent the average colorectal survivor.

II.7.B.3. Other Studies

Riley et al. (1995) studied cancer costs, but their results are not recommended due to characteristics of their study design and data quality. They studied Medicare payments from diagnosis to death in elderly cancer patients. Cost estimates presented in the paper were based only on Medicare payments, data that do not include most nursing home care, home health care, pharmaceuticals unless supplied for inpatients, out-of-pocket expenses, deductibles, charges in excess of Medicare paid by other sources (e.g., coinsurance), and other related medical services not covered by Medicare.

Medicare patients younger than 65 years old were not included, and the average age at diagnosis of the colorectal cancer cohort was 76.2 years, in contrast with the national average of 70.4. Riley et al. noted that patients diagnosed at younger ages often incurred higher costs. In addition, those

diagnosed at earlier stages had a better prognosis, but may have had higher medical costs (due to longer continuing care).

Medical costs were reported for all patients diagnosed with colorectal cancer, and did not differentiate between colorectal cancer costs and those of other diseases. Determination of colorectal medical costs were calculated by subtracting background costs. The background cost per year for medical services was estimated by Riley et al., based on the experience of all people over the age of 65 who received Medicare-compensated care. This value was estimated to be $2,250 in 1990 dollars ($3,154 in 1996 dollars, using the CPI 1990-1996 multiplier of 1.4). This estimate excluded costs that occurred during the last year of a person's life. Consequently, the estimated background value reported may underestimate background costs and this omission would lead to a slight overestimate of incremental costs.

Riley et al. estimated that the total average incremental Medicare payment from diagnosis to death for persons diagnosed with colorectal cancer was $51,865 in 1990 dollars ($72,611 in 1996 dollars). This estimate is considerably lower than the estimates obtained from Baker et al. The difference is most likely due to the exclusion of many costs that are not covered by Medicare, in addition to the various other factors described above. As a result of such limitations, the Riley et al. study is not recommended for a benefits evaluation.

II.7.C. Uncertainties and Limitations

There are many limitations in cancer cost estimation. Those common to most cancers are discussed in the introductory cancer chapter: II.1

Link to Chapter II.1

Several aspects of this analysis contain underlying uncertainties based mainly on the limited information concerning some analytical inputs. A discussion of the uncertainty and limitations regarding the data sources of the analysis (Section II.7.C.1) and the scope of the analysis (Section II.7.C.2) follows below.

II.7.C.1. Uncertainties Surrounding Key Inputs to the Analysis

II.7.C.1.1. Analysis of Medical Costs

The cost estimates based on Baker et al. (1989, 1991) have a number of limitations, many of them noted in Baker et al., 1991. Most of these limitations are related to the use of CMHSF. Medicare data have five limitations that decrease their value for calculating the average lifetime direct medical costs of treating lung cancer. First, Medicare covers

medical services for most persons age 65 and over, disabled persons entitled to Social Security cash benefits for at least 24 months, and most persons with end-stage renal disease. All patients not covered by Medicare are excluded from the database, including all non-disabled women under 65, and women over 65 using private health insurance (Baker et al., 1991).

Medicare also does not cover self-administered drugs, intermediate nursing care, long-term nursing care, and some expensive new treatments (such as bone marrow transplants). For some patients these may represent significant percentages of total treatment costs. Most direct medical costs, however, appear to be covered by the CMHSF database and are included in Baker et al.'s 1989 analysis. In addition, Baker et al. made adjustments for some cost elements not covered by Medicare (see Section II.7.B). Another drawback is that Baker et al. were not able to identify colorectal cancer patients in CMHSF whose diagnosis and first course of therapy did not involve hospitalization.

A fourth drawback is that Baker et al. (1989) provide no information concerning the duration of the maintenance period for colorectal cancer. The analysis in this chapter assumed that colorectal cancer survivors incur maintenance care costs for 13.8 years. If the average duration of maintenance care among survivors of lung cancer is shorter (or longer) than 13.8 years, the estimates of the costs incurred by survivors would be biased upward (or downward).

A fifth limitation with using Medicare data is that the data used by Baker are from the period 1974 to 1981. The age of the data causes uncertainty regarding changes in treatment methods and costs.

The reliability of the data contained in the database used by Baker et al. also varies. An independent analysis of CMHSF performed in 1977 by the Institute of Medicine of the National Academy of Sciences found that the frequency of discrepancies in principal diagnoses varied among diseases (Baker et al. 1991). It is unclear, however, whether the presence of misnamed diagnoses contained in CMHSF potentially increases or decreases the resultant cost estimates.

Overall, despite the limitations described above, Baker et al.'s analysis of the CMHSF data represents the most nationally-representative, per-patient lifetime estimate of the direct medical costs of treating colorectal cancer to date. Their cost estimates are based on sound criteria. Because some of the data limitations underestimate costs and others overestimate costs, the sum of the data limitations decreases the magnitude of error. More of the uncertainties in their analysis appear to underestimate costs, however, and poses the problem that the net result may likely be an underestimation of actual direct medical costs.

Although there are some uncertainties associated with the estimation of the survival and mortality probabilities used in the calculation of expected medical costs (discussed below), these uncertainties are likely to be relatively small. As noted in the text, NCI RSRs used to estimate survival and mortality for this analysis are based on the survival experience of a large group of colorectal cancer patients considered in relation to the survival experience of the general population. Although age-specific RSRs for each year post-diagnosis are not available, the age-specific five-year RSRs provided by NCI (1998) suggest that there is relatively little variation in RSRs across ages at diagnosis.

An additional limitation of this analysis is that medical costs incurred as a result of colorectal cancer, but not considered by Baker et al., may arise as a result of treatment. Secondary cancers and other adverse health effects may occur due to radiation, chemotherapy treatment, and other therapies. These effects may occur substantially after colorectal cancer treatment has been completed and can incur added medical costs not considered in this chapter. Data have not yet been located regarding the average duration of maintenance care. For purposes of this analysis, an approximately 14-year period of follow-up care was assumed to be reasonable, due to the severity of the disease and the consequences of colorectal surgery. This assumption may be revised in the future if data are located.

II.7.C.2. Scope of the Analysis

The analysis in this chapter was confined to direct medical costs by the patient. As noted in Chapter I.1, willingness-to-pay has many other cost elements. The analysis does not include time lost by the patient or their family and friends who provide care. Also omitted from cost of illness estimates are pain and suffering on the part of the patient or their family and friends, changes in job status among previously employed patients, training for new job skills due to physical limitations, or medical costs incurred after the ten-year maintenance period. These cost elements may also comprise a substantial portion of the total cost of colorectal cancer.

Link to Chapter I.1

CHAPTER II.8. COST OF BLADDER CANCER

Clicking on the sections below will take you to the relevant text.

CHAPTER II.8. COST OF BLADDER CANCER

II.8.A Background

This chapter contains a discussion of the methods used and results of estimating the direct medical costs incurred by bladder cancer patients. It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter II.1 contains information regarding cancer causality, a list of known and suspected carcinogens, and information on cancer cost estimation.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and II.1
Link to inflation factors

II.8.A.1. Description

Bladder cancers are tumors that arise from the transitional cell lining of the urinary tract. These are a part of a larger group of tumors that are all related and are referred to as urothelial cell cancers. Urothelial cell cancers may occur in the kidneys, ureter, bladder, urethra, and the ducts of the prostate. The most common of these, bladder cancer, is the only cancer discussed in this chapter. Ninety percent of urothelial cell tumors are transitional cell carcinomas, with the remainder composed of squamous cell carcinomas and adenocarcinomas (Bennett and Plum, 1996).

Although a small percentage of bladder cancers differ somewhat from the majority in their cell origin or composition, this chapter contains an evaluation of all types of bladder cancer in aggregate. In addition, most risk assessments that would be used in evaluating benefits do not specify the type of bladder cancer. If a specific type of bladder cancer is of concern, Bennett and Plum (1996) may be consulted for additional information regarding prognostic information and treatment; however, the quantitative data are limited.

Bladder cancer is a common cause of cancer death in men and women in the U.S. (Feld et al., 1995), accounting for two percent of all cancer cases in the U.S.(Abeloff et al., 1995). Approximately 51,200 cases of bladder cancer were diagnosed in 1994 in the United States; approximately 10,600 bladder cancer deaths occurred in that year (Bennett and Plum, 1996). In

1996 the incidence rate was 27.7 per 100,000 in men and 7.4 in women (NCI, 1999).[1] The highest risk group are white men over the age of 64, who have an incidence rate of 217.8 per 100,000 (NCI, 1999).

The incidence of bladder cancer has increased overall by 7.7 percent between 1973 and 1996, due primarily to a 14.5 percent increase among those over the age of 64. The most dramatic increase has occurred among women, with a 22.6 percent increase in white women and a 24.8 percent increase among black women.[2] As discussed under "causality" below, this increase may be due to the increased rate of smoking among women. Incidence rates among black and white men over the age of 65 during the 1973 to 1996 interval have also increased substantially: 24.0 and 22.6 percent, respectively. Fortunately, this trend toward increased incidence has turned around slightly in very recent years (1992-1996) (NCI, 1999).

During the period 1973 to 1996, there has been a small drop in the incidence of bladder cancer among those under the age of 65 years (3.4 percent), driven solely by a decline in bladder cancer among white men and black women under the age of 65 years. Mortality rates have also decreased (discussed under prognosis, below).

Bladder cancer is observed in three times as many men as women. As with most cancers, it also occurs with much greater frequency among the elderly. The average age at diagnosis is between 70 and 75 years. Less than 1.6 percent of bladder cancers are diagnosed before the age of 40, and 21.7 percent are diagnosed over the age of 85 (NCI, 1999). The age distribution at diagnosis of bladder cancer is shown in Figure II.8-1. The steep incline in the probability of bladder cancer diagnosis with age is clear in this diagram. The data used to generate Figure II.8-1 are shown in Table II.8-1. The cumulative percents of bladder cancer at various ages were calculated using the population-weighted distribution of occurrence; these are also shown in Table II.8-1. The age-specific incidence data were used in the Section II.8.B medical cost calculations.

[1] Data on incidence and age at diagnosis were obtained from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) reports and tables. These data were obtained online through the NCI web site at: http://www-seer.ims.nci.nih.gov in 1999.

[2] Racial designations are listed as specified by NCI.

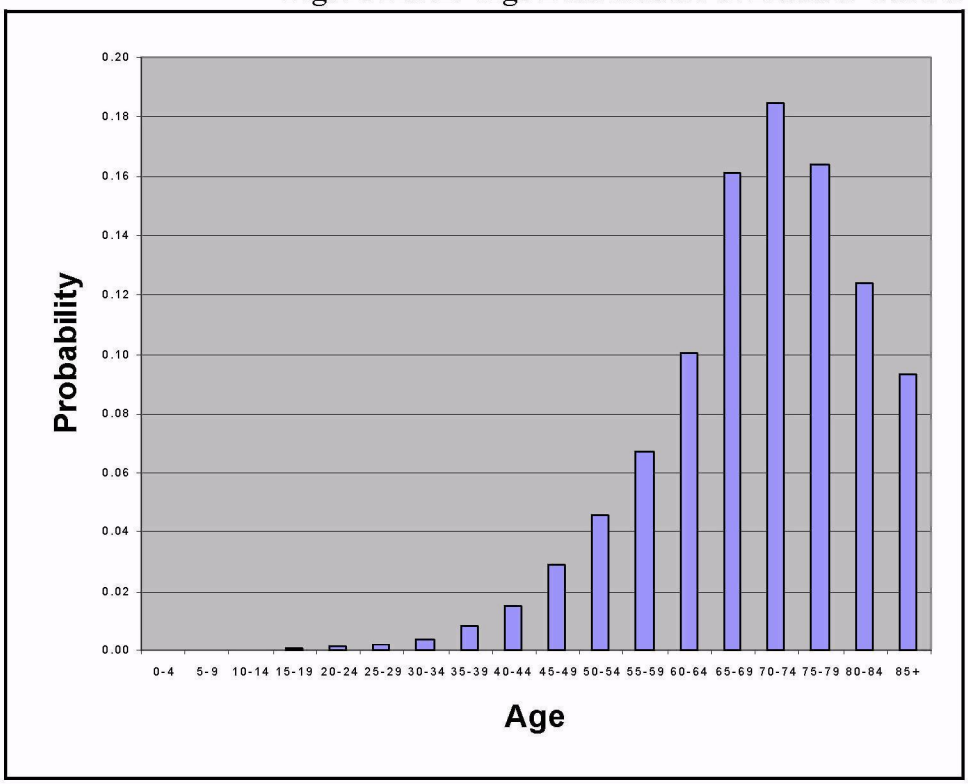
Table II.8-1. Age-specific Incidence of Bladder Cancer			
Age Group	Age-specific Rate of Diagnosis Per 100,000	Percent of All Bladder Cancer Occurring in Age Group	Cumulative Percent of Bladder Cancer
0 - 14	0.0	0.0	0.0
15 - 34	0.5	0.8	0.8
35 - 39	2.0	0.8	1.6
40 - 44	4.0	1.5	3.1
45 - 49	9.0	2.9	6.0
50 - 54	18.1	4.6	10.6
55 - 59	32.2	6.7	17.3
60 - 64	51.9	10.0	27.3
65 - 69	84.4	16.1	43.4
70 - 74	110.7	18.5	61.9
75 - 79	130.2	16.4	78.3
80 - 84	148.8	12.4	90.7
85+	138.2	9.3	100.0
Based on NCI, 1999			

II.8.A.2. Concurrent Effects

As with all cancers, bladder cancer may spread to other organs. In addition, treatment of cancer, which usually includes chemotherapy, radiation, and surgery, has numerous adverse side effects and may, in itself, lead to death. This is particularly true of the agents used to treat bladder cancer (Abeloff et al., 1995). Radiation treatments of cancer have led to increased risks of other types of cancer, sterility, etc. Surgery, especially the removal of a bladder, may cause long-term changes in health status, including reduced capacity or increased susceptibility to respiratory disease that may lead to death. These effects are associated with additional medical costs are considered in this chapter if they occur during the treatment period.[3]

[3] The source of direct medical costs for this chapter (Baker et al., 1979 and 1981) include all medical costs for cancer patients, minus usual background medical costs. This incremental approach allows for the inclusion of medical costs that are associated with treatment and side effects, and discussed in more detail in Section B.

Figure II.8.1. Age Distribution of Bladder Cancer



Bladder cancer has multiple concurrent symptoms that require treatment in addition to the treatments directed at the primary medical goal of cancer eradication. Many of these additional symptoms are related to chemotherapy. Effects observed include: hematuria (blood in urine) and irritative bladder symptoms, bladder obstruction leading to hydronephrosis, tumor infiltration of regional nerves or bone causing pain, and lymphedema as a result of lymphatic obstruction due to lymph node metastasis (Bennett and Plum, 1996; Abeloff et al., 1995), increased risk of epididymitis, orchitis (male reproductive disorders), pneumonitis, hepatitis, and sepsis (Abeloff et al., 1995).

There is a strong link between bladder cancer and smoking. Bladder cancer patients are much more likely to have smoked than people who have not been diagnosed with bladder cancer (causality is discussed below). Smoking is also associated with increased risks of many other diseases, including other cancers. There is no indication, however, that bladder cancer *causes* these other diseases. The simultaneous or sequential occurrence of the diseases are likely due to their common causal link to smoking.

The same pollutants that cause bladder cancer may cause other adverse effects, especially of the urogenital system. These effects can incur added medical costs not considered in this chapter. The risk assessment that serves as the basis for a benefits evaluation should include all adverse effects anticipated to result from exposure to the agent of interest.

II.8.A.3. Causality & Special Susceptibilities

The causality and progression of this disease are not fully understood. It has been hypothesized that bladder cancer may develop from a preneoplastic and preinvasive localized condition to hyperplasia and then to atypical hyperplasia and dysplasia. In some cases, the pathology progresses further to neoplasms (Abeloff et al., 1995). As discussed below, chemical irritants and other irritants are associated with bladder cancer and may cause the observed cell proliferation and hyperplasia, as well as the sometimes observed sequelae — bladder cancer. Experimental evidence suggests that the DNA-damaging effects of carcinogens on the urothelium causes cell proliferation. When the body is unable to repair DNA adequately, progression to bladder cancer may occur. For more detailed information on this topic see Abeloff et al. (1995).

Bladder cancer has been associated with environmental exposures for more than 100 years. Exposure to aromatic amines and working in the dye industry (especially with 2-naphthylamine) were known to cause high rates of bladder cancer among workers. More recently, workers in the rubber, electric, cable, paint, and textile industries had substantially higher incidences of bladder cancer, with exposures to benzidine, auramine, and 4-nitrophenol (Bennett and Plum, 1996), and arylamines from cigarettes and other sources (Jones and Ross, 1999) were particularly noted. Arsenic is also known to increase bladder cancer occurrence (ATSDR, 1998). It is difficult to identify exposures that result in bladder cancer because the latency period is between 15 and 50 years (Abeloff et al., 1995).

As noted above, cigarette smoking is also associated with a higher bladder cancer risk and may account for one-half of all cases (Bennett and Plum, 1996; Abeloff et al., 1995). The prevalence of smoking and occupational exposure among men may account for some or all of the increased incidence seen in men versus women. The dramatic increases in bladder cancer among women in recent years may be due to the relatively recent entrance of women into the workforce, and their recent increase in tobacco use. These factors would result in bladder cancer rates that are only recently observed to increase, due to the long latency of most solid tumors and the typically elderly age of diagnosis for bladder cancer.

In other parts of the world, infection with Schistosoma haemotobium is responsible for a large proportion of bladder cancer cases in less-developed countries (e.g., as studied in Egypt (Abeloff et al., 1995; Bennett and Plum, 1996)). Pharmaceuticals, including cyclophosphamide used in treating malignancies, and the analgesic phenacetin, are also associated with increased bladder cancer risk (Bennett and Plum, 1996; Abeloff et al., 1995).

Although genetic abnormalities are associated with bladder cancer, it is not clear wither these occurred as a result of the disease (or biomarker) or preceded the disease. Chromosome 9 abnormalities, particularly monosomy, occurs early in bladder cancer. 11p and 18p abnormalities are found in more advanced tumors (Bennett and Plum, 1996). For a more complete discussion of cellular-level changes and genetic markers for bladder cancer, see Jones and Ross (1999) and Abeloff et al. (1995). Individuals with a family history of bladder cancer before the age of 45 have a risk that is approximately 50 percent greater than the general population risk (Abeloff et al., 1995). Other genetic risks are suggested by data regarding cigarette smokers. Some individuals who detoxify cigarette toxins more slowly are theorized to have higher risks associated with smoking (Abeloff et al., 1995).

Other factors that may increase the risk of bladder cancer are chronic bladder irritation, bladder infections, and urinary nitrites (Abeloff et al., 1995).

Table II.1-1 in Chapter II contains a list of many of the chemicals known to cause or suspected of causing cancer (as reported in the EPA databases IRIS, HEAST, and HSDB). Most chemicals in the table were carcinogenic in animal studies. These studies do not provide organ-specific data because it is not generally assumed that cancer induction will necessarily occur at the same site in humans as in animals. Consequently, the chemicals listed in Table II-1 may cause bladder cancer and/or other types of cancer. Evaluation of the likelihood of this occurrence would require additional research (e.g., risk assessment).

Link to Table II.1-1

Bladder cancer is much more prevalent in the United States and in Spain than in many other countries. Rates here are 25 to 30 cases per 100,000, in contrast with a baseline rate of 2 per 100,000 in a typical low-rate area (Bennett and Plum, 1996). Bladder cancer also has a positive association with socioeconomic status (Jones and Ross, 1999; Abeloff et al., 1995), which has not yet been explained.

NCI provides age-, sex-, and race-specific data regarding diagnosis of bladder cancer from 1990 to 1994, which may be used to evaluate susceptibilities among population subgroups. The data must be used with care because diagnostic rates indicate occurrence only, and may or may not indicate differences in susceptibility. See Chapter I.1 for a more detailed discussion of susceptibilities.

Link to Chapter I.1

II.8.A.4. Treatments and Services

As noted above, bladder cancer is usually treated with surgery, chemotherapy, and/or radiation, depending on the type of bladder cancer, the stage of cancer at diagnosis, patient health, and other factors. The treatment of bladder cancer can be defined more precisely by histologic type and specific location of the cancer in the bladder. In this analysis, which is concerned with the average cost for all bladder cancers, all histologic types and sub-sites are considered together.

Treatment is carried out in phases including initial diagnosis, initial treatment, follow-up and maintenance treatment, and, for those who do not survive, terminal treatment and palliative care. Although there are some components of each treatment that are unique to each phase, most medical activities and services may occur more than once over the course of the disease from diagnosis to death or cure. For example, X-rays may be used in diagnosis, to provide ongoing status updates, to assist in determining initial and subsequent surgical and other treatment interventions, etc.

Initial diagnostic activities may include an evaluation of signs and symptoms, abdominal, pelvic, bone, and chest scans, intravenous pyelogram, cystoscopy, urinary cytology, computed tomography (CT) scans, magnetic resonance imagery (MRI), biopsies, and other procedures (Bennett and Plum, 1996; Abeloff et al., 1995). Staging of the disease occurs during this phase and is critical to determination of subsequent medical actions. Most tumors are confined to the transitional cell layer and these are generally treated only with surgery. The tumors often recur, which requires frequent cystoscopy with subsequent removal of recurrent tumors as necessary. Higher-grade tumors require chemotherapy or immunotherapy. Invasive cancers with a higher metastatic potential often require total removal of the bladder, and subsequent reconstruction of an alternative urinary reservoir (Bennett and Plum, 1996)

Although there is an 80 to 90 percent survival rate among bladder cancer patients during initial diagnosis and treatment, tumors recur in 30 to 80 percent of patients, and 30 percent progress to a higher stage or grade. Often chemotherapy is used to control or prevent this progression; however, this entails the use of chemicals that are toxic to other organ systems (Abeloff et al., 1995). Photodynamic therapy has also been used recently with success, without the chemically-induced side effects (Abeloff et al., 1995).

The small percentage of patients who cannot be cured receive terminal care, which may include a variety of medical services, long-term care in a nursing facility, palliative care, family counseling, etc.

II.8.A.5. Prognosis

II.8.A.5.1 Background

The prognosis for bladder cancer is relatively good, compared to many cancers. Approximately 26 percent of patients with bladder cancer die of the disease.[4] Mortality rates for bladder cancer patients have decreased overall by 24 percent from 1973 to 1996. The most dramatic improvements have been made among blacks under the age of 65 years, with a 46.5 percent reduction in mortality among those diagnosed with the disease (NCI, 1999). Improvements in survival are due to both better diagnostic methods and improved treatments.

The overall prognosis for bladder cancer patients is good, with an average of only 19 percent of patients dying of the disease within five years. Among younger patients the survival rates are better, with those diagnosed under the age of 45 having a 7.9 percent mortality rate over the first five years post-diagnosis. Those with more limited tumors have a much better prognosis than those with metastatic tumors (discussed below), with a range of 6.9 percent mortality with localized tumors to 93.6 percent mortality among those with distant tumors (based on 1989 to 1995 data) (NCI, 1999).

Tumors that are restricted to a single site, or that occur in multiple sites within the bladder, provide the best prognosis. Most bladder cancer cases are superficial tumors of the transitional cell layer with a low potential for metastatic spread. Those that invade multiple layers of the organ wall and/or metastasize to other organs yield a poorer prognosis. Death occurs primarily as a result of uncontrolled growth of metastatic tumors.

A dynamic observed with bladder cancer, but not common to cancers, is a long-term increase in mortality over 20+ years. Most cancers cause high rates of mortality during the first few years, but are often considered "cured" if the patient survives without recurrence of the cancer for five years. Based on National Cancer Institute (NCI) statistics, bladder cancer continued to cause increased mortality for at least 20 years (the maximum length tracked) post-diagnosis. This trend is discussed in more detail below.

II.8.A.5.2 Relative Survival Rates (RSRs)

The NCI Surveillance, Epidemiology, and End Results (SEER) data reports were accessed online to obtain information regarding mortality and survival probabilities and the duration after diagnosis until death (NCI, 1999). Basic survival statistics on bladder cancer are provided in this

[4] This value is relevant for patients diagnosed at the age of 70 years (the average age of diagnosis for bladder cancer) and is based on a follow-up period of 20 years. The method of calculating this value is discussed below in Section II.8.A.5.2, and source values are listed in column (6) of Table II.8-3.

section because they relate to prognosis. Methods used to convert the NCI statistics to survival probabilities are discussed briefly in this section and in detail in Chapter II.2 on stomach cancer.

Link to Chapter II.2

NCI provides the relative survival rate (RSR) for each year post-diagnosis. The RSR is the number of observed survivors among these patients, divided by the number of "expected" survivors among persons with the same age and gender in the general population (observed/expected). The equation for this is:

$$RSR = \frac{\textit{observed survival rate among bladder cancer patients}}{\textit{survival rate among age- and sex-matched cohort in the general population}}$$

The RSR takes into account that there are competing causes of death that increase with age. The RSR for bladder cancer patients during the first year post-diagnosis is 0.86 (NCI, 1999). This value indicates that a person with bladder cancer would have, on average, a one-year survival probability that is 86 percent of someone of the same age and gender in the general population. The RSRs provided by NCI for each year post-diagnosis are averages obtained from all ages at diagnosis.

An evaluation of the RSRs for bladder cancer over the past 20 years indicates that (1) survival has increased notably (up to ten percent) over the 20 years, and (2) mortality from bladder cancer, while at much lower rates than for some other cancers, continues at non-negligible rates for at least 20 years post-diagnosis. This trend differs from other cancer evaluations previously carried out for this handbook. Due to the long-term dynamic of increasing mortality for bladder cancer, the medical and opportunity costs incurred by bladder cancer patients were estimated for 20 years post-diagnosis (previous chapters considered ten years).

Because the RSRs for many years (e.g., 20 years) post-diagnosis incorporate the survival probabilities of bladder cancer patients who were diagnosed many years ago (e.g., in 1975), direct reliance on the RSRs provided by NCI will result in downward-biased estimates of what RSRs would be for patients who are *currently* being diagnosed with bladder cancer. This bias occurs because the RSRs at each year post-diagnosis are currently significantly higher than they were many years ago (i.e., the survival for years one through five post-diagnosis in the late 1980s is higher than for years one though five in the 1970s).

To provide a more accurate estimate of what the RSRs (and the corresponding survival and mortality probabilities) for bladder cancer patients are likely to be for the next 20 years, we estimated RSRs for each

year post-diagnosis using a two-step procedure. This procedure focuses on using the most current data available for each year post-diagnosis. In the first step, we assumed that the ratio of the RSR at n years post-diagnosis to the RSR at $(n-1)$ years post-diagnosis in the most recent year for which we have data is what that ratio will be in future years. For example, the most recent year for which we have an RSR for one year post-diagnosis for bladder cancer is 1995. The RSR in 1995 is 0.91, which we assume will be the RSR for one year post-diagnosis in future years. The most recent year for which there is an RSR for two years post-diagnosis is 1994. We assume that:

$$\frac{RSR_2^{1994}}{RSR_1^{1994}} = \frac{RSR_2^{future}}{RSR_1^{future}}$$

so that

$$RSR_2^{future} = RSR_1^{future} \times \frac{RSR_2^{1994}}{RSR_1^{1994}} \ .$$

Using the most recent RSR for one year post-diagnosis (0.91), and the RSRs we have from 1994 for one year and two years post-diagnosis (0.911 and 0.865, respectively), the RSR for two years post-diagnosis is estimated to be $0.91 \times (0.865/0.911) = 0.8641$. This estimate of the RSR for two years post-diagnosis is then used to estimate the RSR for three years post-diagnosis, using the above formula. We continue this process until we have generated RSRs for each of twenty years post-diagnosis.

The RSRs, derived as described above, are only *estimates* of the underlying population RSRs (i.e., the RSRs for the entire population of bladder cancer patients in the United States). As such, they display some of the "bumpiness" that data often contain. In step two, a plot of these estimated RSRs against years post-diagnosis was generated. It shows that they follow a general exponential decay trend. Rather than use these estimated RSRs, regression was used to estimate the smooth trend described by the estimates derived in step one. In particular, we estimated the model:

$$\ln(RSR) = a + b \times \ln(\text{years post-diagnosis})$$

using the RSRs estimated in step one. The intercept (a) was estimated to be -0.131866 and the slope (b) was estimated to be -0.0134114. The fit was excellent, with an R^2 of 0.952. Exponentiating the predicted natural logarithms of RSR yielded the predicted RSRs shown in Table II.8-2.[5]

[5] All vital statistics data in this document applicable to the general population were obtained from the National Center for Health Statistics (NCHS) Vital Statistics in the United States (NCHS, 1993).

Some bladder cancer patients will die of bladder cancer, but most die of other causes. The probability of a bladder cancer patient dying of causes other than bladder cancer cannot be assumed to be the same as the probability of someone in the general population dying of other causes, particularly in the first few years post-diagnosis, when a bladder cancer patient's probability of dying of bladder cancer is not trivial.[6] This becomes clear in the extreme case in which the probability of dying of an illness is extremely high. Suppose, for example, that the probability of dying of all causes except for illness X is 0.025 in the general population. Suppose that in a cohort of patients diagnosed with illness X the probability of dying from illness X in the first year post-diagnosis is 0.99. If dying of other causes in this cohort were the same as in the general population (0.025), then their probability of dying would be greater than 1.0.

[6] This difference becomes clear in the extreme case in which the probability of dying of an illness is extremely high. Suppose, for example, that the probability of dying of all causes except for illness X is 0.025 in the general population. Suppose that in a cohort of patients diagnosed with illness X, the probability of dying from illness X in the first year post-diagnosis is 0.99. If the probability of dying of other causes in this cohort were the same as in the general population (0.025), then the probability of someone in the cohort dying would be greater than 1.0.

Table II.8-2. Estimated RSRs* for Bladder Cancer for the First 20 Years Post Diagnosis	
Years Post-Diagnosis (n)	**Estimated RSR for n Years Post-Diagnosis**
1	0.86
2	0.85
3	0.84
4	0.83
5	0.82
6	0.81
7	0.80
8	0.79
9	0.78
10	0.77
11	0.76
12	0.75
13	0.74
14	0.73
15	0.72
16	0.71
17	0.70
18	0.69
19	0.68
20	0.67
*The estimated RSR for each year post-diagnosis is the result of a two step procedure, using the set of RSRs reported by NCI (1999), as described in the text above.	

The probability of a bladder cancer patient dying of bladder cancer and the probability of a bladder cancer patient dying of some cause other than bladder cancer in the *n*th year post-diagnosis, given survival to the *n*th year, were each derived from two known probabilities:

1) the probability of a bladder cancer patient surviving through the *n*th year post-diagnosis, given survival to the *n*th year; and
(2) the probability of dying of causes other than bladder cancer in a matched cohort in the general population.

The derivation is explained in detail in the Appendix to Chapter II.2.

Link to Chapter II.2, Appendix II.2-A

Because each of the known probabilities depends on the number of years post-diagnosis and (minimally) on age at diagnosis, the derived

probabilities were calculated for each of the 20 years post-diagnosis and for the average age at diagnosis (70 years).[7] The following probabilities are shown in Table II.8-3:

1) survival through the *n*th year,
2) dying of bladder cancer during the *n*th year, and
3) dying of some other cause during the *n*th year.

Probabilities of survival and dying of all causes among all members of the general population aged 70 were obtained from the National Center for Health Statistics (NCHS) Vital Statistics in the United States (NCHS, 1993). They are also shown in Table II.8-3. The values in this table are used in Section II.8.B to calculate the expected medical costs of bladder cancer patients. The probabilities in the general population of dying from bladder cancer are 0.00020 in the 70-74 year age group, 0.00031 in the 75-79 year age group, 0.00047 in the 80-84 year age group, and 0.00069 in the 85+ age group. The probabilities in column (3) were derived by subtracting these probabilities from the corresponding probabilities of dying from any cause in the *n*th year, given survival to the *n*th year. The Chapter II.2 Appendix contains a detailed explaination of the derivation of survival and mortality probabilities.

Link to Chapter II.2, Appendix II.2-A

The mortality rate of 26 percent, cited in the introduction to this section, was calculated for patients who are diagnosed at age 70 as the sum of the probabilities of their dying of the disease in each year post-diagnosis. This rate was calculated for 20 years post-diagnosis, using the data shown in Table II.8-3. The probabilities of dying of bladder cancer during each year post-diagnosis, shown in the column titled "probability of dying of bladder cancer in the *n*th year post-diagnosis" were summed to obtain a value of 26 percent.

[7] Twenty years is period that captures most of the deaths due to bladder cancer among those diagnosed with the disease. This period is a reasonable maximum duration of maintenance care and treatment for those who do not die of bladder cancer.

Table II.8-3. Survival and Mortality Probabilities for the Average Bladder Cancer Patient[a]						
	A Cohort in the General Population (Matched)		A Cohort of Bladder Cancer Patients			
Years post-diagnosis (n)	Probability of surviving *n* years	Probability of dying in *n*th year of causes other than bladder cancer, given survival to the *n*th year	Relative Survival Rate (RSR)	Probability of surviving through the *n*th year post-diagnosis	Probability of dying of bladder cancer in the *n*th year post-diagnosis[b]	Probability of dying of other causes in the *n*th year post-diagnosis
0	1.000	---	---	1.0	---	---
1	.973	.027	0.86	.842	.134	.025
2	.945	.029	0.85	.806	.011	.024
3	.915	.031	0.84	.771	.011	.025
4	.884	.034	0.83	.735	.010	.026
5	.852	.037	0.82	.698	.010	.027
6	.817	.040	0.81	.661	.009	.028
7	.782	.043	0.80	.624	.009	.028
8	.745	.047	0.79	.586	.008	.029
9	.707	.051	0.78	.549	.008	.030
10	.667	.056	0.77	.511	.007	.030
11	.626	.061	0.76	.473	.007	.031
12	.584	.067	0.75	.436	.006	.031
13	.541	.073	0.74	.398	.006	.032
14	.497	.081	0.73	.361	.005	.032
15	.451	.090	0.72	.324	.005	.032
16	.410	.090	0.71	.290	.004	.029
17	.373	.090	0.70	.260	.004	.026
18	.339	.090	0.69	.234	.004	.023
19	.308	.090	0.68	.210	.003	.021
20	.280	.090	0.67	.188	.003	.019

a. The survival and mortality probabilities for bladder cancer patients presented here are derived from the RSRs estimated from RSRs obtained from NCI and the survival probabilities for a matched cohort in the general population. The average age of diagnosis of 70 years was used. See text for an explanation calculation methods.

b. When the probalities in this column are summed, they yield the probability of dying of bladder cancer over 20 years post-diagnosis, which is equal to 26 percent.

There is likely to be additional loss, although at a very low rate, beyond 20 years; however, data were not available on those values. Impacts beyond 20 years are unlikely to have a substantial impact on cost analyses because there are many competing causes of death when a person reaches 90 years of age.

The RSR can be used to approximate the probability of mortality at young ages, when the background death rate is minimal. The bladder cancer mortality rate is approximated by 1 – RSR when background age-related mortality from other causes is not considered. In the case of bladder cancer, the RSR is 0.67 and 1 - RSR = 0.33. In reality, there is always a background death rate in a population, and this rate increases with age. As noted previously, most bladder cancer patients do not die of bladder cancer. Only 18.8 percent of the population diagnosed with bladder cancer survive to 20 years post-diagnosis, but most of these losses are due to other causes of death than bladder cancer. The RSR, used with the background mortality rates of the population at the average age at diagnosis, provides clear information on the survival and mortality dynamic of that specific population. If the cancer occurs at a younger age than usual due to its genesis (e.g., chemical induction), however, then the mortality statistics obtained through the method described above will underestimate bladder cancer-related mortality. In these cases, the RSR itself is a better approximation of survival (and derived mortality), allowing estimation of mortality at young ages when background mortality is negligible.

Some environmentally-induced cancers, such as arsenic-induced skin cancer, occur at much younger ages than those at which the cancers are typically observed in the general population. Consequently, the use of the inverse of survival, 1 – RSR (e.g., 0.33 in the case of bladder cancer), as an estimate of mortality may be very relevant for calculating benefits associated with the avoidance of some environmentally-induced cancers. Due to the higher mortality estimates that this approach will always generate, the benefits of avoiding the disease will be larger when the RSR is used directly to estimate cancer mortality. When there is no evidence that the disease will occur at an age that is younger than that of the general population, the calculations that precede this — that link morbidity and mortality to the *average* age at diagnosis — are used to estimate direct medical costs.

II.8.B Costs of Treatments and Services

II.8.B.1. Methodology

II.8.B.1.1 Overview

There is no single typical case or treatment pattern for bladder cancer due to individual differences in the stage of cancer at diagnosis, multiple treatment options, patient health and age, and other factors; however, average costs can be calculated. Treatment of bladder cancer may occur over a brief or extended period of time, and costs may be limited or substantial. As discussed in Section II.8.A, bladder cancer has a relatively low mortality rate, with a relative survival rate of 0.67. The medical costs of those who die of the disease are usually very different than for those who survive (this is discussed in more detail in Chapter I.1). This chapter therefore provides costs for the "average" bladder cancer patient, as well as for survivors and nonsurvivors as separate patient groups.

Link to Chapter I.1

II.8.B.1.2 Medical Cost Data

II.8.B.1.2.1 Sources

Medical cost data would ideally be obtained on current medical expenditures. Although data files are maintained by public and private sector sources, they are not generally available for public use. In addition, to obtain reliable cost estimates it is necessary to evaluate very large databases of charges from a variety of sources. This method was neither practical nor cost-effective for the development of this chapter, given the availability of summary data from other sources. A data search was conducted to locate information in the medical economics literature regarding medical costs associated with bladder cancer. In addition to a literature search, most federal agencies dealing with cancer, disabilities, medical costs and their management, and related issues were contacted for information, and the various federal databases were discussed with senior staff at these agencies.

Very recent cost data were not located.[8] However, current (1994) cancer data were obtained regarding incidence and survival (as reported in Section II.8.A, above), and were used with cost data from the 1980s described below. The cost estimates presented in this section are based primarily on the work of Baker et al. (1989) and Hartunian et al. (1981), respectively, and on two sources of statistical data: the National Cancer Institute (1999) and Vital Statistics of the United States, 1993 (NCHS, 1997).

[8] Studies were located that used more recent cost data than those used in this analysis. Due to serious limitations (i.e., data were incomplete), the studies were not used. They are reported in the "Other Studies" section at the end of Section II.8.B.

Based on the 1997 review of the medical literature carried out for the development of this chapter, there do not appear to be widely-adopted new treatment methods for bladder cancer that alter either the medical costs or the survival rates for most patients substantially. Consequently, the cost estimates presented in this chapter may be considered appropriate under most circumstances (e.g., regional costs may vary).

II.8.B.1.2.2 Baker et al.'s Cost Estimation Method

Baker et al. (1989) used the Continuous Medicare History Sample File (CMHSF) to estimate the per-patient average lifetime medical cost of treating bladder cancer based on data files from 1974 to 1981. They chose CMHSF because:

1) it is a nationally representative sample of the Medicare population (five percent), covering over 1.6 million patients;
2) it is longitudinal, dating from 1974 to 1981; and
3) it captures the majority of medical expenses for each beneficiary.

Five Medicare files are included in the CMHSF, which cover:

1) inpatient hospital stays,
2) skilled nursing facility stays,
3) home health agency charges,
4) physicians' services, and
5) outpatient and other medical services.[9]

Costs not included are outpatient prescription medications and nursing home care below the skilled level.

Because CMHSF provides no indication of initial diagnosis, Baker et al. assumed that disease onset occurred when a diagnosis of bladder cancer was listed on a hospitalization record following a minimum of one year without a bladder cancer diagnosis. This assumption is reasonable due to the high frequency of hospitalization associated with the disease (i.e., individuals diagnosed with bladder cancer would be hospitalized). Only patients with an initial diagnosis during the years covered by the database (1974-1981) were included.

[9] See Baker et al. (1989 and 1991) for further details. Baker et al. (1991) contains additional descriptive data regarding the database and methods used for the cost analysis; however, it does not contain cost data for bladder cancer.

Costs associated with bladder cancer were assigned to three post-diagnostic time periods:

- initial treatment, during the first three months following diagnosis;
- maintenance care, between initial and terminal treatment; and
- terminal treatment during the final six months prior to death.

As noted in Chapter I.1, the amount paid for service may differ from the actual medical costs because many insurers and federal programs either 1) pay only a portion of total costs, or 2) pay more than actual costs to underwrite the care providers' losses due to underpayment from other sources.

Link to Chapter I.1

Baker et al. used provider charges, rather than Medicare reimbursements (which represent only a portion of most total charges), thus providing a more accurate cost estimate. To improve the accuracy of the cost estimates, Baker et al. included cost data on coinsurance, deductibles, and other cost components. They made four adjustments to the cost estimates calculated from the CMHSF. First, charges were added for skilled nursing facilities (SNFs) not covered by Medicare by multiplying the "length of stay" at an SNF (computed from admission and discharge dates) by the average daily SNF charge. Second, the annual Medicare Part B deductible of $60 was added to the reimbursed charges in the database. Third, since Medicare pays only 80 percent of physicians' charges, Baker et al. scaled these reimbursements to 100 percent of physicians' charges to better reflect social costs. Finally, they inflated all dollar values to 1984 dollars using the Medical Care component of the Consumer Price Index.

II.8.B.1.2.3 Cost Estimates by Treatment Period

Medical costs associated with the initial, maintenance, and terminal cancer care treatment periods were itemized in Baker et al. (1989) and are shown in Table II.8-4. The 1989 paper did not report incremental costs or the costs of other medical services, which would be anticipated to occur while the patient was receiving cancer treatment (i.e., co-morbidity/background costs). In order to estimate the incremental costs, a co-morbidity cost of $2,988 per year (1984 dollars) from Baker et al. (1991) was used in this analysis. (This is equivalent to $6,394 in 1996 dollars using the CPI multiplier of 2.14 for 1984 to 1996.) The co-morbidity cost was pro-rated for this analysis using the specified durations for the initial (three-month) and terminal (six-month) treatment periods.

Table II.8-4 lists the incremental costs calculated for the three treatment periods. Total costs are reported for the initial and terminal care periods. Annual costs for the maintenance period are shown and are further

discussed in the "Lifetime Costs" section below. Using the Medical Care component of the Consumer Price Index (CPI-U), all costs are inflated to 1996 dollars for purposes of this handbook. (The adjustment factor for 1984 to 1996 is 2.14; Bureau of Labor Statistics.)

Table II.8-4. Average Per Patient Costs for the Three Periods of Treatment for Bladder Cancer in 1996 dollars
Costs adjusted for inflation using the Medical Care component of the Consumer Price Index (CPI-U) 1996:1984 = 2.14 (Bureau of Labor)

Treatment Period	Incremental Cancer Treatment Cost
Initial (3 months)	$16,527
Maintenance (per year)	$13,277
Terminal (6 months)	$36,558

Based on Baker et al., 1989, with comorbidity charges from Baker et al., 1991.

II.8.B.1.3 Calculation of Lifetime Cost Estimates for the "Average" Bladder Cancer Patient

This section contains a discussion of the calculation of lifetime medical costs for the "average" bladder cancer patient. The sections that follow discuss methods and results of calculations for estimating costs for survivors and nonsurvivors of bladder cancer separately. These separate approaches were used to address specific requirements of different activities that EPA carries out using direct medical cost data. Although Baker et al. (1989) provide useful cost estimates for the three treatment periods, they do not provide information on two critical aspects of medical costs:

1) costs for survivors versus nonsurvivors of bladder cancer. These may differ substantially. For example, survivors would not have terminal care costs and may receive maintenance services for an extended time period.; and
2) estimates of the duration of the maintenance periods.

Data regarding age at diagnosis of bladder cancer were obtained from NCI (1999). Survival and mortality probabilities for each year post-diagnosis were derived from relative survival rates obtained from NCI (1999), as discussed in Section II.8.A.5.2.

Link to II.8.A.5.2

This information was used to address many time-related medical cost issues. For some aspects of the analysis, however, detailed information

was not available and average values have been used as a reasonable approximation (e.g., a 20-year maintenance period was assumed for survivors of bladder cancer). When average values or other assumptions are used in this analysis, they are so noted.

As previously noted, there are no substantial differences in survival related to age at diagnosis, and NCI does not provide age-specific relative survival rates for each year post-diagnosis. Consequently, it was assumed for this analysis that the relative survival rates for bladder cancer were the same for all ages. The survival and mortality probabilities for bladder cancer patients, which are incorporated into calculations of expected medical costs as discussed below, are based on this assumption.

The analysis assumes that death always occurs midyear. All bladder cancer patients are therefore assumed to incur the costs of initial treatment during the first three months of the illness. The costs incurred after that during the first year depend on whether the patient:

1) survives through the year,
2) dies of bladder cancer during the year, or
3) dies of some other cause during the year.

Patients who survive through the year incur the costs of initial treatment ($16,527.2) during the first three months, and then incur nine months' worth of maintenance care costs (0.75 × $13,276.6 = $9,957.4) during the remainder of the year. The total cost incurred during the first year by those patients who survive the year is therefore $16,527.2 + $9,957.4 = $26,485.

Bladder cancer patients who die of bladder cancer during the first year incur the initial treatment cost and then incur terminal care costs for the remaining three months of their lives (because those who die are assumed to die midyear). Total costs during the first year post-diagnosis in this case are therefore $16,527.2 + (0.5 × $36,557.6) = $34,806.

Finally, the small percentage of bladder cancer patients who die of causes other than bladder cancer during the first year post-diagnosis incur the initial treatment costs and then incur three months' worth of maintenance care costs. Total first-year costs for these patients are therefore $16,527.2 + 0.25 × $13,276.6 = $19,846.

The expected medical costs for bladder cancer patients during the first year post-diagnosis, then, may be expressed as:

> **Expected First-Year Cost: initial treatment costs + [maintenance care costs for nine months × probability of survival through first year + terminal care costs for three months × probability of dying of bladder cancer during first year + maintenance care costs for three months × probability of dying of other causes during the first year]**

Example: Expected first-year medical costs of a bladder cancer patient diagnosed at age 70

As noted above, all bladder cancer patients incur an initial treatment cost of $16,527. Those who survive through the year also incur maintenance care costs for the remaining three quarters of the year. The total first-year costs of those who survive the year are:

Initial treatment:	$16,527.2
Maintenance treatment:	$9,957.4 (.75 × $13,276.6)
Total First-Year Cost	$26,485

About nine percent of bladder cancer patients die of bladder cancer during the first year. Those who do will incur the initial treatment costs plus half of the terminal care costs. The total first-year costs of those who die of bladder cancer during the year are:

Initial treatment:	$16,527.2
Terminal care:	$18,278.8 (.50 × $36,557.6)
Total First-Year Cost	$34,806

Finally, a small percentage of patients will die of competing illnesses during the first year. Because those who die of causes other than bladder cancer are assumed to die at the midpoint of the year, costs during the first half of the year are assumed to consist of the initial treatment costs for three months, plus three months of maintenance care costs as follows:

Initial treatment:	$16,527.2
Maintenance treatment:	$3,319.1 (.25 × $13,276.6)
Total First-Year Cost	$19,846

For each subsequent year, costs consist entirely of maintenance care costs for those who survive the year. For those who do not survive the year, costs depend on whether death was due to bladder cancer or other causes.

For those who die of bladder cancer during the *n*th year, costs incurred that year consist of six months of terminal care costs, or $36,558. For those who die of other causes during the *n*th year, there are six months of maintenance care costs, or 0.5 × $13,276.6 = $6,638.

The expected first-year medical cost incurred by the "average" bladder cancer patient diagnosed at age 70 is a weighted average of the costs of those who survive the first year, those who die of bladder cancer during the first year, and those who die of other causes during the first year, where the weights are the probabilities of each of these occurrences.[10] The weighted average medical costs were calculated for 20 years post-diagnosis and expected costs were summed over the 20 years. This timeframe was assumed to be a reasonable period over which additional medical costs associated with bladder cancer (i.e., maintenance care costs) would be incurred by bladder cancer patients.

Although the actual average period of maintenance care for bladder cancer is not known, the resulting uncertainty about the expected maintenance costs during a 20-year period is somewhat lessened by the fact that a large percentage of bladder cancer patients diagnosed at age 70 die within the 20-year period (mostly of other causes), and would therefore not incur maintenance costs for the full 20 years anyway.

The expected medical costs for bladder cancer patients during the *n*th year post-diagnosis, for $n>1$, then, may be expressed as:

> **Expected *n*th-Year ($n>1$) Cost: [maintenance care cost for one year × probability of survival through *n*th year + terminal care cost for six months × probability of dying of bladder cancer during the *n*th year + maintenance care cost for six months × probability of dying of other causes during the *n*th year]**
>
> **Expected Lifetime Cost = Expected first-year cost + the sum of the (discounted) expected subsequent-year costs**

[10] Although this analysis focuses on costs incurred by a patient diagnosed with bladder cancer at the average age of diagnosis (70 years), some environmentally-induced cancers are diagnosed at earlier ages than those commonly reported for the cancers (e.g., arsenic-induced skin cancer). As noted in Section II.8.A, this earlier diagnosis has an impact on the mortality dynamics and on the direct medical costs. The uncertainty analysis contained in Section II.8.C includes an age-specific analysis of direct medical costs, that demonstrates the differences that can result in earlier ages of onset than those used in the basic analysis for this chapter.

The first year of treatment is calculated differently from other years because the first three months of that year are spent in "initial" treatment and the costs for that period of intensive medical care and surgery are calculated separately.

The mathematical equation for the expected lifetime medical costs incurred by the "average" bladder cancer patient over a 20-year period is:

$$\$16{,}527 + (\$13{,}277 \times 0.75 \times ps_1) + (\$13{,}277 \times 0.25 \times pm_1{}^{o}) + (\$36{,}558 \times 0.5 \times pm_1{}^{bc})$$

$$+\sum_{y=2}^{20}\left[(ps_y \times \frac{\$13{,}277}{(1+r)^{y-1}}) + (pm_y{}^{o} \times \frac{\$6{,}638}{(1+r)^{y-1}}) + (pm_y{}^{bc} \times \frac{\$36{,}558}{(1+r)^{(y-1)}})\right]$$

Where:

y	=	the year post-diagnosis,
ps	=	the probability of surviving through the year,
pm^{bc}	=	the probability of dying of bladder cancer during the year,
pm^{o}	=	the probability of dying from other causes during the year, and
r	=	the discount rate.

The cost estimates for each year post-diagnosis and the estimate of undiscounted expected total cost for a 20-year period are shown in Table II.8-5 for the "average" bladder cancer patient diagnosed at age 70. The survival and mortality probabilities necessary for the calculations of costs are shown in Table II.8-3.

Link to Table II.8-3

II.8.B.1.4 Calculation of Lifetime Cost Estimates Separately for Bladder Cancer Survivors and Nonsurvivors

II.8.B.1.4.1 Survivors and Nonsurvivors

As noted above, there are differences in medical services provided to bladder cancer patients who survive the disease (survivors) versus those who die of the disease (nonsurvivors). Based on cost estimates by Baker et al. (1989), terminal care is provided for approximately six months to terminally ill cancer patients. The costs to nonsurvivors for this care ($36,558) is considerably higher than costs for survivors who receive maintenance care for the same period of time ($6,638).[11]

EPA may use the value of a statistical life (VSL) for nonsurvivors and thus calculate separate costs for survivors and nonsurvivors. The method

[11] Nonsurvivors include only those who die of bladder cancer and do *not* include those who die of any other causes.

shown above to calculate costs for the "average" patient uses the unconditional probabilities of survival and mortality listed in Table II.8-3. The method used to calculate costs for survivors and nonsurvivors separately requires the probabilities that are conditional on being either a survivor or nonsurvivor of bladder cancer.

Link to Table II.8-3

The conditional probability of a bladder cancer nonsurvivor dying in the *n*th year is the number of nonsurviving bladder cancer patients who die of bladder cancer during the *n*th year divided by the total number of bladder cancer nonsurvivors. Likewise, the conditional probability of a bladder cancer survivor dying in the *n*th year is the number of bladder cancer survivors who die (of causes other than bladder cancer) during the *n*th year divided by the total number of bladder cancer survivors. A detailed explanation of the derivation of these values is provided in Chapter II.2. The conditional probabilities of survival and mortality for survivors and nonsurvivors of bladder cancer are given in Table II.8-6.

Link to Chapter II.2

II.8.B.1.4.2 Calculation of Lifetime Cost Estimates for Bladder Cancer Survivors

As shown in the example portion of Section II.8.B.1.3, cost estimates are calculated by summing the costs of the different treatment phases over the lifetime of the bladder cancer patient.

Link to Section II.8.B.1.3

Table II.8-5. Expected Costs of Medical Services (in 1996$) for Bladder Cancer Patients (Age of Onset = 70)[a]

	Medical Costs in the *n*th Year (undiscounted)			
Years Post-Diagnosis (n)	if survive through the *n*th year	if die of bladder cancer in the *n*th year	if die of other causes in the *n*th year	Expected Medical Costs for the *n*th Year Post-Diagnosis[c] (Undiscounted)
1[b]	26,485	34,806	19,846	27,432
2	13,277	36,558	6,638	11,276
3	13,277	36,558	6,638	10,790
4	13,277	36,558	6,638	10,299
5	13,277	36,558	6,638	9,802
6	13,277	36,558	6,638	9,301
7	13,277	36,558	6,638	8,794
8	13,277	36,558	6,638	8,283
9	13,277	36,558	6,638	7,769
10	13,277	36,558	6,638	7,254
11	13.277	36,558	6,638	6,740
12	13.277	36,558	6,638	6,224
13	13.277	36,558	6,638	5,708
14	13.277	36,558	6,638	5,195
15	13.277	36,558	6,638	4,685
16	13.277	36,558	6,638	4,205
17	13.277	36,558	6,638	3,772
18	13.277	36,558	6,638	3,384
19	13.277	36,558	6,638	3,035
20	13.277	36,558	6,638	2,723
Expected Total Cost Through the 20th Year Post-Diagnosis for a Bladder Cancer Patient Diagnosed at Age 70				156,670

a. The probabilities used in this table are from Table II.8-3. The costs are from Table II.8-4.

Links to Tables II.8-3 and II.8-4

b. First-year costs include the charge for "initial" therapy ($16,527). The duration of maintenance care is adjusted accordingly (see text for discussion).

c. Calculated using the probabilities in Table II.5-3 and the costs in Columns (2),(3), and (4) of this table.

Link to Table II.5-3

Table II.8-6. Conditional Probabilities of Survival and Mortality for Survivors and Nonsurvivors of Bladder Cancer (Age of Onset = 70)[a]

Years Post-Diagnosis (n)	Bladder Cancer Survivors		Bladder Cancer Nonsurvivors	
	Conditional probability of:		Conditional probability of:	
	Surviving through the *n*th year	Dying of some other cause during the *n*th year	Surviving through the *n*th year	Dying of bladder cancer during the *n*th year
1	.966	.034	.494	.506
2	.934	.033	.451	.043
3	.900	.034	.410	.041
4	.865	.035	.371	.039
5	.828	.036	.334	.037
6	.791	.037	.299	.035
7	.752	.039	.266	.033
8	.713	.040	.234	.031
9	.672	.041	.205	.030
10	.631	.041	.177	.028
11	.589	.042	.151	.026
12	.546	.043	.127	.024
13	.503	.043	.105	.022
14	.459	.044	.085	.020
15	.415	.044	.067	.018
16	.376	.039	.051	.016
17	.341	.035	.036	.015
18	.309	.032	.023	.013
19	.281	.028	.011	.012
20	.255	.025	.000	.011

a. As noted for Table II.8-3, the conditional survival and mortality probabilities for bladder cancer patients presented here are derived from the RSRs estimated from RSRs obtained from NCI and the survival probabilities for a matched cohort in the general population. See Section II.8.A.5.2 for an explanation of the estimation of RSRs.

Link to Section II.8.A.5.2

The expected medical costs for bladder cancer survivors during the first year post-diagnosis may therefore be expressed as:

<u>Expected First-Year Cost:</u> initial treatment costs + [maintenance care costs for nine months × probability of survival through first year + maintenance care costs for three months × probability of dying of other causes during the first year]

The expected medical costs for bladder cancer survivors during the *n*th year post-diagnosis, for $n>1$, then, may be expressed as:

> **<u>Expected *n*th-Year (*n*>1) Cost:</u> [maintenance care cost for one year × probability of survival through *n*th year + maintenance care cost for six months × probability of dying of other causes during the *n*th year]**
>
> **<u>Expected Lifetime Cost</u> = Expected first-year cost + the sum of the (discounted) expected subsequent-year costs**

Note that the probabilities used in these calculations are the conditional probabilities given in Table II.8-6. They are conditional on the bladder cancer patient not dying of bladder cancer.

Using the initial, maintenance, and terminal care costs from Table II.8-6, the mathematical equation for the lifetime costs incurred by bladder cancer survivors is:

$$\$16{,}527 + pm_1^{\,s} \times 0.25\ (\$13{,}277) + ps_1^{\,s} \times .75 \times \$13{,}277 + \sum_{y=2}^{20} \left[ps_y^{\,s} \frac{\$13{,}277}{(1+r)^{y-1}} + pm_y^{\,s} \frac{\$6{,}638}{(1+r)^{y-1}} \right]$$

where:

y	=	the year post-diagnosis;
ps^s	=	the conditional probability of survival for that year, conditional on being a survivor of bladder cancer;
pm^s	=	the conditional probability of mortality for that year, conditional on being a survivor of bladder cancer; and
r	=	the discount rate.

The expected medical costs for bladder cancer survivors for each year post-diagnosis, as well as the expected total medical costs over 20 years post-diagnosis, are shown in Table II.8-7.

Table II.8-7. Expected Undiscounted Costs of Medical Services (in 1996$) for Survivors of Bladder Cancer (Age of Onset = 70)			
Years Post-Diagnosis (n)	Medical Costs Through the 20th Year Post-diagnosis[a] (undiscounted)		
	Medical Cost if Survive Through the *n*th Year	Medical Cost if Die of other Causes in the *n*th Year	Total Cost Based on Weighted Average[b]
1[c]	26,485	19,846	26,262
2	13,277	6,638	12,613
3	13,277	6,638	12,172
4	13,277	6,638	11,713
5	13,277	6,638	11,238
6	13,277	6,638	10,748
7	13,277	6,638	10,243
8	13,277	6,638	9,724
9	13,277	6,638	9,193
10	13,277	6,638	8,649
11	13,277	6,638	8,096
12	13,277	6,638	7,535
13	13,277	6,638	6,965
14	13,277	6,638	6,389
15	13,277	6,638	5,808
16	13,277	6,638	5,255
17	13,277	6,638	4,759
18	13,277	6,638	4,315
19	13,277	6,638	3,916
20	13,277	6,638	3,559
Expected Total (Undiscounted) Cost Through the 20th Year Post-Diagnosis:			**179,153**

a. Costs are based on data reported in Table II.8-4, adapted from Baker et al., 1989. Probabilities of survival and mortality, taken from Table II.8-6, are conditional on surviving bladder cancer.
b. Weighted average of the costs incurred by survivors who survive the year and the costs incurred by survivors who die of other causes during the year. Weighting is based on the conditional probabilities provided in Table II.8-6.
c. Costs during the first year include a charge for "initial" therapy ($16,527), and the duration of maintenance or terminal care is adjusted accordingly. See text for discussion.

II.8.B.1.4.3 Calculation of Lifetime Cost Estimates for Bladder Cancer Nonsurvivors

Nonsurvivors of bladder cancer will incur initial, maintenance, and terminal costs. Their lifetime medical costs associated with the disease can be calculated from the costs per treatment period shown in Table II.8-4 and the conditional probabilities for nonsurvivors of bladder cancer shown in Table II.8-6.

Links to Tables II.8-4 and II.8-6

As Table II.8-6 indicates, about 55 percent of bladder cancer nonsurvivors die within one or two years of diagnosis. Of the remaining 45 percent of nonsurvivors, death from bladder cancer may occur anywhere within the remaining 18 years of the 20-year period considered in this analysis, with the conditional probabilities of death ranging from four percent in the third year post-diagnosis to about one percent in the twentieth year. As with bladder cancer survivors, medical costs for nonsurvivors each year post-diagnosis were calculated as a weighted average of the costs incurred by those who survive the year and those who die (of bladder cancer) during the year.

It was assumed that those who die during a year receive six months of care (as was done for the survivors above). It was also assumed that terminal care lasting six months would be provided to all nonsurvivors. Therefore, unless death occurred during the first year, when initial care was assumed to occur, the care costs assigned to the last year of life were terminal costs. If death occurred during the first year post-diagnosis, it was assumed that initial care and three months (half of the total) of terminal care were provided.

The general description of medical costs for nonsurvivors may be expressed as:

> **Expected First-Year Cost: [initial costs + half the terminal costs] × probability of mortality during the first year + [initial costs + maintenance care costs for nine months] × probability of survival for first year**
>
> **Expected *n*th-Year (*n*>1) Cost: maintenance care cost for one year × probability of survival through *n*th year + terminal costs × probability of mortality in *n*th year**
>
> **Expected Lifetime Cost = Expected first-year cost + the sum of the (discounted) expected subsequent-year costs**

As with the cost calculations for bladder cancer survivors, the probabilities used in these cost calculations are the conditional probabilities given in Table II.8-6, in this case, conditional on dying of bladder cancer.

Link to Table II.8-6

Using the initial, maintenance, and terminal care costs from Table II.8-6, the mathematical equation for the expected lifetime costs incurred by nonsurvivors is:

$$\$16{,}527 + pm_1^{ns} \times 0.5\ (\$36{,}558) + ps_1^{ns} \times .75 \times \$13{,}277 + \sum_{y=2}^{20} \left[ps_y^{ns} \frac{\$13{,}277}{(1+r)^{y-1}} + pm_y^{ns} \frac{\$36{,}558}{(1+r)^{y-1}} \right]$$

where:

y	=	the year post-diagnosis;
ps^{ns}	=	the conditional probability of survival for that year, conditional on being a nonsurvivor of bladder cancer;
pm^{ns}	=	the conditional probability of mortality for that year, conditional on being a nonsurvivor of bladder cancer; and
r	=	the discount rate.

The costs are summed over all years from diagnosis to death. Maintenance care costs are not added in the last year of life because the patient is assumed to receive terminal care during the six months assumed to constitute this period. (The discounted results are shown in the "Results" section that follows.) The approach is the same as that shown in the example in Section II.8.B.1.3. When the costs for each year are summed over a period of 20 years post-diagnosis, the total 20-year cost per nonsurvivor is obtained. These costs are shown in Table II.8-8.

Link to Section II.8.B.1.3

The results shown above can be used to calculate costs for an "average" bladder cancer patient, from the costs calculated for survivors and nonsurvivors. The expected medical costs of a bladder cancer patient can be calculated as a weighted average of the expected costs of survivors and nonsurvivors of bladder cancer. This approach, which was not used to calculate costs for the "average" patient in this chapter, yields the same results as the approach that was shown in Section II.8.B.1.3. In brief, the approach used in this chapter for the average patient (in Section II.8.B.1.3) uses cost data for all patients, weighted by their average utilization of services. If the survivor and nonsurvivor data were used, which incorporate utilization of services, the cost results obtained through separate calculations for the two subgroups are simply re-aggregated based on each group's proportional contribution to the cost. A discussion of why these two approaches yield the same results is provided in Chapter II.2 (Section II.2.B.2.3)

Link to Chapter II.2.B.2.3

Table II.8-8. Expected Undiscounted Costs of Medical Services (in 1996$) for Nonsurvivors of Bladder Cancer (Age of Onset = 70)			
	Medical Costs Through the 20th Year Post-diagnosis[a] (undiscounted)		
Years Post-Diag-nosis (n)	Medical Cost if Survive Through the *n*th Year	Medical Cost if Die in the *n*th Year	Total Cost Based on Weighted Average[b]
1[c]	26,485	34,806	30,699
2	13,277	36,558	7,543
3	13,277	36,558	6,936
4	13,277	36,558	6,352
5	13,277	36,558	5,793
6	13,277	36,558	5,264
7	13,277	36,558	4,750
8	13,277	36,558	4,261
9	13,277	36,558	3,797
10	13,277	36,558	3,359
11	13,277	36,558	2,955
12	13,277	36,558	2,564
13	13,277	36,558	2,200
14	13,277	36,558	1,862
15	13,277	36,558	1,551
16	13,277	36,558	1,274
17	13,277	36,558	1,016
18	13,277	36,558	784
19	13,277	36,558	577
20	13,277	36,558	390
Expected Total (Undiscounted) Cost Through the 20th Year Post-Diagnosis:			**93,927**

a. Costs are based on data reported in Table II.8-4, adapted from Baker et al., 1989. Probabilities of survival and mortality, taken from Table II.8-6, are conditional on dying of bladder cancer within 10 years post-diagnosis.

Links to Tables II.8-4 and II.8-6

b. Weighted average of costs incurred by nonsurvivors who survive the year and those who die during the year. Weighting is based on the conditional probabilities shown in Table II.8-6.

c. Costs during the first year include "Initial" therapy ($16,527) , and pro-rated maintenance or terminal care. See text for discussion.

II.8.B.2. Results of Medical Cost Analysis

The per-patient lifetime direct medical costs calculated for the "average" bladder cancer patient (as shown in Table II.8-5), bladder cancer survivors (as shown in Table II.8-7) and bladder cancer nonsurvivors (as shown in Table II.8-8) diagnosed at age 70 are listed in Table II.8-9. Undiscounted costs and costs discounted at three, five, and seven percent back to year

one (time of diagnosis) are shown.[12] Discounting was carried out for 20 years following diagnosis and comprises the assumed full duration of maintenance care for survivors.

Links to Tables II.8-5 and II.8-7

Table II.8-9. Incremental Per-capita Medical Costs for the Average Bladder Cancer Patient, Survivors, and Nonsurvivors (Diagnosed at Age 70) Undiscounted and Discounted at 3, 5, and 7 Percent ($1996)

	Discount Rate			
Patient Group	**Undiscounted**	**3**	**5**	**7**
Survivors	$179,153	$148,149	$132,653	$120,132
Nonsurvivors	$93,927	$83,449	$77,983	$73,424
Average Patient	$156,670	$131,081	$118,231	$107,811

See text for a definitions of patient groups.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

The results show substantially higher costs for survivors than nonsurvivors, due primarily to their ongoing maintenance care. It is noted that although a 20-year maintenance period for bladder cancer survivors is assumed (with adjustment for background mortality that reduces utilization), the actual average period of maintenance is not known. Maintenance periods are likely to vary considerably among individuals, depending on age, health status, access to care, and other factors. Maintenance care costs comprise the major cost element in determining the "average" patient costs, due to the relatively low mortality attributable to bladder cancer. The uncertainty surrounding the period of maintenance care for survivors could therefore have an impact on the cost estimates for the "average" patient and for survivors of bladder cancer. Because less than half of bladder cancer patients diagnosed at age 70 survive beyond the first ten years post-diagnosis (most die of causes other than bladder cancer), the impact of maintenance care costs on the costs of the "average" 70-year-old patient is less than it would be if there were a lower overall mortality rate (i.e., if diagnosis occurred at younger ages).

[12] As noted previously, costs will be higher if ages of diagnosis are earlier. The uncertainty analysis in Section II.8.C contains additional cost estimates for earlier ages of diagnosis.

II.8.B.3. Other Studies

A number of other studies were reviewed for this analysis. Most had shortcomings with respect to the duration of the study (e.g., only one year of medical cost data obtained) or the age of the data. A select group of these are discussed below.

II.8.B.3.1 Hartunian et al.

Hartunian et al.'s (1981) method of estimating the costs of illness has been discussed in Chapter I.1. The authors defined expected treatment on a yearly basis, developed annual costs of the treatment, and combined the cost data with survival data. Using this method, they estimated the costs of cancer at eight sites, including cancer of the urinary system, which includes bladder, kidney, and related structures.

Link to Chapter I.1

Hartunian et al. estimated the costs of inpatient stays using a 1976 study by Scotto and Chazze of newly diagnosed cancer patients followed over a two-year period to establish hospitalization and payment patterns. These data were supplemented by questionnaire data. The Hartunian data are quite old (over 20 years) and both survival and treatment methods have changed since that time. Their estimated survival for bladder cancer was 0.15 percent, which is considerably lower than the current survival statistics and impacts the percentage of patients who access care components (reducing medical cost estimates through high death rates). Medical treatment has also changed considerably since their data were obtained. In addition, they also limit their analysis to two years post-diagnosis, which is not sufficient due to both the prolonged period of detailed follow up care that is required (note the 20 year post-diagnosis time frame for increased mortality) and the frequency of relapse.

II.8.B.3.2 Riley et al.

A study of Medicare payments from diagnosis to death in elderly cancer patients was carried out by Riley et al. (1995). The cost estimates are based on Medicare payments only, which do not include: most nursing home care, home health care, pharmaceuticals unless supplied for inpatients, out-of-pocket expenses, deductibles, charges in excess of Medicare paid by other sources (e.g., coinsurance), and other related medical services not covered by Medicare.

Medicare patients younger than 65 were not included and the average age at diagnosis of the bladder cancer cohort was 75.2 years, in contrast with the 70 year national average. Riley et al. note that patients diagnosed at younger ages have higher costs. In addition, those diagnosed at earlier stages have a better prognosis but may have higher medical costs (due to longer continuing care).

Medical costs are reported for all patients who were diagnosed with bladder cancer, regardless of other diseases or their ultimate causes of death. Due to the links among bladder cancer, smoking, and numerous other diseases, this method is especially problematic because costs associated with other illnesses may be commingled with the bladder cancer costs.

The background cost per year for medical services was estimated by Riley et al. to be $2,250 ($3,154 in 1996 dollars), based on the experience of all people over the age of 65 who received Medicare-compensated care. The study excluded those costs that occur during the last year of a person's life. Consequently, the estimated background value may underestimate background costs, especially as age and associated mortality risks increase over the age of 65.

Riley et al. estimated that the total average Medicare payment from diagnosis to death for persons diagnosed with bladder cancer was $57,629 in 1990 dollars, adjusted to $80,796 in 1996 dollars (CPI 1990:1996 = 1.402). This estimate is considerably lower than those obtained from Baker et al. The difference is most likely due to the exclusion of many costs not covered by Medicare, and the various other factors described above that tend to reduce the cost estimate. Due to these limitations, the Riley et al. study is not recommended for a benefits evaluation.

II.8.C. Uncertainties and Limitations

As noted periodically in the above discussion, there is uncertainty surrounding various aspects of the analysis. Information concerning some inputs to the analysis was limited. Although a complete uncertainty analysis is beyond the scope of this work, the significant sources of uncertainty are discussed. Limitations of the scope of the analysis are also discussed.

II.8.C.1. Uncertainties Surrounding Key Inputs to the Analysis

II.8.C.1.1. Analysis of Medical Costs

The cost estimates based on Baker et al. (1989, 1991) have a number of limitations, many of them noted by Baker et al. (1991), Mor et al. (1990), and Mor (1993). Most of these limitations arise from the use of CMHSF. Medicare data have five limitations that decrease its value for calculating the average lifetime direct medical costs of treating bladder cancer. First, Medicare covers medical services only for most persons age 65 and over, disabled persons entitled to Social Security cash benefits for at least 24 months, and most persons with end-stage renal disease. All patients not covered by Medicare are excluded from the database, including all non-

disabled women under 65, and women over 65 using private health insurance (Baker et al., 1991).

Given that diagnosis of bladder cancer occurs in almost half of all patients before age 65, the CMHSF excludes a significant number of younger patients. According to Mor et al., treatment for younger women for other cancers tends to be more intensive (and therefore more costly per unit time) than treatment for older women, though older women tend to have longer hospital stays. This is likely to be the case for bladder cancer as well, and may be supported by the improved cancer-specific five-year survival observed among younger versus older patients. Because these differences counteract each other, the omission of younger patients from the Baker et al. analysis is not expected to affect the results substantially. In addition, the majority of senior citizens are enrolled in Medicare (Ibid); differences in medical costs incurred by senior citizens not using Medicare should have little effect on overall cost estimates.[13]

Medicare also does not cover self-administered drugs, intermediate nursing care, long-term nursing care, and some expensive new treatments (such as bone marrow transplants). For some patients, these costs may represent significant percentages of total treatment costs. Most direct medical costs, however, appear to be covered by the CMHSF database and are included in Baker et al.'s analysis. In addition, Baker et al. made adjustments for some cost elements not covered by Medicare (see Section II.8.B).

Another drawback is that Baker et al. were not able to identify bladder cancer patients in CMHSF whose diagnosis and first course of therapy did not involve hospitalization. In an analysis of Rhode Island non-bladder cancer patients covered by Medicare, Mor et al. determined that a small percentage of patients were initially diagnosed without hospitalization, and had substantially lower initial and subsequent treatment costs (Mor et al., 1990). This omission likely causes average treatment costs to be overestimated, though by relatively little.

A fourth drawback is that Baker et al. (1989) provide no information concerning the duration of the maintenance period for bladder cancer. The analysis in this chapter considers a 20-year period. If the average duration of maintenance care among patients of bladder cancer is shorter (longer) than 20 years, the estimates of the costs incurred would be biased upward (downward). This function is true for survivors as well as nonsurvivors of bladder cancer.

[13] This figure represents those enrolled in Medicare Part A; 95 percent of those enrolled in Medicare Part A choose also to enroll in Medicare Part B.

A fifth drawback is that the data used by Baker are from the period 1974 to 1981, leading to uncertainty regarding changes in treatment methods and costs.

Finally, the reliability of the data contained in the database used by Baker et al. varies. An independent analysis of CMHSF performed in 1977 by the Institute of Medicine of the National Academy of Sciences found that the frequency of discrepancies in principal diagnoses varied among diseases (Baker et al., 1991). It is unclear whether the presence of misnamed diagnoses contained in CMHSF potentially increases or decreases the resultant cost estimates.

Overall, despite the limitations described above, Baker's analysis of the CMHSF data represents the most nationally-representative, per-patient lifetime estimate of the direct medical costs of treating bladder cancer to date. Their cost estimates are based on sound criteria. Some of the data limitations underestimate costs, and others overestimate costs; the sum of the data limitations therefore decreases the magnitude of error. More of the uncertainties in their analysis appear to underestimate costs, however; the net result is a likely underestimation of actual direct medical costs. Although there are some uncertainties associated with the estimation of the survival and mortality probabilities used in the calculation of expected medical costs (discussed below), these uncertainties are likely to be relatively small. As noted in the text, NCI RSRs used to estimate survival and mortality for this analysis are based on the survival experience of a large group of bladder cancer patients considered in relation to the survival experience of the general population.

An additional limitation of this analysis is that medical costs incurred as a result of bladder cancer, but not considered by Baker et al., may arise as a result of treatment for bladder cancer. Secondary cancers and other adverse health effects may occur due to radiation, chemotherapy treatment, and other therapies. These effects may occur substantially after bladder cancer treatment has been completed and can incur added medical costs not considered in this chapter. Many concurrent and related costs are included, however, due to the methods used by Baker et al. The authors considered all costs due to any medical services, minus the background costs of all individuals who did not have cancer.

As with all chronic diseases, it is difficult to estimate the period following diagnosis and initial treatment, during which additional medical monitoring and follow-up care take place. Data have not yet been located regarding the average duration of maintenance care for bladder cancer. For purposes of this analysis, 20 years of follow-up care was assumed to be reasonable, due to the severity of the disease and the consequences of bladder surgery.

As noted above, there is a prolonged period during which mortality continues to increase, indicating that morbidity must be monitored for many years post-diagnosis. The estimated time required for maintenance care may be revised in the future if data are located.

There is additional uncertainty associated with the age of onset of the disease and the resulting medical costs. If bladder cancer is induced at an earlier than average age (70 years), as may be the case with arsenic-induced bladder cancer if it follows the skin cancer pattern, the direct medical costs will be greater, particularly the maintenance costs. Younger patients will survive to require medical treatment and follow-up for a longer period (on average) than those who are diagnosed at age 70, because they have fewer competing causes of death. In addition, bladder cancer frequently recurs and patients require careful monitoring; some require treatment for recurrent cancer. The latter is more likely with young patients who may survive for many decades after initial diagnosis.

II.8.C.2. Scope of the Analysis

The analysis in this chapter was confined to direct medical costs by the patient. As noted in Chapter I.1, willingness-to-pay has many other cost elements.

Link to Chapter I.1

The analysis does not include time lost by the patient or their family and friends who provide care. Also omitted from cost of illness estimates are pain and suffering on the part of the patient or their family and friends, changes in job status among previously employed patients, training for new job skills due to physical limitations, or medical costs incurred after the 20-year maintenance period. These cost elements may comprise a substantial portion of the total cost of bladder cancer.

CHAPTER III.1. INTRODUCTION TO THE COSTS OF DEVELOPMENTAL ILLNESSES AND DISABILITIES

Clicking on the sections below will take you to the relevant text.

CHAPTER III.1. INTRODUCTION TO THE COSTS OF DEVELOPMENTAL ILLNESSES AND DISABILITIES

III.1.A Overview

This section of the handbook focuses on developmental illnesses and disabilities that may be associated with exposure to environmental agents. Its chapters (III.2 through III.9) provide data on the direct medical costs of individual effects or groups of similar types of developmental effects. As in previous chapters, information is not included on all elements of willingness to pay (WTP) to avoid the illness. A summary of the cost elements that comprise WTP is provided in Chapter I.1. Due to the availability of data on some additional cost elements in the source used to obtain direct medical costs, data are provided on the additional cost elements at the end of some chapters in this section.. Some of elements for which cost estimates are not available, such as the WTP to avoid pain and suffering in children, are likely to be very substantial in the case of adverse developmental effects.

Link to Chapter I.1.

This chapter contains a description of some aspects of the environmental causes of developmental toxicity, types of effects, and general issues related to economic valuation of developmental effects, as well as a list of agents associated with developmental toxicity and genotoxicity.

III.1.A.1 Description

Developmental effects cover a wide spectrum of short- and long-term illnesses, disabilities, and conditions. Pre- and postnatal exposure of children carries risks that differ in many respects from those of adults due to the unique physiological characteristics of developing individuals, their food consumption patterns, other exposure characteristics, and other factors (NAS, 1994).[1] For example, children (especially infants) have a much higher food intake than adults in relation to their body weight. They may have much greater contact with soil, and their skin absorption differs from adults.

Developmental illnesses and disabilities may be referred to in some EPA sources as "adverse developmental effects," and are defined in this handbook as any adverse health effect resulting from exposure of the mother or father pre-conception, of the mother during pregnancy, or of a

[1] These differences are described in a recent NAS report, developed by pediatricians, epidemiologists, toxicologists, and environmental scientists.

child to toxic substances. Adverse developmental health effects range from physical deformities such as cleft palate, cleft lip, and shortened limbs, to cognitive impairments such as mental retardation, hyperactivity, and delayed cognitive development. Effects also include reduced birth weight, growth retardation, adverse hormonal changes, and abnormalities in physiology (e.g., liver and kidney function) and effects resulting from genetic abnormalities (e.g., Down syndrome).[2]

There are hundreds of developmental effects listed under the general category of congenital anomalies in the International Classification of Diseases (ICD-9-CM).[3] ICD-listed effects include structural abnormalities that result from errors in embryogenesis or the fetal period (Bennett and Plum, 1996) and are usually identifiable at, or shortly after, birth. Synonyms include congenital malformations, birth defects, or structural anomalies (Bennett and Plum, 1996). Other developmental effects include non-structural abnormalities such as physiological disturbances. Still other effects may occur during childhood; for example, lead-induced brain damage can occur up through late adolescence (discussed in Chapter III.9).

Those developmental effects chosen for inclusion in this handbook include illnesses and disabilities that could reasonably be associated with environmental exposures to chemicals and that had sufficient medical cost information to be of use in economic valuations.

Major congenital anomalies, which comprise the majority of developmental effects discussed in this handbook, are identified in two to three percent of all newborn infants, independent of ethnic group or country of origin. Many anomalies are not detected at birth. During the first year of observing the child, as developmental milestones are anticipated, the rate of diagnosis doubles. By school age (five years) approximately five to seven percent of children have been diagnosed with a major congenital anomaly or learning disability (Bennett and Plum, 1996). (Learning disabilities are not included in this edition of the handbook but may be included in the future.)

III.1.A.2 Overall Costs

The medical and related costs of developmental effects are substantial. Low birth weight (LBW), which is a relatively common occurrence in the

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[2] Many of these are referred to as "birth defects" in the popular press, especially physical effects. They fall into the broad categories of structural abnormalities, functional deficiencies, and growth alterations (Kimmel, 1993).

[3] Adverse developmental effects, which include all of the types of effects discussed above, are referred to as "developmental effects" subsequently in this chapter, for brevity. The term implies adverse effects, rather than simply any effect that deviates from the norm.

United States, has been estimated to cost approximately 35 percent ($4 billion) of the $11 billion spent on health care for infants. Medical care resulting from LBW may cost in excess of one million dollars for a single child (Lewitt et al., 1995). Congenital anomalies, which are a subset of all developmental effects, were estimated to cost $6.3 billion in 1980 in the United States and represented 1.4 percent of the total cost of illness (Rice et al., 1985). This estimate included direct medical costs and lost productivity, but not special educational costs and developmental services. A similar type of evaluation in 1991 found the national cost of a single effect, cerebral palsy, to be $1.2 billion. This estimate did not include long-term institutional care, which is often very costly (National Foundation for Brain Research, 1992).

Over one half of children evaluated in subspecialty medical clinics or admitted to hospitals in North America are treated due to disorders arising from congenital anomalies. Two thirds of deaths in pediatric hospitals are also due to these anomalies. In addition, the rate of congenital anomalies in early miscarriages is approximately ten times higher than that observed in infants (Bennett and Plum, 1996). Serious developmental effects are likely to be the cause of pregnancy loss in many cases.

III.1.B Causes of Developmental Effects

The biology of developmental toxicity proceeds by two primary routes: damage to heritable cell lines and damage to somatic cell lines. Heritable cells carry the genetic materials from generation to generation (egg and sperm) and damage typically involves alterations in chromosomes. Genotoxic chemicals cause mutations or death of heritable cell lines and the mutations (genetic changes) may be perpetuated through generations.[4] When cell death occurs, there is no perpetuation of cell lines, whether mutated or not. Somatic cells (non-reproductive cells) may also be damaged by genotoxins or other types of toxins. Somatic cell damage or death affects those cells directly exposed or proceeding from the exposed cells in the same individual (damage is not conveyed from one generation to the next). This section is provided to explain the rationale for including heritable and non-heritable birth defects in the COI handbook. It also provides information on the biological mechanisms behind some birth defects.

[4] Genotoxicity deals with the effects of chemicals on DNA and on mechanisms of inheritance in cells and organisms, focusing on the process of mutagenesis (Hoffmann, 1991).

III.1.B.1 Somatic Cell Damage

Chemicals may cause cellular toxicity, including toxicity to genetic material. Somatic cell damage affects the exposed individual primarily by altering cell structure or function. Exposure to chemicals that are genotoxic or toxic to the cells in other ways during the prenatal period can cause damage to somatic cell lines during development by altering or killing cells. Exposure thus results in damage to cells, or in the absence of cells that would arise from the damaged cell. Although redundancy occurs in many developing systems and damage does not always lead to birth defects, somatic cell damage from cellular toxicity may be responsible for many of the birth defects discussed in this section. For example, genotoxicity, and other types of cellular toxicity that prevent cell replication, limit the production in the embryo of neurons in the central nervous system (CNS). They also limit the development of limb buds that eventually become limbs and digits, resulting in shortened or absent limbs (discussed in Chapter III.4). Cleft lip or palate (discussed in Chapter III.3), some heart anomalies (discussed in Chapter III.5), and spina bifida (discussed in Chapter III.6) may also result from failure of early cells to form and migrate properly. (There may also be a heritable component to some occurrences of these effects that affects cell replication and movement, as discussed in Section III.1.B.2 below.)

Changes in somatic cells may also affect the offspring of an exposed woman when the cellular damage alters her physiology or reproductive system in such a way that it impacts her children (e.g., via maternal toxicity). For example, a woman whose toxic exposure caused severe kidney damage may not have the necessary capacity in her kidneys to adequately process the substantial increase in fluid load that accompanies pregnancy. Renal failure and the related toxicity to the mother will have a serious and sometimes fatal impact on the child. Generally, when past toxicity to the mother is the cause of an adverse developmental effect, it is not reported in the toxicological literature. This omission occurs because the studies are looking for toxicity in the offspring that is independent of maternal toxicity, and is appropriate from a scientific perspective to evaluate some aspects of developmental toxicity. Information is then lacking, however, that may be appropriate for a benefits assessment on the simultaneous occurrences of maternal and offspring toxicity.

III.1.B.2 Heritable Cell Damage

Heritable cells carry the genetic materials from generation to generation (via egg and sperm) and damage typically involves alterations in chromosomes in these cells. Changes in heritable cells may be perpetuated through generations. The mutations include alterations in specific

chromosomes, as well as in the number of chromosomes (e.g., Down syndrome occurs when three of chromosome number 21 are present rather than the usual two chromosomes).

The mutations may be observable in all persons with the chromosomal alteration (dominant disorders), or may be expressed only when two chromosomes (one from each parent) with the same alteration are present (recessive disorders). Consequently, many mutations are not continuously observable because they are recessive, but may appear when both parents have the same recessive mutation (Hoffmann, 1991). Many important areas of the chromosomes have substantial redundancy so that mutations in small portions of the chromosome are compensated for by other portions that carry out the same function and remain intact.

Numerous repair mechanisms operate in cells so that exposure to genotoxins does not necessarily result in permanent damage to cells (Hoffmann, 1991). When a chemical is shown by studies to be genotoxic, however, it has the potential to cause chromosome damage. The specific site of chromosome damage cannot be predicted because chemicals alter the basic structure or mechanisms related to DNA replication. Consequently, damage may occur at any site and the nature of any resulting defect can vary accordingly.

In 1984, the National Academy of Sciences estimated that about 0.3 to 0.4 percent of infants have syndromes associated with chromosomal abnormalities (NAS, 1984). More recently these have been associated with approximately seven to ten percent of stillbirths and infant deaths (Bennett and Plum, 1996). As the human genome is mapped, understanding and identification of genetic defects will increase. Some relatively common effects that are based on genetic changes include Down syndrome (discussed in Chapter III.8), Turner's syndrome, and Klinefelter syndrome. Some genetic diseases that are recessive (e.g., cystic fibrosis, Tay-Sachs, and phenylketonuria) are thought to occur primarily through inheritance rather than new mutations (Hoffmann, 1991).

III.I.B.3 Developmental Toxicity Studies

Most evidence of developmental toxicity is obtained from human epidemiological studies or animal toxicity studies. The majority of data are obtained from animal studies due to ethical issues and difficulties in conducting large-scale controlled human studies. As discussed above, many developmental effects are not observed until many years after birth; consequently, birth defects are poorly tracked in the population with only a small percentage reported formally (i.e., on birth certificates). Other complicating factors include large variations in exposure, lifestyle, and genetically-determined risks of birth defects within most populations.

Animal studies are often preferred due to the difficulty in conducting human studies and for a variety of other reasons. These reasons include cost, ethical considerations, and the level of control over exposure concentrations and durations. Confounding study factors are limited in an animal study and an evaluation of all observable structural and functional effects is possible. There are many limitations to animal studies, including considerable interspecies differences in neurological capabilities and potential damage, and some physiological differences between study mammals and humans.

Often the implications of effects observed in human and animal studies are not clear from a health or economic perspective. For example, a recent study by Kanitz et al. (1996) found that some water disinfection chemicals were associated with reduced infant head size and body length in some communities (characteristics easily extracted from birth certificates). These features usually suggest retarded development. Although giving clear reason for concern, the immediate and long-term health effects of these measures aren't clear. Such external measures don't provide specific information on the more important internal effects on the brain or other organ systems or on future development. Consequently, the data cannot be easily used to establish the benefits of avoidance, even though most people would agree that a considerable benefit is to be gained from avoiding the observed effects. Some human studies (e.g., of mercury) provide more straightforward indications of developmental toxicity.

Animal studies of developmental toxicity have been carried out for many environmental agents, and are required by the federal government for some groups of chemicals (e.g., as part of the registration process for pesticides and some pharmaceuticals). Although effects seen in humans may be different than those seen in animal studies, it is assumed that developmental effects in animals indicate the potential for developmental toxicity in humans (EPA, 1991). Agents associated with developmental toxicity are listed in Section III.1.D below.

III.1.B.4 Genotoxicity

Genotoxicity, as discussed above, may result in mutations or death of somatic or heritable cell lines. Ethical considerations preclude the testing of toxic agents on humans, but data on genotoxicity exist from studies of occupationally-exposed workers. Incidental exposure to some chemicals present in the workplace has been shown to cause chromosomal damage in some workers. For example, exposure to vinyl chloride, styrene, benzene and ethylene oxide have been positively associated with chromosomal aberrations (Hoffmann, 1991). A high incidence of spontaneous abortions was observed in nurses exposed to genotoxic cancer therapy drugs. Even when these studies have been carried out, it is very difficult to

establish unequivocally whether a chemical causes genotoxicity in humans using epidemiological studies, due to a number of factors, including:

- the inability to fully characterize all exposures that may contribute to genotoxicity;
- the likelihood that severe damage will result in early miscarriage and not be observable ;
- the largely random occurrence of many birth defects (e.g., Down syndrome); and
- the separation in time between germ-cell mutations and effects in subsequent generations (Hoffmann, 1991).

In addition, damage to cells, whether heritable or somatic, may be followed by cell repair or death, which may not result in an adverse outcome. Multiple factors determine whether an adverse effect at the cellular level will result in damage to a child.

Some studies in animals have been performed. The availability, however, of relatively quick and inexpensive in vitro assays on human or other mammalian cell cultures using somatic and reproductive cells, or on small animals or microorganisms, make these the methods of choice for most genotoxicity tests. In addition, researchers are beginning to study the mutagenicity of environmental mixtures that occur in their natural setting. Hannigan et al. (1996) recently evaluated the mutagenicity of urban particulate air pollution samples. This type of research has the potential to provide very useful information regarding the mutagenic potential of environmental pollutants.

Thousands of chemicals have been evaluated using various in vitro tests of genotoxicity to determine the potential for genotoxic effects.[5] This information has been commonly used as an indicator of a chemical's carcinogenic potential, because there is a link between genotoxicity and cancer (Hoffmann, 1991). This information also has implications for a chemical's potential to cause developmental toxicity. Genotoxicity is not, however, used at this time to establish a *causal* link between developmental effects and exposure. Even when human data are available indicating that an agent causes mutations, it is not possible to predict the type of developmental effect that would arise from the mutation because damage can occur at thousands of sites on the chromosomes.

Agents associated with genotoxicity are listed in Section III.1.D. below.

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[5] The Environmental Mutagen Information Center in Oak Ridge, Tennessee, had data on 21,000 chemicals in their database in 1990 (Hoffmann, 1991).

III.1.B.5 Categories of Causes of Developmental Damage

The contributions to congenital anomalies by various factors have been estimated:

congenital infection	2 - 3%
maternal diabetes	1.5%
other maternal illness	<1.5%
chromosomal	6%
monogenic	7.5%
multifactorial	20%
maternal medication	1 - 2%
unknown	**>50%**

(Bennett and Plum, 1996)

As this list indicates, most congenital anomalies have no clear origin (more than 50 percent). They may arise from a single factor or a specific combination of factors. Interference with the normal progress of development during a pregnancy may result from genotoxic effects, cellular toxicity, or other factors. Adding to the complexity of evaluating developmental toxicity is the fact that the nature of the developmental effects often depend on the period of development during which exposure occurred.

III.1.C Valuation Issues

III.1.C.1 Short- Versus Long-term Effects

Developmental effects can be organized in many different ways, and are typically approached by the medical community on an organ system basis (e.g., neural damage, skeletal abnormalities) or by syndrome (e.g., Down). Approaching these effects from an economic perspective may require a different approach that takes into account issues of cost, such as long- versus short-term care. Economic evaluations differ substantially depending on whether effects are time-limited or not. For example, treatment and monitoring for elevated blood-lead levels is usually time-limited, while medical treatment and services for cerebral palsy require long-term medical and other interventions. Most developmental effects required long-term follow-up and care, often including a variety of medical specialities, leading to relatively high lifetime care costs.

Federal and state agencies tend to group many of the effects that require long-term care under the heading of "disabilities." This term includes physical and mental disabilities, which share the common requirement that long-term care is required. Many of the disabilities are classified by the

Department of Health and Human Services and enable families to receive special funding for medical care, maintenance, and other costs incurred by the disabled child and adult. Funding is carried out through programs such as Supplemental Security Income (SSI). The availability of federal databases that track these types of disabilities and costs improves our ability to estimate the treatment patterns and costs.

Fewer data are available for disabilities not covered under federal programs. Care may be received from a variety of specialists and is often difficult to estimate, due to variations in the types of services that are required. There is considerable variation in services and costs among children with the same disabilities, due to differences in the severity of their disabilities. An example of this can be observed among children with Down syndrome, who may range from mildly affected by the chromosomal abnormality to severely incapacitated. With the advent of managed care, there has been an effort to evaluate the overall costs of caring for children with disabilities that do not qualify for government supplements, so that capitation costs can be estimated. This process is still in its infancy, although some data are available that have been developed for this purpose.

III.1.C.2 Occurrence of Illnesses

Tracking of occurrence is poor because only a small percentage of developmental effects is reported on birth certificates. Many effects are not noted at birth and may be observable only after a child begins to develop and is observed to miss critical developmental milestones. Severe birth defects are more often reported because they are observed at birth and are typically reported; however, many of these are very rare. (e.g., spina bifida, Down Syndrome) (McManus et al., 1996 in Altman and Reinhardt, Eds., 1996). Their rarity occurs in part because severe impairments often result in miscarriage rather than a live birth. When the occurrence of a disease is infrequent, it is particularly important to access data on large population groups to obtain reasonable estimates of average costs.

Recent work using a large set of California databases has been carried out by Waitzman et al. (1996), used in Chapters III.3 through III.8 in this section and described in Chapter III.3. In addition, the Agency for Toxic Substances and Disease Reduction is funding studies in numerous states that provide training for medical staff and follow-up evaluations for children to better ascertain the actual rates of developmental effects. These efforts are linked to studies of environmental pollutants and developmental effects. A better understanding of the occurrence and causation of developmental effects is expected to result from these studies.

III.1.C.3 Multiple Effects

A single chemical often induces an array of effects on different organ systems. The occurrence of multiple effects has been reported in both the human epidemiological and animal toxicological literature. Most animal studies report multiple effects when developmental effects are observed. This observation is supported by the public health literature on children with disabilities, which indicates that disabled children often have multiple disabilities. For example, low birth weight is associated with physical and cognitive disabilities, and with liver, kidney and brain damage (Hacket et al., 1994; see also Chapter III.2). The multiple simultaneous occurrences of effects are reported in the chapters within this section that discuss specific developmental effects. When data were available, the chapters provide information on the likelihood of co-occurrence of effects. The information provided on the costs of developmental effects reflects these complexities. The clustering of effects differs considerably among individuals, however, and introduces uncertainty into the analysis.

The developmental effects of chemicals differ, depending on when exposure occurs, because different components of organs are developing at different stages during a pregnancy and postnatally. For example, development within the CNS occurs over many years, with especially rapid development during early life. Some milestones in the development of the human nervous system are listed below:

Prenatal:	
neural tube closes	22-26 days
first neurons born	22-26 days
cortical neurons migrate	6 weeks
mesencephelon expands considerably	9 weeks
cerebellum is visible	12 weeks
reflex actions are observable	3 months
most major nerve tracks have been formed	6 - 9 months
Postnatal:	
cortical migration complete	5 months
neuron proliferation complete	12 months
myelin 50 percent complete	18 months
visual system connections complete	3 - 4 years
brain is mature in form	20 years

Cell proliferation and neural connections occur continuously during early life, and interference in this process may lead to impaired or altered neural functioning. The CNS is particularly susceptible because it produces many cell types over an extended period and thus is subject to injury at more stages than other organs. It also does not have the ability to replace missing neurons when the developmental period for that neuron is past

(Rodier, 1994). Although the CNS is particularly vulnerable, all organ systems go through many stages during the prenatal period and have varying susceptibilities and manifestation of toxicity during early life.

The effects discussed in this section often occur in multiples, and the costs of concurrent effects are incorporated into the costs for some effects (those discussed in Chapters III.2 through III.8). Generally, however, medical costs are presented for each illness or disability separately (this is discussed in more detail in Chapters III.2 and III.3). Based on the nature of the economic analysis and the supporting scientific data for the chemicals of concern, it may be appropriate to include an illness with its related effects. Inclusion is a matter of judgement. For example, a large percentage of children with Down syndrome have hearing loss and serious visual problems. Inclusion of treatments would be logical, since these conditions are so strongly associated with the syndrome. Alternatively, children with many of the cardiac defects presented in Chapter III.5 often have related cardiovascular problems. These problems are often treated with the predominant effect presented in the chapters, and are part of the costs of both immediate surgical intervention and follow-up care. Consequently, separate calculations of the benefits of avoiding these related effects would not be necessary.

III.1.C.4 Prognosis

Developmental diseases and disabilities vary widely in their progression. Some types of anomalies have a relatively good prognosis (e.g., correction of cleft lip and palate), with most patients achieving a normal quality of life. Others, such as Down syndrome patients, have lifelong costs associated with their multiple symptoms and have a shortened lifespan. Some effects, such as very low birth weight are usually fatal. Although generalizations can be made regarding the "average" prognosis for specific effects, the prognosis for survival and the length of time over which treatment is required varies widely among individuals. Consequently, the cost estimates presented in the chapters in this section use estimates of the average treatment and survival rates to obtain representative estimates of the medical costs.

III.1.D Environmental Agents Associated with Developmental Toxicity

This section contains lists of agents associated with developmental toxicity and genotoxicity. As previous sections discussed, these data have many limitations. Additional information on each chemical may be obtained from the listed source and from a Medline or Toxnet search.

III.1.D.1 Developmental Toxicity Agents

Table III.1-2 lists many of the chemicals that have evidence of developmental toxicity in animals or humans. Due to the orientation of this handbook toward environmentally-induced illnesses, the discussion focuses on induction by environmental agents. The information in this table was obtained from journal articles, toxicology texts, and study reports submitted to the government by pesticide registrants and other chemical industry sources. The table does NOT provide an exhaustive list of chemicals that cause developmental toxicity, but instead gives an indication of the diversity of chemicals that have been associated with these effects. Information is provided below on genotoxins, which are potential causative agents with a less established but no less important link to adverse developmental effects. (Many chemicals have evidence of both developmental toxicity and genotoxicity.)

TABLE III.1-1.
CHEMICALS ASSOCIATED WITH DEVELOPMENTAL EFFECTS[1]

DATA FROM HUMAN AND ANIMAL STUDIES ARE INCLUDED.

CHEMICAL	REFERENCE
*ACETONE	1
*ACROLEIN	3
*ACRYLIC ACID	7
*ACRYLONITRILE	1
*ALACHLOR	4
*ALDICARB	1
AMINOPTERIN	3
*AMITRAZ	1
*AMITROLE	3,5
ANTU	1
*AROCLOR 1016 (A PCB)	7
*ARSENIC COMPOUNDS	3
*ARSENIC	3
ASULAM	7
*ATRAZINE	9
AVERMECTIN B1	7
*BENOMYL	7,1
*BENZENE	5
*BENZO(A)PYRENE	14
BIORESMETHRIN	10
BISULFAN	14
BORIC ACID	3
BRADIFACOUM	3,4
BUSULFAN	3
BUTACHLOR	1
*CADMIUM	14
CAPROLACTAM	7
CAPTAFAL	6
*CAPTAN	7,1,2
*CARBARYL	1,2,5
*CARBOFURAN	1
*CARBON TETRACHLORIDE	5

TABLE III.1-1.
CHEMICALS ASSOCIATED WITH DEVELOPMENTAL EFFECTS[1]

DATA FROM HUMAN AND ANIMAL STUDIES ARE INCLUDED.

CHEMICAL	REFERENCE
*CARBON DISULFIDE	5,7
CARBOPHENOTHION	6
*CHLORDANE	12
CHLORDECONE	11
CHLORDIMEFORM	6
CHLORFENVINPHOS	6
CHLORMEQUAT	5
*CHLOROBENZILATE	7
*CHLOROBIPHENYLS (INCLUDES PCB'S)	3
*CHLOROFORM	5
CHLOROPHACINONE	1
CHLOROPHENOXY HERBICIDES	15
CHLOROPROPHAM	7
*CHLOROTHALONIL	4
CHLORPROPHAM	1
*CHROMIUM	17
*COPPER SULFATE	5
COUMACHLOR	1
COUMAFURYL	3,4
COUMATETRALYL	3,4
*CYANIDES	3
*CYCLOHEXANE	1
CYCLOHEXANONE	8
CYCLOHEXIMIDE	5
CYCLOPHOSPHAMIDE	14,3
*CYHALOTHRIN	7
*2,4-D	4,6
DALAPON	1
DECAMETHRIN	9
DEET (DIETHYLTOLUAMIDE)	9
DFP	2
DI(2-ETHYL HEXYL) ADIPATE	7
*DIBROMOCHLOROPROPANE	5
*DICAMBA	7
DICHLOBENIL	4
*O-DICHLOROBENZENE	1
*P-DICHLOROBENZENE	1
DICHLOROETHYL ETHER	1
1,3-DICHLORORROPENE (2,3 ON TRI)	1
*DICHLORVOS	1
DIETHYLSTILBESTROL (DES)	3,14
DIFENACOUM	3,4
*DIMETHOATE	5,6
DIMETHYL SULFOXIDE	3,5
DINOSEB	14,7
*DIOXANE	1
DIOXIN	2
DIPHACINONE	3,4
DIPHENYLHYDANTOIN	3
DIQUAT	4
DISULFOTON	6
*DIURON	5
ENDRIN	6

TABLE III.1-1.
CHEMICALS ASSOCIATED WITH DEVELOPMENTAL EFFECTS[1]

DATA FROM HUMAN AND ANIMAL STUDIES ARE INCLUDED.

CHEMICAL	REFERENCE
*EPICHLOROHYDRIN	5
EPN	6
*EPTC	7
ETHANOL	14
ETHYL CHLORIDE	7
*ETHYL BENZENE	7
ETHYLENE DIBROMIDE	5,6
*ETHYLENE DICHLORIDE	1
*ETHYLENE THIOUREA	14
*ETHYLENE OXIDE	5
ETHYLNITROSUREA	3
EUGENAL	1
*FENBUTATIN OXIDE	4,6
*FERBAM	5
*FLUOMETURON	1
FLURPRIMIDOL	7
FLUTOLANIL	7
*FOLPET	9,3,6
*FORMALDEHYDE	5
GLYCEROL FORMAL	5
GLYPHOSATE	7
HALOXYFOP METHYL	7
*HEXACHLOROBENZENE	5
*HEXACHLOROPHENE	5
*LEAD	14
*LINDANE	6
*LINURON	4,6
*LITHIUM (TRI LISTED AS LITHIUM CARBONATE)	3
*MALATHION	5
*MALEIC HYDRAZIDE	10
*MANEB	1
*MANGANESE	16
*MCPA (METHOXONE)	4,6
*MERCURY	7
METALDEHYDE	5
METHIDATHION	5
METHIMAZOLE	3
METHOMYL	1
*METHOXYCHLOR	5,7
*METHYL ETHYL KETONE (MEK)	7
METHYL BROMIDE	6
*METHYL METHACRYLATE	3,5
METHYLCHOLANTHRENE	14
METHYLENE CHLORIDE	5
METOLACHLOR	4,7
MEXACARBATE	1
MIREX	14
MNNG	3
*MOLINATE	9
*NABAM	5
*NAPHTHALENES	9
NAPROPAMIDE	7
*NICOTINES	8

TABLE III.1-1.
CHEMICALS ASSOCIATED WITH DEVELOPMENTAL EFFECTS[1]

DATA FROM HUMAN AND ANIMAL STUDIES ARE INCLUDED.

CHEMICAL	REFERENCE
*NITRATE	7
NITRITE	7
*NITROFEN	4
NITROGUANIDINE	7
*OXYFLUORFEN	1
*PARAQUAT	8
*PARATHION	5,2
*PCBS	2
PENTACHLORONITROBENZENE	10,9,6,5
*PENTACHLOROPHENOL	5
*PERCHLOROETHYLENE	5
*PERMETHRIN	6
PHENMEDIPHAM	1
*PHENOL	7,1
*O-PHENYLPHENOL	5
PHOSMET	6
*PICLORAM	5
PIDRIN	7
PINDONE	3,4
*PIPERONYL BUTOXIDE	5
PIRIMICARB	4,6
PIRIMIPHOS-ETHYL	6
*PIRIMIPHOS-METHYL	1
2-PIVALYL-1,3 INDANDIONE	3,4
*PROPACHLOR	1
*PROPARGITE	7,6
PROPHAM	1
*PROPOXUR	1,9
*PROPYLENE OXIDE	1
PROPYLENE DICHLORIDE	1
PYRAZON	5
*PYRIDINE	8
RADIONUCLIDES (ALPHA, BETA, & GAMMA EMITTERS)	3
*RESMETHRIN	7
RONNEL	5
ROTENONE	9,7
SODIUM CHLORATE	1
*STRYCHNINE	1
SULFUR DIOXIDE	5
2,4,5-T	4
TCDD	14
2,4,5-TP	6
*TETRACHLORVINPHOS	6
TETRACYCLINES	3
THERAM	2
*THIABENDAZOLE	5
*THIOPHANATE-METHYL 6	1
*THIRAM	5
*TOLUENE	5
*TOXAPHENE	6
*TRICHLORFON	6
*1,2,4-TRICHLOROBENZENE	7
*1,1,1-TRICHLOROETHANE	5

TABLE III.1-1.
CHEMICALS ASSOCIATED WITH DEVELOPMENTAL EFFECTS[1]

DATA FROM HUMAN AND ANIMAL STUDIES ARE INCLUDED.

CHEMICAL	REFERENCE
*TRICHLOROETHYLENE	5
TRIDIPHANE	7
*TRIFLURALIN	4,6
*TRIFORINE	4
TRIMETHADONE	3
*URETHANE	14
VALPROIC ACID	3
VERNAM	7
*WARFARIN	3,4
*WHITE PHOSPHORUS	7
*XYLENE	5
*ZINEB	3,6
ZIRAM	9,10

* = Listed in TRI. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals.

Footnotes:

1. This includes a wide range of effects including skeletal deformities (increased or reduced number of digits or ribs, limb shortening or malformation, spina bifida, cleft lip or palate, etc), neurological impairment (altered cognitive functioning, learning disorders including retardation, palsy, inappropriate responses to stimuli, etc), and structural or functional changes in organs (cardiomyopathy, renal agenesis, sterility, etc).

References

1. Cunningham and Hallenbeck (1985).
2. Stellman, J.M. (1983).
3. Doull et al. (1980).
4. U.S. EPA (1983a).
5. U.S. Department of Health and Human Services, NIOSH (1983a).
6. U.S. EPA (1983b).
7. IRIS, EPA online database.
8. Clayton and Clayton (1982).
9. Hayes, W.H. (1982).
10. Vettorazzi, G. (1979).
11. Council on Environmental Quality (1981).
12. International Agency for Research on Cancer (1979).
13. Chambers and Yarbrough (1982).
14. Key et al. (1977).
15. Garry et al. (1996).
16. Webster and Valois (1987).
17. ATSDR (1993).

III.1.D.2 Genotoxic Agents

Table III.1-2 lists agents for which there is evidence of genotoxicity. The evidence varies for each agent and is based on a variety of in vitro and/or in vivo analyses.[6]

TABLE III.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS

DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.

CHEMICAL	REFERENCES
*ACETONE	5
*ACROLEIN	4
*ACRYLIC ACID	7
*ACRYLONITRILE	5
*ALACHLOR	1
*ALDICARB	1
AMINOPTERIN	3
*AMITRAZ	6
*AMITROLE	5
ANTU	5
*AROCLOR 1016 (A PCB)	7
*ARSENIC COMPOUNDS	6
*ARSENIC	6
ASULAM	7
*ATRAZINE	9
AVERMECTIN B1	7
*BENOMYL	1,7
*BENZENE	5
*BENZO(A)PYRENE	14
BIORESMETHRIN	1
BISULFAN	14
BORIC ACID	5
BRADIFACOUM	1
BUSULFAN	3
BUTACHLOR	4
*CADMIUM	14
CAPROLACTAM	7
CAPTAFAL	6
*CAPTAN	7,6
*CARBARYL	6
*CARBOFURAN	6
*CARBON TETRACHLORIDE	1
*CARBON DISULFIDE	5
CARBOPHENOTHION	1
*CHLORDANE	12
CHLORDECONE	1
CHLORDIMEFORM	6
CHLORFENVINPHOS	6
CHLORMEQUAT	5
*CHLOROBENZILATE	7
*CHLOROBIPHENYLS (INCLUDES PCBS)	3

[6] Results of genotoxic tests are often mixed because they evaluate different aspects of a chemical's ability to cause genetic damage and impair cell replication.

TABLE III.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.	
CHEMICAL	**REFERENCES**
*CHLOROFORM	1
CHLOROPHACINONE	1
CHLOROPROPHAM	7
*CHLOROTHALONIL	1
CHLORPROPHONE	1
*CHROMIUM	16
*COPPER SULFATE	5
COUMACHLOR	1
COUMAFURYL	1
COUMATETRALYL	1
*CYANIDES	1
*CYCLOHEXANE	5
CYCLOHEXANONE	5
CYCLOHEXIMIDE	5
CYCLOPENTAPYRENE	2
CYCLOPHOSPHAMIDE	14
*CYHALOTHRIN	7
*2,4-D	6
DALAPON	5
DECAMETHRIN	1
DEET (DIETHYLTOLUAMIDE)	5
DI(2-ETHYL HEXYL) ADIPATE	7
*DIBROMOCHLOROPROPANE	5,6
*DICAMBA	7
DICHLOBENIL	1
*O-DICHLOROBENZENE	1
*P-DICHLOROBENZENE	5
DICHLOROETHYL ETHER	5
1,3-DICHLORORROPENE (2,3 ON TRI)	5
*DICHLORVOS	13
DIETHYLSTILBESTROL (DES)	3
DIFENACOUM	1
*DIMETHOATE	6
DIMETHYL SULFOXIDE	5
DINOSEB	14
*DIOXANE	5
DIPHACINONE	1
DIPHENYLHYDANTOIN	3
DIQUAT	5
DISULFOTON	1
*DIURON	5
ENDRIN	6
*EPICHLOROHYDRIN	5
EPN	1
EPTC	7
ETHANOL	14
*ETHYL BENZENE	
ETHYLENE DIBROMIDE	8,6
*ETHYLENE DICHLORIDE	5
*ETHYLENE THIOUREA	14
*ETHYLENE OXIDE	5
ETHYLNITROSUREA	3
EUGENAL	5
*FENBUTATIN OXIDE	1

TABLE III.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS

DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.

CHEMICAL	REFERENCES
*FERBAM	1
*FLUOMETURON	6
FLURPRIMIDOL	7
FLUTOLANIL	7
*FOLPET	8
*FORMALDEHYDE	5
GLYCEROL FORMAL	1
GLYPHOSATE	7
HALOXYFOP METHYL	7
*HEXACHLOROBENZENE	5
*HEXACHLOROPHENE	1
*LEAD	14
*LINDANE	1
*LINURON	5
*LITHIUM (TRI LISTED AS LITHIUM CARBONATE)	3
*MALATHION	1
*MALEIC HYDRAZIDE	5
*MANEB	6
*MCPA	1
*MERCURY	7
*MERCURY COMPOUNDS	15
METALDEHYDE	5
METHIDATHION	1
METHIMAZOLE	3
METHOMYL	6
*METHOXYCHLOR	5,7
*METHYL ETHYL KETONE (MEK)	7
METHYL BROMIDE	1
*METHYL METHACRYLATE	5
METHYLCHOLANTHRENE	14
METHYLENE CHLORIDE	5
METOLACHLOR	1,7
MEXACARBATE	1
MIREX	14
MNNG	3
*MOLINATE	1
*NABAM	5
*NAPHTHALENES	1
NAPROPAMIDE	7
*NICKEL	15
*NICOTINES	1
*NITRATE	7
NITRITE	7
*NITROFEN	4
NITROGUANIDINE	7
*OXYFLUORFEN	6
*PARAQUAT	5
*PARATHION	1
*PCBS	
PENTACHLORONITROBENZENE	1
*PENTACHLOROPHENOL	1
*PERCHLOROETHYLENE	1
*PERMETHRIN	1
PHENMEDIPHAM	1

TABLE III.1-2. CHEMICALS ASSOCIATED WITH GENOTOXIC EFFECTS DATA FROM HUMAN, ANIMAL, AND IN VITRO STUDIES ARE INCLUDED.	
CHEMICAL	**REFERENCES**
*PHENOL	1,7
*O-PHENYLPHENOL	5
PHOSMET	1
*PICLORAM	1
PIDRIN	7
PINDONE	1
*PIPERONYL BUTOXIDE	1
PIRIMICARB	1
PIRIMIPHOS-ETHYL	1
*PIRIMIPHOS-METHYL	6
2-PIVALYL-1,3 INDANDIONE	1
*PROPACHLOR	4
*PROPARGITE	7
PROPHAM	1
*PROPOXUR	1
*PROPYLENE OXIDE	5
PROPYLENE DICHLORIDE	5
PYRAZON	1
*PYRIDINE	5
RADIONUCLIDES (ALPHA, BETA, & GAMMA EMITTERS)	3
*RESMETHRIN	7
RONNEL	1
ROTENONE	1
SODIUM CHLORATE	5
*STRYCHNINE	5
SULFUR DIOXIDE	5
TCDD	14
2,4,5-T	1
2,4,5-TP	1
*TETRACHLORVINPHOS	1
TETRACYCLINES	3
*THIABENDAZOLE	5
*THIOPHANATE-METHYL 6	6
*THIRAM	1
*TOLUENE	5
*TOXAPHENE	6
*TRICHLORFON	13
*1,2,4-TRICHLOROBENZENE	7
*1,1,1-TRICHLOROETHANE	5
*TRICHLOROETHYLENE	5
TRIDIPHANE	7
*TRIFLURALIN	6
*TRIFORINE	1
TRIMETHADONE	3
*URETHANE	14
VALPROIC ACID	3
VERNAM	7
*WARFARIN	1
*WHITE PHOSPHORUS	3
*XYLENE	5
*ZINEB	5
ZIRAM	1

* = Listed in TRI. When "compounds" of a metal were listed on TRI, all compounds of that metal in this table are considered to be TRI chemicals.

References

1. Cunningham and Hallenbeck (1985).
2. Archer and Livingston (1983).
3. Doull et al. (1980).
4. U.S. EPA 1983A).
5. U.S. Department of Health and Human Services, NIOSH (1983).
6. U.S. EPA (1983B).
7. IRIS, EPA online database.
8. Clayton and Clayton (1982).
9. Hayes (1982).
10. Vettorazzi (1979).
11. Council on Environmental Quality (1981).
12. International Agency for Research on Cancer (1979).
13. Chambers and Yarbrough (1982)
14. Key et al. (1977).
15. Tice et al. (1996).
16. ATSDR (1993).

CHAPTER III.2. COST OF LOW BIRTH WEIGHT

Clicking on the sections below will take you to the relevant text.

CHAPTER III.2. COST OF LOW BIRTH WEIGHT

III.2.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with low birth weight (LBW). It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. Chapter III.1 contains information regarding the causes and special characteristics of developmental illnesses and disabilities, as well as environmental agents linked to these disorders.

Link to Chapters I.1 and III.1

Low birth weight is a serious medical condition that occurs in approximately seven percent of all infants born in the United States (Oski, 1993). It is associated with multiple adverse effects in numerous organ systems and carries a much higher risk of death than normal birth weight. Consequently, considerable medical resources are devoted to the treatment of LBW infants and the medical expenditures on these infants is estimated to be $5 billion per year (Lewit et al.,1995). This chapter contains a detailed estimate of the medical and related costs associated with LBW for children through age ten and limited additional information for older individuals. Data regarding special education and aggregate costs are included due to their availability, although they are not in the usual scope of this handbook. The chapter also contains a brief discussion of the medical science related to LBW.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to inflation factors

III.2.A.1 Description

LBW babies are defined as having a weight less than 2,500 grams (5.5 lbs), and very low birth weight infants weight is defined as a birth weight under 1,500 grams (3.3 lbs). "Low birth weight results when infants are born prematurely or grew too slowly in utero, or a combination of the two" (Paneth, 1995). These children may be 1) full-term infants with intrauterine growth retardation (IUGR, see below); 2) born prematurely,

with IUGR; or 3) appropriate for their gestational age, but with LBW due to their prematurity. Regarding the full-term infants, IUGR is considered a "final common pathway by which genetic and environmental influences result in low birth weight for gestational age" infants (Oski, 1994). These are infants that are born after a normal duration pregnancy, but have retarded growth, and are born smaller and in a more immature condition than normal infants.

There are varying degrees of severity of LBW. Infants who are 1,501 to 2,500 grams are considered moderately low birth weight and comprise 82 percent of LBW infants. At 1,001 to 1,500 grams they are very low birth weight infants; this occurs among 12 percent of LBW infants. Six percent of LBW infants weigh 1,000 grams or less at birth are designated as extremely low birth weight children (Oski, 1993).

Regardless of the child's status with respect to pregnancy duration, there are serious consequences associated with low birth weight in many children. More than three-quarters of all infant deaths have been attributed to LBW (Paneth, 1995). When compared to normal-weight infants, moderate, very low, and extremely low birth weight infants have a risk of death that is 40 times, 200 times, and 600 times higher, respectively, than the risk of death among normal-weight infants. Children who survive often face multiple medical disorders arising from LBW (Oski, 1993).

In LBW infants, the basic mechanisms for survival outside the womb are often lacking. Premature LBW infants typically have very limited body fat (energy stores), inability to maintain an acceptable body temperature, and less available energy resources that are required for vital cellular processes, including protein synthesis and other basic physiological processes. Organ systems may be functionally immature, including the respiratory system. An inability to maintain fluid balance leads to patent ductus arteriosus in 15 to 35 percent of very LBW and extremely LBW infants. This condition is associated with myocardial stress, pulmonary congestion, progressive heart failure, hepatic congestion, and a constellation of progressively serious disorders. Intracranial hemorrhage occurs in 40 to 50 percent of LBW infants and is a major cause of morbidity and mortality (Oski, 1993).

LBW is associated with other developmental abnormalities including delayed cognitive development and other central nervous system (CNS) disabilities. For example, approximately 20 percent of infants born at weights between 500 and 1500 grams have brain injury (Hack et al., 1994). These acute problems often result in chronic medical conditions in the LBW child. The disorders and diseases may occur in any organ system, but are often seen in the gastrointestinal system (necrotizing enterocolitis), respiratory system (bronchopulmonary dysplasia), the nervous system, and the eyes (retinopathy of prematurity) (Oski, 1993).

Many babies with birth weights as low as 750 grams (1 pound, 10 ounces) are surviving due to technology available in neonatal intensive care units (Hack et al., 1994). This technology is expensive. The medical costs associated with LBW have been estimated to be $5.4 billion per year (incremental direct costs among children ages birth to 15 years in 1988) (Lewit, et al., 1995). This value does not include the costs of long term care, special services, and special education, which are estimated to add an additional $500 million per year. The medical expenditures for LBW children is approximately one-tenth of the total expenditure for health care for all children (Lewit et al., 1995).

III.2.A.2 Concurrent Effects

Concurrent effects are those that often occur with, but are not necessarily caused by, the disease or disorder under discussion. LBW is a condition that causes many adverse effects, and also occurs concurrently with certain types of conditions and diseases. It is not always possible to determine whether LBW was a causative agent for a specific medical condition, or whether the disorders occurred independently, but in tandem, perhaps arising from the same cause. Often the factors or agents responsible for LBW are linked to concurrent disorders.

LBW has been linked with most developmental defects. As noted above, children with low birth weight are often afflicted with severe brain damage, cerebral palsy, and disorders of multiple organs (e.g., lung and liver disease, learning disabilities, asthma, and attention disorders). Children may be born with low birth weight because of birth defects that cause growth retardation. Alternatively, children may have a number of birth defects because their birth weight and development are considerably retarded. Finally, as noted above, the low weight at birth may be simply concurrent with other birth defects, when the factors that lead to low birth weight also cause other birth defects (Oski, 1993).

Although long-term disabilities and illnesses may be associated with LBW, the medical costs associated with these effects are not discussed individually in this chapter, but are included in the final cost estimates. The estimated costs in this handbook for LBW incorporate *all* costs of medical treatment that exceeded those for a non-LBW child. Consequently, these incremental medical costs include the costs of treating concurrent effects, are included in the final incremental cost estimate.

Many of the long-terms effects are discussed in subsequent chapters (e.g., cerebral palsy) because these effects also occur independently of LBW. The occurrence and costs estimates presented in this chapter are based on the incidence in the overall LBW population. If an agent is known to cause LBW plus another disorder (e.g., cerebral palsy) at a higher rate than is usually found in the LBW population as a result of environmental agents

than is typically observed with LBW in the general population, it would be necessary to add costs associated with the excess probability of the disorder. By providing cost estimates of each effect separately in subsequent chapters, the reader can use the information as required by their risk data.

III.2.A.3 Causality and Special Susceptibilities

As described above, LBW may result from prematurity (a pregnancy of less than 38 weeks with or without growth retardation) or from delayed growth of an infant that is full-term (38+ weeks).

III.2.A.3.1 Introduction

Prematurity may result from a variety of factors, including external factors, maternal health, and the condition of the fetus. The causes in humans are difficult to evaluate through the usual animal toxicology studies because rodents are usually used in studies of reproductive outcomes. The rodent gestation period is short, and there is a small window in time when pregnancy could be observed to result in a live, but premature birth. More often the studies yield results that include miscarriage, which is a delivery prior to full-term that results in the death of the offspring. Numerous chemicals are associated with miscarriage in toxicological studies of pollutants. Many of these are listed in Table III.1-1 in Chapter III.1

Link to Table III.1-1

III.1.A.3.2 Data on Causality

Intrauterine growth retardation (IUGR) results in infants who have retarded growth, and are born smaller and in a more immature condition than normal infants. They are often LBW infants. Among chemicals that cause reproductive disorders, it is very common to observe retarded growth as one of the effects. Retarded growth is often coupled with other effects, including structural abnormalities and functional anomalies. For example, chromium, which has been the subject of multiple developmental toxicity studies, is associated with delayed bone formation, decreased fetal size, skeletal anomalies, increased resorptions (fetal death) and postimplantation loss (embryonic loss). This cluster suggests a variety of developmental impacts, including growth retardation.

Many of the objective measures of developmental toxicity in animals are highly specific (e.g., delayed bone ossification, decreased fetal weight); however, when considered as an overall description of the condition of the offspring, they are analogous to growth retardation in humans. Developmental toxicity studies in animals usually evaluate the offspring very near the time of, but prior to, birth, and in the process they sacrifice the animals (this is why studies report "fetal" rather than "offspring" abnormalities). Consequently, animal studies provide limited predictive

information regarding the postnatal disorders associated with low birth weight in humans. Multigeneration studies and postnatal studies may be carried out, but are more expensive and so are less frequently available.

There are a very limited number of studies evaluating low birth weight and intrauterine growth retardation in humans in relation to environmental exposure. It is both difficult and expensive to carry out well-controlled human development studies. This is illustrated by a recent study by Munger et al. (1997) that found an association between herbicide-contaminated drinking water supplied in the Midwestern United States and intrauterine growth retardation. The presence of very commonly encountered pesticides (e.g., atrazine, metolachlor, and cyanazine) were linked to growth retardation after controlling for multiple potential confounders (e.g., smoking, nutritional status, alcohol consumption). Low birth weight was also marginally increased among the exposed population. As is the case for most environmental studies, exposures occurred simultaneously to the mixture of chemicals, with varying concentrations over time. Conclusions can be drawn regarding an association between the cluster of chemical and growth retardation. However, the ability to establish causality for specific chemicals in this study is questionable.

III.1.A.3.3 Environmental Agents of Concern

Human data on environmental risk factors associated with LBW are very limited, but dozens of chemicals have been demonstrated to cause LBW in experimental animals, including many common pollutants. Table III.1-1 in Chapter III.1 lists some of the chemicals associated with developmental toxicity. Many of these are linked to growth retardation and/or prematurity. Many chemicals have been shown to cause LBW in experimental animals. Delayed development and reduced body weight are relatively common observations in developmental toxicity studies on chemical pollutants.

Link to Chapter III.1, Table III.1-1

Some chemicals associated specifically with LBW are acrylic acid, aroclor 1016 (a PCB), chlorobenzilate, captan, benomyl, cylothrin, dimethyl sulfoxide, dicamba, dinoseb, flutolanil, methyl ethyl ketone, metholchlor, napropamide, nitroguanidine, phenol, propagite, resmethrin, rotenone, vernam (IRIS), and chromium (ATSDR, 1993). LBW is also strongly associated with pre-term delivery due to substance abuse, smoking, diabetes, poor prenatal nutrition and care, and other causes.

II.2.A.3.4 Susceptible Subpopulations

African-American infants are twice as likely as white infants to be born with LBW and their risk is even greater for very LBW births. The causes of this increased rate are not know. Although social and economic factor, access to medical care, and other societal issues are considered to be

responsible in part (Shiono and Behrman., 1995), very recent studies that have controlled for these factors have found an increase in LBW among African-American infants. It has been theorized that some groups may be genetically at greater risk for LBW, suggesting a sensitive subpopulation that may merit consideration in a benefits assessment. Additional support for this argument can be obtained from the literature, which indicates that the rates of LBW among other ethnic minorities in the United States (i.e., Hispanic, Native American, and Asian American) are similar to those of the white population (Paneth, 1995). Consequently, biological and genetic factors may be important considerations (Shiono and Behrman, 1995). In an environmental risk benefit context, African Americans may be considered to be at higher risk, and benefits of avoiding environmental agents that pose risks of LBW should be considered accordingly. Additional research is required in this area to fully explore the risk factors involved.

III.2.A.4 Treatment and Services

Medical services in the neonatal period address the numerous acute medical problems described above (see "Description"). They are designed to eliminate the short-term crisis and mitigate long-term health problems. Extensive medical services are often required whether the LBW results from a preterm delivery or a IUGR condition. Treatment often includes monitoring in a neonatal intensive care unit; extensive testing to determine the functional status of various organ systems; surfactant therapy to preserve lung structure; specialized nutrition; fluid management; and management of respiration, glucose levels, temperature, and other basic physiological processes at a normal level to minimize damage (Oski, 1993).

Prenatal evaluations may provide information regarding intrauterine growth retardation (IUGR), and medical intervention may begin considerably prior to the birth of the child to address problems that have been diagnosed. The costs of these types of services are not included in the estimates provided below. They typically would be considered a part of prenatal costs and would be attributed (in most accounting methods) to the mother, rather than the child. Their lack of inclusion in this chapter generates a cost estimate that underestimates true costs by the amount spent prenatally to minimize exposure.

III.2.A.5 Prognosis

Although mortality among LBW infants declined rapidly into the 1970s, the morbidity among the survivors has increased, due to the survival of much smaller and more seriously ill infants. Table III.2-1 shows the morbidity pattern for some major categories of illnesses arising from LBW in relation to the size of the infant at birth. It demonstrates that there is an increasing risk of morbidity and mortality associated with progressively smaller birth

weight. The table includes selected outcomes for the most seriously underweight infants, and does not include those in the moderate LBW category, defined above as having a birth weight of 1,501 to 2,500 grams.

Table III.2-1. Morbidity and Mortality Among Very Low Birth weight Infants.

Based on data from the National Institute of child Health and Human Development Neonatal Network. Adapted from Oski, 1993 and originally based on Hack et al., 1991.

	Weight at Birth (in grams)			
Effect	**501-750**	**751-1000**	**1001-1250**	**1251-1500**
morbidity among survivors (%)	56	39	25	15
chronic lung disease (%) among survivors	26	14	7	3
intracranial hemorrhage (%) among survivors	26	17	13	6
enterocolitis(%) among survivors	3	8	6	4
death (%)	66	34	13	7

Although survival among LBW has improved considerably in recent years, those that survive often have long-term health and developmental problems (Oski, 1993). The long-term prognosis for LBW children depends greatly on the severity of their initial condition, as well as the medical services provided shortly after birth. Researchers have found that "Infants with IUGR secondary to environmental insult or decreased growth potential generally have outcomes that are poor and reflect the underlying neuropathology of conditions caused by the environmental or genetic insult." (Oski notes: "environmental" in this context refers to all factors outside the mother and child). Infants with normal brain growth generally have a more favorable prognosis. Most full-term IUGR infants have normal intelligence, and even many preterm IUGR infants achieve normal intelligence by school age (Oski, 1993). Conversely, children with LBW are more likely than children with normal birth weight to have attention disorders, developmental impairments, breathing problems (e.g., asthma), and learning disabilities (Shiono and Behrman, 1995). All categories of LBW children are more likely to be enrolled in special education classes than normal birth weight children, and half of all children who were very LBW are enrolled in special education classes (Hack et al., 1995).

III.2.B Costs of Medical Treatment and Other Services

The overall costs associated with LBW infants are very high and comprise a substantial portion of all pediatric costs. While costs vary considerably depending on the individual and the severity of their condition, the costs for a single infant with LBW may exceed $1 million. The average cost for initial hospitalization (only) for surviving infants weighing 500 to 600

grams was $1 million per child (Pomerance et al., 1993). This weight group is the most seriously affected, but their costs give some indication of the potential magnitude of the medical costs. Most LBW infants require some additional care, at an increase in cost over the usual pediatric care expenditures. It has been estimated that of the $11 billion spent on health care for infants, approximately 35 percent ($4 billion) is spent on the incremental costs of medical care for LBW infants (Lewit et al., 1995).

There are two studies of the costs of LBW discussed in this section. The Lewit et al. (1995) study, discussed in detail below, is more comprehensive and is recommended for use in cost estimates. A study by McCormick et al. (1991) is also briefly discussed, but is not recommended for use in evaluating LBW costs due to its limitations.

III.2.B.1 Methodology

III.2.B.1.1 Data from Lewit et al.

A recent comprehensive analysis of LBW was published in 1995 by Lewit et al. They analyzed the incremental direct costs of low birth weight using a prevalence approach. These costs, estimated for children aged 0 to 15, include expenditures for health care, child care, special education, and grade repetition (considered to be related to special education). Each type of cost is itemized, and although the handbook focuses on medical costs, the costs of related professional services (e.g., special education) are included in the material presented in this chapter. Child care, while a direct cost, is not estimated in other chapters of this handbook and was not included this chapter. (The study authors note that their comprehensive approach offers an opportunity to evaluate the impact of LBW in a single metric. Readers may wish to consult their work, depending on the goals of their morbidity valuation.)

Lewit et al. (1995) used a number of sources for their study. Estimates for LBW babies during the first year of life were obtained by combining data from two other studies, as well as the data from the CIGNA Corporation's national employer-based business survey. The data were obtained from a private source; the birth weight-specific cost ratios were therefore adjusted to match the actual distribution of birth weights in the 1988 U.S. birth cohort. The population-weighted relative cost ratios were applied to the estimated national expenditures for infant health care in 1988 to determine the allocation of expenditures between LBW and normal birth weight infants.

To estimate the incremental increase in costs for LBW children beyond the first year of life, the 1988 Child Health Supplement of the National Health Interview Survey and the 1991 National Household Education Survey were used. The large number of children involved in the surveys allowed for evaluation of age-specific resource utilization. Data regarding birth weight,

hospitalization costs, and other relevant data were used. Multivariate statistical analyses were conducted to control for the effects of potential confounding variables, such as income and the mother's educational level. Estimates of health care costs are also largely based on a previous study that used the 1987 National Medical Expenditure Survey (USDHHS, 1988).

The incremental costs of special education and of repeating a grade were estimated by Lewit et al. for children through the age of 15 years. Inclusion in special education classes and grade repetition both occur with greater frequency among LBW children than among non-LBW children. Although they are not a part of medical costs, they are included as supplemental information and may be considered to be a part of special services related to a medical condition.

The Lewit et al. (1995) analysis of children's medical costs after the first year of life includes *only* the hospital and medical fees associated with hospitalization. They evaluated the different hospitalization rates for LBW and non-LBW children and used this ratio, with the average annual hospital costs per child for all children, to estimate the incremental annual hospitalization costs for LBW children. This approach will underestimate total medical costs because it does not include office visits, pharmaceuticals, therapy, and other medical services that are not a part of a hospitalization incident. For example, annual medical costs for asthmatic children may be high, even when they are not admitted to the hospital. (Chapter IV.2 contains a discussion of costs associated with asthma.) LBW children have an increased rate of asthma occurrence and would be expected to have this type of non-hospitalization cost. This cost is not included in the Lewit cost estimate because it is not a hospitalization cost. There are likely to be many other medical services required for LBW children that do not require hospitalization; the costs of services were not calculated by Lewit et al.

Link to Chapter IV.2

This handbook addressed the lack of cost data for medical services unrelated to an inpatient visit (hospital stay) for children over the age of one by applying an inpatient/outpatient factor obtained from another study to estimate the costs of outpatient services. A number of data sources were considered for this factor, including data obtained from costs of treating birth defects (Waitzman et al., 1996 data as discussed in Chapters III.3 through III.8) and the Health Care Financing Administration (HCFA) data. A prominent consideration in selecting the source of the factor was the anticipated medical services required for LBW children after the age of one year. It was assumed that much of the care would be for chronic health problems and that surgical intervention would be minimal. These assumptions would lead to an allocation of services more heavily weighted

toward outpatient care than would be the case for treatment of diseases that require substantial surgical intervention, such as treatment of many of the birth defects discussed in Chapters III.1 through III.8 of this handbook. Consequently, costs from those chapters were not considered optimal. Likewise, the HCFA data, which includes surgical and other acute care as a major component, was not considered appropriate for establishing the ratio for chronic care treatment of LBW children.

Due to its focus on chronic care after initial diagnosis, cost data for the treatment of asthma, discussed in Chapter IV.2 of this handbook, was selected as having the most analogous type of care and cost requirement to the chronic care provided for LBW children. The inpatient/outpatient cost ratio can be calculated from the data provided in Chapter IV.2. The costs for young children (ages 4 to 5) shown in Table IV.2-15 were used to estimate the ratio. The sum of the office visit, drug therapy and emergency room costs is $605.37 per year, and the hospitalization cost is $105.79 per year. The outpatient/inpatient ratio was calculated to be 5.72. This value was used to estimate the outpatient costs for LBW children by multiplying the inpatient costs times 5.72. This value is a source of considerable uncertainty in the cost estimate. However, it was felt that it would be better to provide an estimate than to omit the costs for outpatient care altogether.

Link to Chapter IV.2, Table IV.2-15

Additional data will be sought on this issue and the value may be updated in the future. Results obtained from application of this factor are shown in the "Results" section below.

III.2.B.1.2 Supplementary Cost Estimates

Lewit et al. (1995) did not estimate incremental medical costs for ages 1 to 2 years and for children over 11 years of age. An estimate of the costs for the missing years was made for this handbook, to provide a more comprehensive estimate. Costs were estimated for the missing years as follows:

1 -2 years. To estimate costs for this age group, the two closest age groups were considered as sources of information. It was assumed that the medical and related costs of LBW are highest in infancy, and that these costs should drop off quite quickly after the first year of life. Consequently, the incremental cost during the first year of life, of approximately $25,000, was not considered an appropriate data source. The cost per year for three- to five-year-olds was assumed to be the most representative of the one- to two-year age group, although some of the substantial medical costs seen in infancy may persist into this age group for those children most seriously affected (i.e., the very low birth weight infants). Despite this drawback, the three- to five-year-olds' cost per year

was assumed to be the best option for the estimate and was used for ages one and two.

11 - 15 years. Although incremental educational costs were estimated for this group by Lewit et al., the researchers did not estimate the costs for medical services for this age group. The costs were extrapolated from the costs per year for six- to ten-year-olds because it was assumed that the medical costs would be very similar. LBW children often have health problems (as noted in Section II.2.A, above) that are chronic and continue through the life of the individual (Lewit et al., 1995). For example, Section II.2.A noted that LBW children are more likely to have neurological damage, asthma, and gastrointestinal disorders. These disorders are not age-limited. Although many very serious acute health problems related to LBW are addressed in the first year of life, those that persist into school age are chronic health problems that are likely to recur over the lifetime of the individual. Consequently, the increased costs seen during childhood in the post-acute treatment period (e.g., ages five to ten years) are a reasonable estimate of the costs that may be incurred later in childhood, as well as in adulthood (see below).

15 - 75 years. LBW children have higher hospitalization rates and require more medical services in both the preschool- and school-age years than non-LBW children (Corman and Chaikind, 1993; Corman, 1994). Due to the inability to track many children over the age of 15 years (as a result of their dropping out of school, etc.) and corresponding lack of good tracking data, the analysis was not conducted on children over the age of 15 by Lewit et al. Increased medical and related costs are likely to continue for these individuals, due to persistent medical and, in some cases, social and educational costs. To address this factor, an estimate was made of the potential lifetime incremental medical costs of LBW, assuming that the increased yearly costs seen in the six- to ten-year-old age cohort would be representative of the costs over a lifetime. As noted above, in all cases the cost data are for increased rates of hospitalization only and do not include outpatient services, long-term care facilities, pharmaceuticals, etc. The values are underestimates of the actual total incremental medical costs associated with LBW.

III.2.B.2 Results

This section contains both comparative information regarding the costs for LBW infants versus normal weight infants, and costs associated with LBW over the childhood years.

III.2.B.2.1 Aggregated First-Year Costs for All Infants

Table III.2-2 shows the total and incremental costs for LBW infants during the first year of life, in contrast with normal birth weight infants. The LBW costs, based on 1988 data from Lewit et al. (1995), are weighted averages

based on the costs for all LBW categories and the proportion of infants in those categories. The costs are updated using the Consumer Price Index (CPI) for medical care from 1988 to 1996 dollars (1996:1988=1.6465). The total costs and costs for all births and normal weight infants are provided for comparative purposes.

Table III.2-2. Comparative Medical Costs for LBW and Normal Birth Weight Infants During the First Year of Life in 1996 Dollars.

Birth Weight Group (in grams)	Number of Births in 1988 in the U.S.	Incremental Cost per Child in 1996 Dollars (1st year)	Total Costs in 1996 Dollars (billions)	Percentage of Total Health Care Costs for Infants
all births	3,871,000	3,128	12.2	100%
normal weight (2,500+)	3,600,000	1,554	5.6	65%
LBW[a] (<2500)	271,000	24697	6.6	35%
extremely LBW (<1,000) or having respiratory distress syndrome	57,000	52,688	3.0	16%
other LBW (1,000 -2500 without respiratory distress syndrome)	214,000	16,465	3.6	19%

Source: Lewit et al., 1995 adjusted for inflation using CPI (1996:1988=1.6465)
a. Average for all LBW infants.

III.2.B.2.2 Annual Per Capita Costs for LBW Infants

Table III.2-3 shows the incremental direct costs per year estimated by Lewit et al. (1995) for each age group for the average LBW infant. It also shows outpatient cost estimates derived in this handbook from the ratio of outpatient to inpatient costs (see methodology section for detail).

As noted above, Lewit et al. (1995) estimated health care costs for ages through ten years only and did not estimate any costs for ages 1 and 2 years. As noted above, these gaps were addressed by using costs for the 3 to 5 year old age group as representative of the costs for ages 1 and 2 years. In addition, the medical costs for the 11 to 15 year olds and the 16 to 75 year olds were extrapolated from the costs per year for 6 to 10 year olds.

Table III.2-3. Annual Incremental direct costs per LBW child (1996$)			
Age Group	**Cost Type**	**Mean Cost per Year per LBW Child**	**Outpatient Cost Estimate Based on Ratio[3]**
Infancy	Health Care (all medical costs)	$24,697[1]	(not calculated separately)
1 to 2 years	Health Care (inpatient only)	$477[2]	$2,728
3 to 5 years	Health Care (inpatient only)	$477[1]	$2,728
6 to 10 years	Health Care (inpatient only)	$774[1]	$4,427
6 to 15 years	Special Education	$247[1]	N/A
11 to 15 years	Health Care (inpatient only)	$774[2]	$4,427
11 to 15 years	Grade Repetition	$74[2]	N/A
16 to 75 years	Health Care (inpatient only)	$774[2]	$4,427

[1] Costs from Lewit et al. (1995), adjusted for inflation, as shown in Table III.2-2.

[2] Costs based on Lewit et al., estimated and modified as discussed in the Methods section of this chapter.

[3] Outpatient costs were estimated based on an outpatient/inpatient ratio derived from treatment of asthma patients. See Methods section of text for discussion.

Lewit et al. estimated that there were approximately four million LBW children from ages birth to 15 years in 1988 and that their total incremental direct costs were $5.4 trillion in 1988 dollars. Using the Consumer Price Index (CPI) for medical care from 1988 to 1996 dollars (1996:1988=1.6465), the total cost in 1996 dollars (assuming a population the same size as in 1988) is $8.91 billion.

III.2.B.2.3 Childhood Costs

The direct medical costs for ages 0 to 15 years are shown in Table III.2-4 at four discount rates (zero, three, five, and seven percent). These are average values; as Table III.2-2 demonstrated, the costs are much higher for some children, born with extreme low birth weight and/or respiratory distress.

Link to Table III.2-2

The total estimated cost for special education, grade repetition, and medical care (as itemized in Table III.2-3) for ages 0 to 15 years is $85,447 (undiscounted in 1996$).

Table III.2-4: Discounted childhood medical care costs (Age 0-15) for Low Birth Weight in 1996$				
	0%	3%	5%	7%
Inpatient and Estimated Outpatient Medical Care	$82,607	$69,765	$63,292	$58,052

III.2.B.2.4 Lifetime Costs

Medical and other costs for LBW individuals persist into adulthood. They often have health problems (as noted in Section III.2.A, above) that are chronic and continue through the life of the individual. To address this factor, an estimate was made of the potential lifetime incremental medical costs of LBW, as described in Section III.2.B.1, above. Table III.2-5 below provides an estimate of lifetime incremental medical costs that may be incurred.

In reality, it is most likely that those individuals most seriously affected by LBW will have substantially increased medical costs that exceed the estimate given below (e.g., those with serious brain damage, respiratory insufficiency), and that many individuals with moderate LBW will have minimal incremental costs associated with their birth condition. The values below are an estimate of the likely average costs that may be incurred.

Link to Section III.2.B.1

The total estimated cost for special education, grade repetition, and medical care (as itemized in Table III.2-3) is $436,514 for a full lifetime of 75 years (undiscounted in 1996$).

Table III.2-5: Discounted lifetime medical costs (Age 0-75) for Low Birth Weight in 1996$				
	0%	3%	5%	7%
Inpatient and Estimated Outpatient Medical Care	$348,227	$148,406	$103,601	$80,578

III.2.B.2.5 Limitations

The data provided in the Lewit et al. (1995) study have several limitations, discussed briefly below, with regard to determining average costs.

The data used by Lewit et al. had very few observations of very low birth weight children. The cost estimates may be underestimated because very LBW children incur the highest costs.

The authors noted that the costs may be underestimated due to limited access to data on charges in the neonatal intensive care unit (NICU, where the most significant charges are incurred) and on subsequent hospital stays.

The data used by Lewit et al. were from one geographic area. There are likely to be some regional differences in practices and costs.

Some aspects of the cost estimate relied on parental surveys, which introduce uncertainty.

Data regarding some age groups are lacking. Best estimates of the costs for age cohorts 11 to 15 years and 16 to 75 years were made based on reasonable use of the existing data. Actual cost data would be preferable. The lack of data for the one to two years age group is particularly problematic. Because the one- and two-year-old child is still very close in age to the birth experience and attendant medical problems, they are more likely to require continuing medical and developmental services than they would in at ages three to five. The three- to five-year age group was the source of the cost data extrapolated to the one to two year age group. The costs for the three- to five-year-olds are likely to underestimate the medical costs for the 1 to 2 year age group, especially among the very low birth weight children.

Finally, the most serious limitation is the lack of data, aside from hospitalization costs, on non-hospital costs after the first year of life. Hospitalization costs are clearly a significant factor in lifetime costs, but they underestimate the total incremental medical costs by a factor that is unknown. This uncertainty is offset partly by the comprehensive medical costing that was carried out for the first year of life by Lewit et al. The first year is the most expensive for LBW individuals, especially for those with the most costly medical treatment. Accurate accounting during this critical period provides a good basis for the overall cost estimate for LBW. The outpatient cost estimates based on the experience of asthmatics provides a reasonable estimate of outpatient costs for LBW individuals after the first year of life. The lack of comprehensive medical cost data for latter years introduces additional uncertainty into the cost estimate and will result in an underestimate of total costs.

As with all cost estimates in this handbook, changes in technology create uncertainty regarding the costs and practices that are currently relevant.

III.2.B.3 Other Studies

McCormick et al. (1991) provides another estimate of LBW costs, but only for the first year of life. The researchers analyzed the costs incurred by parents of Very low birth weight babies after the initial neonatal hospitalization. Costs were obtained from a study of Very low birth weight infants discharged from the Infant Intensive Care Unit of the Children's Hospital of Philadelphia from July 1983 to October 1984. The study population consisted of 32 infants. Incremental costs were evaluated using

control group of 34 infants born with normal birth weight. Costs were estimated only for the first year of life and obtained solely for the one hospital's birth cohort.

The costs incurred by the family after leaving the NICU were recorded and include hospital care, visits to doctors, diagnostic tests, prescription and nonprescription medication, medical supplies and equipment, and special infant formulas. Other costs reported by McCormack et al. are: hotel charges associated with rehospitalization, renovations to the house, special diets, travel to obtain health care, and the cost of in-home care or day care. While important , they are not discussed in this chapter, since they do not fall within the scope of the handbook.

Total per capita direct costs estimated by McCormick et al., over the first year are presented in Table III.2-6. The estimates are updated from 1984 to 1996 dollars using the Consumer Price Index for medical costs (1996:1984=2.14). The costs were calculated after subtracting the costs for medical care for the control group (the non-LBW children) to obtain incremental costs of LBW.

Table III.2-6: First year medical costs for LBW infants in 1996$ (McCormick et al., 1991)

Type of Costs	Total Year
Hospital Care	$15,705
Physician Visits	$709
Other Direct Medical Expenditures	$2,667
Total	**$19,145**

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below

Link to inflation factors

Additional studies conducted in the 1980s provide some information on this topic (OTA, 1988; Boyle et al., 1983). These studies, however, have several drawbacks. They do not provide complete cost estimates, use data that are not well-suited to this analysis (either Canadian costs, or costs primarily for moderate LBW rather than including very or extremely LBW infants), and the ages of the studies are not optimal, due to rapidly changing medical practices in this field. Additional studies are available on specific population groups, but do not provide representative data on costs (Hack et al., 1995).

III.2.B.4 Conclusions

The Lewit et al. (1995) study is the most comprehensive and uses a number of credible databases and assumptions to derive incremental cost estimates. In addition, costs were extrapolated for ages not covered by the Lewit et al. study; these extrapolations were reasonable and provide an estimate of average costs. The incremental costs for very LBW and extremely LBW infants are likely to be much higher throughout their lifetime due to persistent serious medical conditions. The McCormick et al. study looks only at the first year of life, while the Lewit et al., (1995) study estimates health care costs over the first ten years, and other costs up to age 15. Because of this restriction, cost estimates based on the Lewit et al. results are recommended for use in LBW valuation. As discussed in the "limitations" section above, the Lewit et al. data are likely to underestimate the actual incremental medical costs for LBW.

CHAPTER III.3. COST OF CLEFT LIP AND PALATE

Clicking on the sections below will take you to the relevant text.

CHAPTER III.3. COST OF CLEFT LIP AND PALATE

III.3.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with cleft lip and/or palate, and the results of the analysis.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.3.A.1 Description

Cleft lip and palate occur when structures in the nose and mouth fail to close during embryonic development. These birth defects appear as openings or incomplete structures in the centerline of the face and mouth. They often occur concurrently (approximately 50 percent of the time), due to the mechanism of damage that leads to these defects (Fraser, 1970). Cleft lip and palate may involve a small or large portion of the facial structures associated with the nose and mouth. Without treatment, infants may have problems sucking and swallowing and may aspirate food into their lungs. Other problems arising from this deformity include delayed and distorted speech, ear and sinus infections, reading disabilities, crossbite, and problems with social interactions (Waitzman et al. 1996).

The incidence of cleft lip and palate varies across ethnic groups. Cleft lip, with or without cleft palate occurs in approximately one in 1,000 births among whites, 0.3 in 1,000 among blacks, 3.5 in 1,000 among Native Americans, 1.7 in 1,000 among Chinese, and 2.5 in 1,000 among Japanese (Oski, 1994). Although there are over 300 recognized cleft syndromes, these represent a small percentage of the total cleft cases (Oski, 1994).

[1] "Costs" in this chapter refer to direct incremental per capita medical costs, unless otherwise noted.

III.3.A.2 Concurrent Effects

More than 50 percent of infants born with cleft lip and/or palate have other anomalies of the face, heart, and head (microcephaly). Cleft lip and/or palate occur with slightly greater probability in individuals with Down syndrome than in the general population (Waitzman et al. 1996). Middle ear infections are a common occurrence in children with cleft palate (Oski, 1994).

III.3.A.3 Causality

Cleft lip and palate occur early in development, when the basic skeletal structures are being formed. The latest time that this anomaly can be induced is approximately 36 days post-conception (Bennett and Plum, 1996). Consequently, factors that cause this disorder must occur before the pregnancy begins, or in its very early stages.

Both genetic and environmental factors may be responsible for cleft lip and palate, inhibiting the normal flow of cells during development. A long list of teratogenic substances can cause clefting in rodents, including corticosteroids, folic acid inhibitors, Vitamin A, and phenytoin (Oski, 1994).

Table III.1-1 in Chapter III.1 lists numerous chemicals associated with developmental abnormalities in human and/or animal studies. Many of these have identified structural and anatomical defects. Cleft lip and palate fall into this category of defects. Little human data exist on developmental effects of chemical exposures, as discussed in Chapter III.1, even though birth defects are relatively common occurrences.

Link to Table III.1-1 in Chapter III.1

Twin data suggest some genetic component to the occurrence of cleft lip and palate; however, only 35 percent concordance in the occurrence of the disorder is seen in identical twins. A simple genetic inheritance pattern is therefore not responsible for the disorder in most cases (Oski, 1994), or all identical twins (who have the same genetic composition) would have identical patterns of occurrence (i.e., either both or neither would have the anomalies).

A recently completed study of the offspring of pesticide application workers found that their incidence of skeletal anomalies (as well as respiratory system, circulatory system, and urogenital anomalies) were significantly greater than those of the general population in the same area of the United States (Garry et al., 1996). Musculoskeletal anomalies include any abnormality in the size, shape, or function of part of the skeletal system, muscles, and related tissues (e.g., cartilage). They include

the absence or shortening of limbs (as discussed in Chapter III.4) and the abnormal formation of part of the skeleton or related soft tissue and cartilage, as is the case in cleft lip and palate. The chemicals evaluated in the Garry et al. study that were associated with the birth defects were trifluralin, triazine herbicides (including atrazine, a very common well contaminant in agricultural areas), and chlorophenoxy herbicides (including MCPA and 2,4-D, a pesticide with very high usage). There was also a significant increase in birth defects among infants conceived in the spring (i.e., during peak chlorophenoxy use) compared to infants conceived during other periods of the year (Garry et al., 1996).

As indicated in Chapter III.1, the timing of exposure is often a critical determinant of whether and what type of effects will occur. Generally, the earlier during a pregnancy that damage occurs, the more serious the effect will be because all cells developing from the damaged cells may also be damaged, and basic structures are being formed during the first trimester (three months). Although Garry et al. do not provide detailed information on the specific nature of the anomalies, this information can be obtained from the authors of the study or from EPA (the work was funded by U.S. EPA).

Link to Chapter III.1

III.3.A.4 Treatment and Services

Cleft lip and palate are typically corrected during infancy or early childhood. They are usually treated surgically shortly after birth to close the lip. Surgical correction of the palate typically occurs at 6 to 18 months. Remaining defects are corrected during adolescence. Speech and orthodontic services are frequently required (Waitzman et al., 1996). A medical team consisting of a maxilofacial surgeon, audiologist, speech pathologist, prosthodontist, otolaryngologist, pediodontist, and geneticist are often involved in the treatment of this disorder over an extended period during childhood.

III.3.A.5 Prognosis

Long-term survival and quality of life after the first year of life are good, in the absence of other medical problems. As noted under concurrent effects above, other anomalies that frequently accompany cleft lip and palate may shorten life and diminish abilities (Waitzman et al., 1996). The mortality experience in California of individuals born with cleft lip and/or palate as reported by Waitzman et al. is discussed in Section III.3.B.

III.3.B Costs of Medical Treatment and Other Services

Cleft lip and palate are typically corrected during infancy or early childhood; consequently, their cost evaluation is simpler than many of the other developmental effects discussed in this handbook. Cleft lip and palate correction focuses on surgical and other medical care that occurs over a relatively short time period. The medical procedures often fully address the problem, and there are not medical costs occurring over the lifespan of the individual, as there often are with effects such as spina bifida and cerebral palsy (Waitzman et al., 1996).

As noted above, cleft lip and palate are very often associated with other birth defects. They also occur with slightly greater probability in individuals with Down syndrome than in the general population. Consequently, it may be necessary to evaluate the costs of multiple effects in addition to cleft lip and palate (Waitzman et al., 1996). The need for this type of analysis is supported by the occurrence of multiple birth defects in toxicological tests of environmental chemical exposures in animals. Multiple effects, which often occur from exposure to chemicals, would all be considered in a comprehensive cost estimate.

III.3.B.1 Methodology

This chapter and chapters III.4 through III.8 in this section use cost of illness estimates developed by primarily Waitzman et al. (1996). The methodology and relevant considerations are discussed in detail in the following sections. The results and elements related specifically to each condition are then discussed in each individual chapter.

To estimate the lifetime medical costs incurred by an individual with a birth defect, Waitzman et al. estimated the average lifetime medical costs for an individual with the birth defect. From this value, the authors subtracted the average lifetime medical costs for an individual without the birth defect. This method has two important implications. First, unlike the costs reported for many of the diseases in this handbook, cost estimates based on Waitzman et al. include the costs of concurrent effects. These estimates yield a more comprehensive assessment of total costs than would be obtained if only individual effects were evaluated. This is of particular use in valuing the avoidance of birth defects because they very frequently occur in clusters within an individual. Second, the Waitzman et al. method estimates the incremental costs for individuals with birth defects — that is, the costs above and beyond the average costs that would be incurred by individuals without the birth defect.

The Waitzman et al. cost estimates are well-researched and up-to-date. These cost estimates are based on ongoing costs of birth defects in California across many ages and the occurrence of birth defects in a large

cohort of children born in California in 1988. The state of California has spent considerable resources to evaluate causes and occurrences of birth defects and has an ongoing birth defects monitoring program. Consequently, the use of this state data provides excellent sources of information on occurrences, costs, and related information. California's large size and diversity makes it a good heterogenous source of cost data.

Waitzman et al. used multiple databases, including the California Birth Defects Monitoring Program incidence, birth, and death records, the National Health Interview survey, The California Office of Statewide Health Planning and Development hospital discharge data, MediCal claims files, California Department of Development Services data, the National Longitudinal Study of Special Education Students, California Special Education Enrollment and Expenditure data, and the Survey of Income and Program Participation. The variable-specific data sources and limitations will be discussed in greater detail in Section III.3.B.1.6.

III.3.B.1.1 Direct and Indirect Costs

Cost of illness studies typically involve analysis of two types of costs: direct and indirect. Direct costs are associated with resources *used* to provide medical care to people with a particular illness. These costs include medical costs such as inpatient and outpatient costs, and nonmedical costs, such as the cost of special education. Indirect costs, on the other hand, are associated with resources *lost* to society as a result of premature mortality and/or morbidity in patients. These costs are related to activity limitations and include foregone earnings.

Waitzman et al. (1996) estimated three categories of costs: direct medical costs, direct nonmedical costs, and indirect costs. Direct nonmedical and indirect costs are reported at the end of this chapter without discussion for the reader's convenience. Direct medical costs, specifically inpatient care, outpatient care, pharmaceuticals, laboratory tests, X-rays, appliances, and long-term care are included in the direct medical cost estimates shown in this chapter. For more information on methods used to derive these costs, the reader may wish to consult Waitzman et al. (1996).

III.3.B.1.2 Prevalence versus Incidence

Cost of illness studies usually employ either a prevalence or an incidence approach. The prevalence of an illness at a given point in time is the number of individuals who have the illness at that time. The prevalent population is defined as a cross section of the population with the disease of interest at a given time. This group may be subdivided into age-specific prevalent populations. Incidence refers to the newly diagnosed cases of an illness. The incidence of an illness in a given year, for example, is the number of cases of the illness that were newly diagnosed in that year.

Prevalence approaches are more useful for assessing treatment strategies. Incidence approaches, on the other hand, are more useful for assessing prevention strategies, because preventing the occurrence of an illness avoids the entire stream of costs that would have resulted from the illness from its inception to the death of the individual. Part of the benefit of preventing an illness is the benefit of avoiding the costs associated with the illness, measured as the present discounted value of the stream of costs that would be incurred over the entire course of the illness (Waitzman et al., 1996).

Waitzman et al. use an incidence-based approach, but use both incidence and prevalence numbers to arrive at the final incidence-based estimates. Cross-sectional cost data from the larger population group of all California residents diagnosed with a condition (i.e., the prevalent population) were divided by the total number of people in this group to obtain estimates of the costs for the cohort of interest (i.e., those born in 1988). These costs were adjusted based on the average cost for a healthy individual, in order to obtain incremental costs (discussed below). The per-capita incremental costs were then multiplied by estimates of the size of the 1988 cohort at each age (i.e., the incident population) to obtain a total incidence-based, age-specific cost estimate for the 1988 cohort. Finally, the total costs were divided by the size of the cohort at birth with each defect to obtain the cost per case.

Table III.3-1 provides California prevalence data for a point in time (July 1, 1988) and California incidence data for infants born in 1988 for cleft lip and palate, along with other commonly observed developmental defects. This table shows the differences between prevalence and incidence, as well as the variation across defects in each. Although no exact relationship between the prevalence of these conditions on July 1, 1988 and their incidence during 1988 exists, the two are highly correlated. For example, the two conditions with the highest incidences in 1988 (cleft lip or palate and cerebral palsy) are also the two most prevalent conditions on July 1, 1988. The third most prevalent condition on July 1, Down syndrome, also has the third greatest incidence during 1988. The least prevalent condition, truncus arteriosis, has the lowest incidence.

Table III.3-1: Prevalence and incidence of the most frequent birth defects in California: 1988*

Condition	Prevalence of the Birth Defect on July 1, 1988**	Incidence of the Birth Defect Among Infants Born in California in 1988***
Spina bifida (Ch. III.6)	8,859	226
Truncus arteriosis (Ch. III.5)	1,591	56
Transposition (Ch. III.5)	7,469	263
Tetralogy of fallot (Ch. III.5)	5,336	187
Single ventricle (Ch. III.5)	1,932	68
Cleft lip or palate	24,956	944
Upper limb reduction (Ch. III.4)	7,895	234
Lower limb reduction (Ch. III.4)	3,856	114
Down syndrome (Ch. III.8)	14,095	558
Cerebral palsy (Ch. III.7)	28,745	656

* Numbers are from Tables 3-1 and 3-4 in Waitzman et al., 1996.

**The prevalence of a birth defect at a given time is the number of individuals (of all ages) who have the birth defect at that time.

***The incidence of a birth defect in a given year is the number of infants born with the birth defect during that year. For example, whereas there were 8,859 individuals (of all ages) in California on July 1, 1988 who had spina bifida, 226 babies were born with spina bifida in California during 1988. Those infants born with spina bifida in California in 1988 on or before July 1 and still alive on July 1 would be counted among the prevalent population on July 1, 1988.

Waitzman et al. estimated the lifetime costs of birth defects in a cohort and therefore used an incidence-based approach. Ideally, they would have tracked the costs of the cohort members over time, until the death of the last cohort member. Because the members of the cohort were born in 1988, however, this was not possible. Instead, estimates of the costs incurred at each age were based on estimates of per capita costs in the prevalent population of that age. The method is described more fully in Section III.3.B.1.5.

III.3.B.1.3 Incremental Costs

Waitzman et al. emphasize that their cost estimates are "cost estimates for individuals with birth defects rather than the costs of the birth defects per se" (Waitzman et al., 1996). They are, moreover, estimates of *incremental*

costs. Because medical costs are incurred by the population as a whole, the costs incurred by an individual with a birth defect must be adjusted to reflect these baseline costs. The per capita *incremental* cost of a birth defect is the cost incurred above and beyond the cost incurred by an "average child" without the birth defect. Waitzman et al. attempted to isolate those costs specifically related to the condition of interest and associated anomalies. In order to do this, the costs for each individual with a particular effect (e.g., cleft lip) were tracked. Costs for the average non-affected person were subtracted from those for the average person with the effect.

III.3.B.1.4 Costs of Concurrent Effects

Many of the defects discussed in the following chapters are associated with other defects. By their nature, Waitzman et al.'s cost estimates include the costs of concurrent effects. As noted above, Waitzman et al. estimated the costs incurred by individuals with birth defects, including all medical costs incurred, rather than the cost of the birth defect per se. For example, the mean per-capita cost incurred by a person with Down Syndrome would include the costs associated with other defects. This approach has advantages and disadvantages (as discussed in detail by Waitzman et al.). If two defects are dependent, then it makes sense to include costs related to both conditions; the benefits of preventing the first would be equal to the costs of both, since prevention of one leads to prevention of the other. Alternatively, if two defects are independent of each other but show up in the same person, this methodology would yield an overestimate of costs.[2] Little is known about the pathogenesis of birth defects, and the assumption is that most defects fall somewhere in between total dependence and independence. Given the relative rarity of many severe birth defects, the probability that they would occur in the same person, without any linkage in causation, is very small.

As Waitzman et al. note, the costs of associated anomalies are included as part of the estimate of the costs incurred by an individual with a given birth defect. For this reason, their cost estimates cannot be aggregated across birth defects because of the possibility of double counting.

Given the large size of the California databases used by Waitzman et al., the combination and frequency of concurrent effects in the authors' sample are likely to be representative of those in the larger United States population, and therefore appropriate for a benefits assessment.

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[2] Waitzman et al. address this situation when they extrapolate the per-capita mean costs to the total mean costs per disease. Rather than including a single person in the incidence totals for both Down syndrome and cleft palate, for instance, they include a person with both defects in the incidence total of the more costly defect. When the per-capita costs are multiplied by the total number of people with the defect, each person is counted only once. The costs in this handbook focus on the per-capita costs only. Consequently, the adjustment described above is not applicable to the costs presented here.

III.3.B.1.5 Analysis

The estimation of the average per capita lifetime cost associated with a birth defect is based on the method of Waitzman et al. (1996). Waitzman et al. estimate both the total lifetime cost for a *cohort* of individuals and the average lifetime cost per case — i.e., for a single individual in the cohort. (The average cost per case is obtained by simply dividing the total cost for the cohort by the original number of individuals in the cohort.) The Waitzman et al. method is discussed briefly below.

Waitzman et al. estimate the present discounted value of lifetime costs associated with a birth defect for a cohort born with the defect in 1988 in California. This value is the sum of costs over all years in which cohort members are alive, with future costs discounted appropriately. The total costs incurred during the first year after birth, denoted TC_1, are the costs incurred by all members of the cohort who survive to one year of age; these costs are discounted back to the year of birth by dividing TC_1 by the discount factor for the first year, $(1 + r)$, where r is the discount rate. The total costs incurred during the second year after birth, denoted TC_2, are the costs incurred by all members of the cohort who survive to two years of age; these costs are discounted back to the year of birth by dividing TC_2 by the discount factor for the second year, $(1 + r)^2$. In general, the costs incurred during the *i*th year after birth, TC_i, are the costs incurred by those members of the cohort who survive to age *i*. These costs are discounted by dividing by the discount factor for the *i*th year, $(1 + r)^i$.

The total cost of the birth defect, COBD, is the sum of these discounted age-specific total costs:

$$COBD = \sum_i TC_i/(1+r)^i .$$

As discussed in Section III.3.B.1.3, the total costs incurred at a given age are *incremental* costs — that is, those costs above and beyond the costs incurred by the average child of that age.

Link to Section III.3.B.1.3

One way to estimate TC_i, the total incremental costs during the *i*th year after birth (i.e., at age *i*), might be to estimate the incremental costs incurred by those members of the cohort who survive to age *i*. For a cohort born in 1988, however, this calculation would be possible only through age nine, because members of that cohort would reach that age in the present year, 1997. Waitzman et al. instead base their estimates of total incremental costs for a given age on costs in the *prevalent* population of that age. For example, the average per capita total incremental cost among 15-year-olds is estimated from data on individuals with the birth defect who are 15 years old (none of whom can be members of a cohort born in

1988). This method assumes that the real costs associated with the birth defect for individuals of a given age will not change appreciably over time — for example, that the real costs for a 15-year-old in the year 2003, when the surviving members of the cohort born in 1988 are 15, will be the same as the real costs for an individual who is 15 years old in the prevalent population examined (e.g., in 1988). Waitzman et al. note that this conclusion in turn rests on the assumption that future treatment patterns will resemble current treatment patterns. An estimate of the per capita cost based on the prevalent population of age *i*, $PCPREV_i$, multiplied by an estimate of the number of individuals in the 1988 cohort who are expected to survive to age *i*, S_i, yields an estimate of the total incremental costs of those cohort members who survive to age *i*:

$$TC_i = (S_i) \times (PCPREV_i) .$$

Waitzman et al. estimate per capita costs in the prevalent population of age *i*, $PCPREV_i$, in two different ways, depending on data availability. One method is to simply divide the total costs in the prevalent population of age *i* by the number of individuals in that population. If the necessary information is not available for this method, an alternative method is used. Not all individuals with birth defects incur incremental costs at each age. The alternative method estimates the proportion of the prevalent population at age *i* who do incur incremental costs, and multiplies that proportion by the average per capita costs incurred by the individuals who incur costs. This second method is used when estimates of the total or per capita costs for the prevalent population of age *i* are not available, but estimates of the average per capita cost for those incurring costs are available.

The focus in this handbook is on the expected lifetime incremental costs for an individual with the birth defect — i.e., the average lifetime cost per case. As noted above, Waitzman et al. obtain this value by simply dividing the total cost for the cohort by the original number of individuals in the cohort. This method is equivalent to following the calculation outlined above, with one alteration: now, the *probability* of surviving to age *i* among those individuals born with the birth defect, ps_i, is used, rather than S_i, the *number* surviving to age *i*.[3] The expected per capita cost at age *i*, PCC_i, of an individual born with the birth defect would then be:

$$PCC_i = (ps_i) \times (PCPREV_i) .$$

[3] To estimate the number of cohort members surviving to a given age, Waitzman et al. multiplied the number in the original cohort by an estimate of the probability of surviving to that age. The data necessary to estimate survival numbers therefore include the data necessary to estimate survival probabilities.

The present discounted value of expected per capita lifetime costs of the birth defect, PCCOBD, is just the sum of these expected age-specific per capita costs, appropriately discounted:

$$PCCOBD = \sum_i PCC_i/(1+r)^i .$$

III.3.B.1.6 Variable-Specific Data Sources

Table III.3.2 lists the data sources used for each variable necessary for the calculations described above. It also briefly describes the limitations associated with each of these sources, and the methodology used to derive the data from the relevant sources.

Table III.3-2: Variable specific data sources and limitations

Variable			Source	Data Limitations
Number surviving to a given age, S = l×m	l (Incident Cases) (not including Cerebral Palsy)		CBDMP [1]	1. Actual numbers were not collected for three major counties, but were estimated for the study. These estimates could be biased. 2. Only live-born children are included. 3. Certain internal defects are not apparent during the first year, and therefore prevalence may be underestimated. 4. Does not account for birth defects treated exclusively on an outpatient basis.
	l (Cerebral Palsy)		CA Cerebral Palsy Project	1. Exceptionally stringent criteria for including cases. May underestimate.
	m (age-specific survival proportion)	Age 0-1	CBDMP linked with death certificates	1. Assumes that mortality at time of database is same at time of study — overestimates costs. 2. Assumes normal mortality beyond a specific age — underestimates costs.
		Quadrant IV conditions	MEDLINE search for each condition	
		Mortality	Review of clinical lit, panel of clinical advisors	1. Assumption of normal mortality beyond a specific age — may overestimate the number of survivors.

Table III.3-2: Variable specific data sources and limitations			
Variable		**Source**	**Data Limitations**
Size of the prevalent population	Age 0-1	CBDMP and incidence estimate (see above)	1. Applied 1983-86 estimates to 1988 — assumes that these numbers are similar. 2. Underestimates # of children who actually used services, i.e, if a child died before the one year cut-off date they would not be included, and yet they may have received care. 3. Assumed first-year mortality was equal among males and females. 4. Net migration not accounted for — may underestimate prevalence if families migrate to CA b/c of the availability of specialized care.
	After age 1	NHIS [2]	1. Assumes no net migration and no mortality over time. These two may actually cancel each other out. 2. Assumes that the prevalence of each defect has been constant over time.
Total incremental costs in the prevalent population (for each age)	Inpatient/Outpatient	OSHPD [3] (adjusted using MediCal and cost-to-charge ratios)	1. Cost-to-charge ratio may be too drastic.
	Long-term (Down syndrome and cerebral palsy)	DDS file [4]	
	Long-term (others)	MediCal	1. Assumed that all costs were borne by Medical. 2. Assumed that expenditures for such care were at cost.
	Other	Shriners' hospitals (add'l data not reported in OSHPD or MediCal)	
	Incremental Costs	NMCES [5]	1. These data may include persons with defects and therefore might be slightly overestimated, making incremental costs slightly underestimated.
PCAFF	Developmental Costs	DDS file	1. Unlikely that all underlying etiologies were recorded — may have underestimated # of people w/ birth defects receiving DDS services.
TC — special education	fc — proportion of the affected population	SRI [6]	1. Assumed the national distribution applied to CA.
	p — proportion receiving special ed	NHIS	1. May underestimate proportion receiving special ed.
	PCFC — per-capita special education costs	CA State Department of Education	
	CALPROP-the distribution of students	CA Department of Education	

[1] California Birth Defects Monitoring Program
[2] National Health Interview Survey
[3] 1988 California Office of Statewide Health Planning and Development hospital discharge file
[4] California Department of Developmental Services Masterfile, 1988-89
[5] National Medical Care Expenditure Survey, 1987
[6] National Longitudinal Transition Study of Special Education Students, 1990

III.3.B.2 Results

III.3.B.2.1 Annual Direct Medical Costs

Waitzman et al.'s (1996) estimates of the total lifetime medical costs of cleft lip and palate are outlined in the following tables. They are updated from 1988 to 1996 dollars based on the medical care cost component of the Consumer Price Index (1996:1988=1.6465). Table III.3-3 shows annual per capita medical costs incurred by individuals with cleft lip and palate by age group.

Table III.3-3: Annual Per-Capita Medical Costs of Cleft Lip and Palate by Age Group (1996$)

Condition	Age 0-1	Age 2-4	Age 5-17	Age 18+
Cleft lip and palate	$11,186	$2,025	$1,510	$1,421

III.3.B.2.2 Incremental Lifetime Direct Medical Costs

The medical cost of the average population was then subtracted from these costs to obtain incremental costs. Waitzman et al. (1996) discounted these costs using three different discount rates: two percent, five percent and ten percent. Although these discount rates do not match the standard EPA rates used in many other chapters in this handbook (zero percent, three percent, five percent and seven percent), there is insufficient information provided in Waitzman et al. (1996) to allow a conversion to discounted costs using standard EPA discount rates. This problem exists in all chapters based on the Waitzman et al. data (Chapters III.3 through III.8). The present discounted values of average per capita lifetime incremental costs, using discount rates of two percent, five percent, and seven percent, are listed in Table III.3-4 below.

Table III.3-4: Per-Capita Incremental Medical Costs, Nonmedical Costs, and Total Costs of Cleft Lip and Palate (1996$)

Cost Element	0%	2%	5%	10%
Direct Medical Costs		$19,758	$18,111	$16,465
Direct Non-Medical Costs:				
Developmental Services		$688	$649	$589
Special Education		$5,218	$3,866	$2,453
Total Direct Costs		$25,664	$22,626	$19,507

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

III.3.B.2.3 Other Costs

Categories of costs that are not usually included in this handbook were available from Waitzman et al. and so are reported in Table III.3-4. For information on their estimation methods see Waitzman et al. (1996).

III.3.B.2.4 Limitations

Reliance on the Waitzman et al. (1996) study has a number of limitations. The first concerns the reliance solely on California data. Medical practices and costs vary across the country, and an ideal data set would contain cost information from a representative sample of the entire United States. As a large state with varied areas (urban, rural, suburban, high, moderate, and low income populations), California is likely to reflect some of the diversity seen throughout the country. The California data are also especially accurate because of the birth defects monitoring program that the state has in place.

Another limitation involves the basis of the Waitzman et al. cost estimates. Waitzman et al. base their estimates of costs on *actual* costs incurred. To the extent that services were not readily available to or obtained by parents of children with birth defects in their sample, the Waitzman et al. estimates may understate the costs necessary for children to receive the level of care considered by doctors to be adequate.

What is considered "adequate" may, of course, vary from one individual to another (just as the willingness to pay to avoid the occurrence of a birth defect may vary from one individual to another). An alternative approach would be to delineate the collection of medical services and treatments that constitute "proper care" for a given birth defect or illness, as defined by consensus among doctors, and estimate the costs associated with that "bundle" of services and treatments. This theoretical cost methodology has the advantage of avoiding the possibility that the cost estimates may reflect the unwillingness or inability of parents to pay for adequate medical care rather than the cost of the care itself. These "ideal" costs are the costs of the care that, according to doctors, *should* be received. They are thus likely to be closer to the benefits to society of avoiding an illness. Actual costs, on the other hand, reflect the care that actually *is* received, and are therefore presumably a more accurate representation of what occurs.

The degree to which actual costs understate "ideal" costs will depend on the illness. Children with a life-threatening heart anomaly (See Chapter III.5) will typically be diagnosed properly at birth and require treatment, whereas children with Down syndrome may receive varying degrees of services to address their needs, depending on parental and other social factors and economic resources.

Waitzman et al. point out other limitations of their study, several of which are likely to lead to underestimates of cost. For example, they underestimate developmental services costs because the Department of Developmental Services file included only public expenditures, not private, out-of-pocket spending. In addition, the databases do not necessarily include complete longitudinal profiles of costs for all individuals because it was not always possible to link an individual's files across the entire lifespan. This omission would also result in underestimates of total lifetime costs. Finally, costs could be either under- or overestimated due to changes in technologies. Because the study attempts to estimate lifetime costs, changes in medical care technologies or policies could be important. These changes could either increase or decrease costs.

A final limitation warrants mention. Only select costs are presented in this chapter. There are other important categories of costs that are not included here. For example, a person born with a birth defect often has a higher probability of early death (see Section III.3.A.5, above); the cost of premature mortality is a real cost associated with many birth defects and illnesses. Individuals with illnesses or birth defects often experience a decrease in productivity, resulting in a loss to society of goods and services. In addition, there are the indirect costs of the pain and suffering of the individual and of family members, as well as the lost productivity of family members. These costs can be considerable (e.g., the direct cost of lost work time calculated for spina bifida by Waitzman et al. was $656,879 in 1996 dollars). These costs, while not presented for most illnesses in this handbook, are valid components of the total economic costs associated with the illnesses and birth defects discussed in this handbook.

Link to Section III.3.A.5

CHAPTER III.4. COST OF LIMB REDUCTIONS

Clicking on the sections below will take you to the relevant text.

CHAPTER III.4. COST OF LIMB REDUCTIONS

III.4.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with limb reductions, and the results of the analysis.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.4.A.1 Description

Limb reductions are the partial (meromelia) or complete (amelia) absence of arms or legs. They vary with respect to the bones, muscles, and other structures affected.

III.4.A.2 Concurrent Effects

Children with limb reductions frequently have other birth defects. In 30 to 53 percent of affected children, other malformations are present, including anomalies of the heart, kidney, anus, abdominal walls, esophagus, vertebrae, and palate. Webbing between digits and spina bifida are also associated with this defect (Waitzman et al., 1996).

III.4.A.3 Causality

Table III.1-1 in Chapter III.1 lists numerous chemicals associated with developmental abnormalities in human and/or animal studies. Many of these chemicals have caused structural and anatomical defects. Limb reductions fall into this category of defects.

Link to Table III.1-1 in Chapter III.1

[1] "Costs" in this chapter refer to direct incremental per capita medical costs, unless otherwise noted.

A recently completed study of the offspring of pesticide application workers found that their incidence of skeletal anomalies, which includes limb reductions, was significantly greater than that of the general population in the same area of the United States (Garry et al., 1996). Respiratory system, circulatory system, and urogenital anomalies also occurred at increased rates. Musculoskeletal anomalies include any abnormality in the size, shape, or function of part of the skeletal system, muscles, and related tissues (e.g., cartilage). They include the absence or shortening of limbs (as discussed in this chapter) and the abnormal formation of part of the skeleton or related soft tissue and cartilage, (as discussed in Chapter III.3). The chemicals evaluated in the study that were associated with the birth defects were trifluralin, triazine herbicides (including atrazine, a very common well contaminant in agricultural areas), and chlorophenoxy herbicides (including MCPA and 2,4-D, a pesticide with very high usage). There was also a significant increase in birth defects among infants conceived in the spring (i.e., during peak chlorophenoxy use) compared to infants conceived during other periods of the year (Garry et al., 1996). As indicated in the introductory developmental effects chapter (III.1), the timing of exposure is often a critical determinant of whether and what type of effects will occur.

Links to Chapters III.3 and III.1

Generally, the earlier during a pregnancy that damage occurs, the more serious the effect will be, because all cells developing from the damaged cells may also be damaged or eliminated, and basic structures are being formed during the first trimester (three months). Although Garry et al. (1996) does not provide detailed information on the nature of the skeletal and other anomalies, information can be obtained from the author or from EPA (which funded the work).

III.4.A.4 Treatment and Services

Individuals with limb reductions are treated using a variety of surgical techniques, are fitted with prostheses, and usually require physical and/or occupational therapy (Mason, 1991). Limb reductions may occur at any point from the joint which attaches the limb to the body (i.e., shoulder or hip) to the distal point of that limb, and may affect some or all of the bones, muscles, cartilage, and other structures comprising the limbs. The structures involved and the types of surgical approaches used are too diverse and numerous to describe in this chapter. Depending on the nature of the limb reduction, this type of birth defect may require multiple complex surgical corrections. Following the initial surgical and related treatments, prostheses are usually replaced each year up to five years. They are replaced biennially after that, up to twelve years, and every two to five years after that (Waitzman et al., 1996).

III.4.A.5 Prognosis

Twelve to twenty percent of infants with limb reductions die during infancy, primarily due to other anomalies (as noted above) (Froster-Iskenius and Baird, 1990). Individuals with limb reductions who have received appropriate medical treatment usually have good functional capabilities (in the absence of other unrelated serious medical problems), although their physical actions may be slowed by their disabilities. There are significant psychosocial implications of these permanent disabilities; these may require medical or other treatment (Waitzman et al., 1996).

III.4.B Costs of Treatment and Services

III.4.B.1 Methodology

Chapters III.3 through III.8 of this handbook use cost of illness estimates developed primarily by Waitzman et al. (1996). Waitzman et al. used the same methodology to estimate the costs incurred by individuals with limb reductions as for all the birth defects for which they estimated costs. The methodology and relevant considerations are detailed in Chapter III.3, including discussions of direct and indirect costs, prevalence versus incidence, incremental costs, and concurrent effects. The analytic method, the sources of data, and the limitations of the Waitzman et al. method are also discussed in Chapter III.3. The methodology is outlined briefly here.

Link to Chapter III.3.

To estimate the lifetime medical costs incurred by an individual with a birth defect, Waitzman et al. estimated the average lifetime medical costs for an individual with the birth defect. From this value, the authors subtracted the average lifetime medical costs for an individual without the birth defect. This yielded the incremental costs associated with the birth defect. Because they estimated lifetime costs, they used an incidence-based approach. Ideally, they would have tracked the costs of the cohort members over time, until the death of the last cohort member. Because the members of the cohort were born in 1988, however, this tracking was not possible. Instead, estimates of the costs incurred at each age were based on estimates of per capita costs in the prevalent population of that age (see Chapter III.3, Section III.3.B.1.2).

Link to Chapter III.3, Section III.3.B.1.2

This method has two important implications. First, Waitzman et al. estimated the costs incurred by individuals with birth defects, including all medical costs incurred, rather than the cost of the birth defect per se.

These cost estimates therefore include the costs of concurrent effects (unlike the costs reported for many of the diseases in this handbook). This method yields a more comprehensive assessment of total costs than would be obtained if only individual effects were evaluated. This method is of particular use in valuing the avoidance of birth defects because they very frequently occur in clusters within an individual. As Waitzman et al. note, however, the costs of associated anomalies are included as part of the estimate of the costs incurred by an individual with a given birth defect. These cost estimates therefore cannot be aggregated across birth defects because of the possibility of double counting.

Second, the Waitzman et al. method estimates the *incremental* costs for individuals with birth defects — that is, the costs above and beyond the average costs that would be incurred by individuals without the birth defect.

Waitzman et al. (1996) estimated three categories of costs incurred by individuals with limb reductions: direct medical costs, direct nonmedical costs, and indirect costs.[2] Direct medical costs, specifically inpatient care, outpatient care, pharmaceuticals, laboratory tests, X-rays, appliances, and long-term care are included in the cost estimates shown in this and other chapters (Chapters III.3 through III.8) based on the work of Waitzman et al. Nonmedical direct costs, specifically developmental services, and special education are also included in this handbook.

The Waitzman estimates of the costs incurred by individuals with limb reductions are based on the costs of this birth defect in California across many ages, and its occurrence in a large cohort of children born in California in 1988. California's ongoing birth defects monitoring program provides an excellent source of data. The California data sets were linked with other national data sets so that Waitzman et al. could estimate the incremental costs associated with limb reductions.

The method of calculating the expected lifetime incremental costs for an individual with a birth defect — i.e., the average lifetime cost per case — is the same for all the birth defects considered by Waitzman et al. The expected per capita cost at age *i*, PCC_i, for an individual born with the birth defect is the probability of surviving to age *i* (among those individuals born with the birth defect), ps_i, times the per capita cost among individuals who do survive to age *i* ($PCPREV_i$, measured in the prevalent population):

$$PCC_i = (ps_i) \times (PCPREV_i) .$$

[2] Indirect costs are not generally discussed in this handbook and so are not included in this chapter. The reader may wish to consult Waitzman et al. (1996) for information on these costs.

Waitzman et al. estimate per capita costs in the prevalent population of age *i*, $PCPREV_i$, in two different ways, depending on data availability (see Chapter III.3).

Link to Chapter III.3

The present discounted value of expected per capita lifetime costs of the birth defect, PCCOBD, is just the sum of these expected age-specific per capita costs, appropriately discounted (as explained more fully in Chapter III.3):

$$PCCOBD = \sum_i PCC_i/(1+r)^i .$$

III.4.B.2 Results

Waitzman et al. (1996) estimate the medical costs of two different groups of limb reductions: upper limb reductions and lower limb reductions. The following tables outline the various costs associated with both types. They are updated from 1988 to 1996 dollars based on the medical care cost component of the Consumer Price Index (1996:1988=1.6465).

Table III.4-1 shows annual per capita medical costs incurred by individuals with limb reductions by age group. Upper limb reductions tend to be correctable at birth, and thus the costs decrease over time. The costs of lower limb reductions, on the other hand, tend to increase with time beyond the initial cash outlay, because lower limb reductions are less correctable and require ongoing medical services.

Table III.4-1: Annual Per-Capita Medical Costs of Limb Reductions by Age Group (1996$)

Condition	Age 0-1	Age 2-4	Age 5-17	Age 18+
Upper Limb Reduction	$8,985	$659	$456	$280
Lower Limb Reduction	$11,888	$1,215	$1,786	$3,492

The medical cost of the average population was then subtracted from these costs to obtain incremental costs. Waitzman et al. (1996) discounted these costs using three different discount rates: two percent, five percent, and ten percent. Although these discount rates do not match the standard EPA rates used in many other chapters in this handbook (zero percent, three percent, five percent, and seven percent), there is insufficient information provided in Waitzman et al. (1996) to allow a conversion to discounted costs using standard EPA discount rates. This problem exists in all chapters based on the Waitzman et al. data (i.e., Chapters III.3 through III.8).

The present discounted values of average per capita lifetime incremental costs, using discount rates of two percent, five percent, and seven percent, are listed in Table III.4-2 below. Direct medical costs and direct non-medical costs are listed separately. The sum of per-capita direct medical and nonmedical costs provides an estimate of the total per-capita costs incurred by individuals with limb reductions.

Table III.4-2: Per-Capita Net Medical Costs, Nonmedical Costs, and Total Costs of Limb Reductions (1996$)

Cost Element	2%	5%	10%
Upper Limb Reduction			
Net medical costs	$8,232	$8,232	$8,232
Net nonmedical costs	$28,372	$21,574	$14,342
Total costs	$36,604	$29,806	$22,574
Lower Limb Reduction			
Net medical costs	$39,515	$26,343	$18,111
Net nonmedical costs	$28,332	$21,537	$14,311
Total costs	$67,847	$47,880	$32,422

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

The costs associated with lower limb reductions are significantly higher than those associated with upper limb reductions. This difference is due to the weight bearing issues associated with lower limb reductions that require more extensive surgical therapy. Because the legs are necessary for proper balance, lower limb reductions often produce more complications, and thus require more surgery than reductions in the arms.

CHAPTER III.5. COST OF CARDIAC ABNORMALITIES

Clicking on the sections below will take you to the relevant text.

CHAPTER III.5. COST OF CARDIAC ABNORMALITIES

III.5.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with cardiac abnormalities and the results of the analysis.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.5.A.1 Description

A number of cardiac anomalies occur at birth or in early infancy, and are quite varied. These are structural defects in the development of the heart, arteries, and associated tissues. They arise when the function, movement and relationships among cardiac cells fail to progress normally. Five defects, all conotruncal heart anomalies, are discussed in this chapter. The specific anomalies include: truncus arteriosus, transposition of the great arteries, double-outlet right ventricle (DORV), single ventricle, and tetralogy of Fallot. They were selected from among the cardiac abnormalities for which cost data are available because they occur with greater frequency than other defects and are not usually fatal when treated. Each anomaly is described below in turn in Section A, followed by the cost data in Section B.[2]

[1] "Costs" in this chapter refers to direct incremental per capita medical costs, unless otherwise noted.

[2] Certain forms of DORV are grouped together for the cost analysis because they resemble transposition and actually fall under the same International Classification of Diseases ICD-9 codes.

III.5.A.2 Causality

Information on causality is discussed for each specific cardiac anomaly described below. Many anomalies occur concurrently with other cardiac or non-cardiac anomalies. Although there appears to be a genetic component in some anomalies, none of the anomalies described below has a strong clear hereditary pattern. The causation of the anomalies is therefore for the most part unknown. These anomalies may be due to a variety of factors, including maternal health, heredity, and environmental factors.

A recently completed study of the offspring of pesticide application workers found that their incidence of circulatory system anomalies was significantly greater than that of the general population in the same area of the United States (Garryet al., 1996). Respiratory system, musculoskeletal, and urogenital anomalies also occurred at increased rates. The chemicals evaluated in the study that were associated with the birth defects were trifluralin, triazine herbicides (including atrazine, a very common well contaminant in agricultural areas), and chlorophenoxy herbicides (including MCPA and 2,4-D, a pesticide with very high usage). There was also a significant increase in birth defects among infants conceived in the spring (i.e., during peak chlorophenoxy use), compared to infants conceived during other periods of the year (Garry et al., 1996). As indicated in the introductory developmental effects chapter (III.1), the timing of exposure is often a critical determinant of whether and what type of effects will occur.

Generally, the earlier during a pregnancy that damage occurs, the more serious the effect will be, because all cells developing from the damaged cells may also be damaged or eliminated, and basic structures are being formed during the first trimester (three months). Although Gerry et al. (1996) do not provide detailed information on the nature of the circulatory and other anomalies, information can be obtained from the author or from EPA (which funded the work).

Table III.1-1 in Chapter III.1 lists numerous chemicals associated with developmental abnormalities in human and/or animal studies. Many of these studies have identified structural and anatomical defects. Cardiac abnormalities fall into this category of defects.

Link to Table III.1-1 in Chapter III.1

III.5.A.3 Truncus Arteriosus

III.5.A.3.1 Description

Truncus arteriosus occurs when abnormalities in major arteries and valves lead to a mixing of oxygenated and de-oxygenated blood. This mixing results in an insufficiently oxygenated supply of blood to tissues. This disorder ultimately leads to congestive heart failure if uncorrected. In the absence of surgery, 75 percent of children die within the first year, and the survivors have severely limited abilities due to heart disease (Oldham et al., 1972). Truncus arteriosus occurs in approximately two percent of children with congenital heart defects (Oski, 1994).

III.5.A.3.2 Concurrent Effects

Children with this defect also frequently have underdevelopment of the aortic arch, displacement or stenosis at the origin of the coronary arteries, and absence of the main pulmonary artery supplying the lungs. This and other cardiac anomalies occur with greater frequency among Down syndrome children (statistics on occurrence were not available) (Waitzman et al., 1996).

III.5.A.3.3 Treatment and Services

Although previously considered an inoperable defect, substantial improvements in surgical and other treatments have been made in recent years. The surgical methods and medical follow-up continue to be refined (Oski, 1994). This defect is usually surgically treated at 6 to 12 weeks through constructive surgery and insertion of valves. Follow-up surgical repair or valve replacement is often required within the first five years after surgery (15 to 50 percent). All valves are replaced at twelve years due to growth. Follow-up surgery (i.e., dilations) is not uncommon (Waitzman et al., 1996).

III.5.A.3.4 Prognosis

Based on a small sample (106 infants) there is a six percent mortality rate prior to surgery and a ten percent mortality rate during the surgical period (Ebert et al., 1984; Bove et al., 1989). Complications may result from follow-up medical treatments (Waitzman et al., 1996).

III.5.A.4 Transposition of the Great Arteries

III.5.A.4.1 Description

Transposition of the great arteries occurs when the major arteries are transposed, leading to insufficient oxygen flow to tissues and lungs. This condition causes widespread cyanosis (Oski, 1994) and is fatal without surgical intervention (Waitzman et al., 1996). Transposition of the great arteries is a common cardiac abnormality, occurring in approximately five percent of all patients with congenital heart disease (Oski, 1994).

III.5.A.4.2 Concurrent Effects

Various associated cardiac abnormalities involving multiple structures within the heart complicate the treatment of this disorder (for a detailed description see Oski, 1994). Ventricular septal defect also occurs in 20 percent of children with this anomaly (Kirklin, 1991).

III.5.A.4.3 Treatment and Services

Surgery to correct this defect is performed shortly after birth. Ten percent of affected individuals require additional surgery within one year (Waitzman et al., 1996). As noted under concurrent effects above, concurrent heart defects often occur, and the constellation of effects is considered when determining the appropriate medical treatment.

III.5.A.4.4 Prognosis

During the immediate post-surgical period, the mortality rate is approximately 14 to 22 percent, depending on the specific nature of the defects and procedures used. Between 30 and 80 percent of children with this defect who have received medical treatment develop cardiac arrhythmias within ten years, again depending on the defects and surgical approaches. Three to ten percent of these children require insertions of pacemakers (Waitzman et al., 1996).

Cardiac dysfunction occurs in approximately ten percent of children within ten years. Arrhythmias and heart failure lead to death in approximately 11 percent of children between 30 days and 10 years after surgery (Morris and Menashe, 1991). Depending on the type of procedures done to correct this disorder, various medical problems may arise, some requiring surgery at a later date. For a detailed description of the common long-term sequelae, see Oski (1994).

III.5.A.5 Double-outlet Right Ventricle

III.5.A.5.1 Description

Double-outlet right ventricle refers to a diverse group of heart defects that occur when both the aorta and pulmonary artery originate from the right ventricle, and a septal defect is present (Oski, 1994). This condition leads to insufficient blood flow to critical tissues, and may cause cyanosis, exhaustion with exercise, heart failure, and pulmonary vascular disease (Waitzman et al., 1996). This disorder occurs in approximately two percent of congenital heart defects. Although sometimes associated with trisomy-18 and material diabetes, most cases occur with no other congenital anomalies (Oski, 1994). The symptoms of this anomaly vary with the specific structural defects and may include cyanosis, congestive heart failure, and related effects.

III.5.A.5.2 Concurrent Effects

Complex lesions of the atrial or ventricular septum, valve defects, mislocation of the heart, and ductus arteriosus have also been observed with this defect (Waitzman et al., 1996).

III.5.A.5.3 Treatment and Services

Surgery is usually performed at 6 to 24 months. Arrhythmias in children are common, even with surgery, and may require follow-up care (Waitzman et al., 1996).

III.5.A.5.4 Prognosis

Various mortality rates have been reported in the literature. A 15 percent post-surgical mortality rate in infants was reported by Judson et al., (1983). Shen et al. (1990) reported that approximately 25 percent of children who have received appropriate medical attention die during childhood, probably due to arrhythmias. More recent reports indicate a much better prognosis with a 90 to 95 percent *post*-surgical survival rate and excellent functional status following surgery (Oski, 1994).

III.5.A.6 Single Ventricle

III.5.A.6.1 Description

Single ventricle occurs when one, rather than the usual two ventricles are present. One may dominate (they are usually balanced) and the other may be very small, or there may be only one present. In either case, there is one that is primarily functional (Oski, 1994). This anomaly causes insufficient blood flow to tissues and can lead to cyanosis, heart failure, and pulmonary vascular disease. There is a 70 percent mortality rate in childhood in the absence of surgery (Waitzman et al., 1996). This disorder is found in approximately one percent of children with congenital anomalies.

III.5.A.6.2 Concurrent Effects

Multiple concurrent cardiac defects occur with this anomaly. Twenty to 40 percent of children also have other non-cardiac problems, including scoliosis and lack of a spleen (Waitzman et al., 1996).

III.5.A.6.3 Treatment and Services

Correction of this defect commonly involves two surgical interventions, one shortly after birth, and one at 18 to 36 months. Additional surgery is required in 14 percent of children (Waitzman et al., 1996).

III.5.A.6.4 Prognosis

With surgery, survival varies considerably. The mortality rate is 29 to 43 percent within ten years. Among survivors, ten percent have limited activity and three percent were severely limited (Waitzman et al., 1996). Most patients exhibit exercise intolerance and cyanosis. Causes of death include dysrhythmia, congestive heart failure, brain abscess, pancreatitis,

cerebral infarction, cerebral embolus, and hemorrhage, and pulmonary embolus and valve occlusion (Oski, 1994). Due to the long-term medical problems associated with this anomaly, research into improvements in surgical and other medical treatments is being carried out. There is not a single currently accepted treatment method at this time, and various approaches are used. (Oski, 1994).

III.5.A.7 Tetrology of Fallot

III.5.A.7.1 Description

Tetrology of Fallot refers to a group of abnormalities of the heart that have the common characteristics of unrestrictive ventricular septal defects and an obstruction of the right ventricular outflow (Oski, 1994). These abnormalities also involve malpositioning of the aorta and thickening of the right ventricular wall (Pinsky and Arciniegas, 1990). The severity varies considerably from a heart murmur to life-threatening hypoxia. If it is not detected during infancy it may lead to a misshapen (boot-shaped) heart (Oski, 1994). This disorder occurs in approximately six percent of children with congenital heart defects (Oski, 1994).

III.5.A.7.2 Concurrent Effects

Multiple additional cardiac defects are associated with this anomaly Waitzman et al., 1996). Non-cardiac abnormalities are associated with this disorder in approximately 16 percent of cases, more so than with most other cardiac defects. The children are also more likely to have concurrent effects that are more serious than those found with other cardiac defects, including cleft lip and palate, hypospadias (reproductive organ abnormality in males), and skeletal malformations (Oski, 1994).

III.5.A.7.3 Treatment and Services

When Tetralogy of Fallot is detected shortly after birth, surgery to correct the defects usually occurs at three to twelve months of age. Depending on the specific nature of the defects, surgery may also be required shortly after birth. Five to fifteen percent of children require additional surgery within thirteen years (Waitzman et al., 1996). Treatment of arrhythmias may be required in some patients long after surgery, and bacterial endocarditis may also occur and require treatment later in childhood or adulthood (Oski, 1994).

III.5.A.7.4 Prognosis

The rate of post-surgical mortality is three to eight percent in infants (Touati et al., 1990; Walsh et al., 1988). At ten years the survival rate is 87 to 90 percent, and 85 percent survive into their twenties. The prognosis for normal function and activity is good in surviving children (Waitzman et al., 1996). As noted under the treatment section above, a number of problems may be anticipated in the long-term follow-up of children with this disorder (e.g., bacterial endocarditis, arrhythmias) and effects of

coronary artery disease at a more advance age may be more severe in people with this disorder (Oski, 1994).

III.5.B Costs of Treatment and Services

III.5.B.1 Methodology

Waitzman et al. (1996) provide an estimate of the direct medical and non-medical costs of treating cardiac abnormalities, specifically for the five types listed above. For the purpose of the cost analysis, transposition and double-outlet right ventricle (DORV) were grouped together. Waitzman et al. used the same methodology to estimate the costs incurred by individuals with each type of cardiac abnormality as for all the birth defects for which they estimated costs. The methodology and relevant considerations are detailed in Chapter III.3, including discussions of direct and indirect costs, prevalence versus incidence, incremental costs, and concurrent effects. The analytic method, the sources of data, and the limitations of the Waitzman method are also discussed in Chapter III.3. The methodology is outlined briefly here.

Link to Chapter III.3

To estimate the lifetime medical costs incurred by an individual with a birth defect, Waitzman et al. estimated the average lifetime medical costs for an individual with the birth defect. From this value, the authors subtracted the average lifetime medical costs for an individual without the birth defect. Because they estimated lifetime costs, they used an incidence-based approach. Ideally, they would have tracked the costs of the cohort members over time, until the death of the last cohort member. Because the members of the cohort were born in 1988, however, this tracking was not possible. Instead, estimates of the costs incurred at each age were based on estimates of per capita costs in the prevalent population of that age (see Chapter III.3, Section III.3.B.1.2).

Link to Chapter III.3, Section III.3.B.1.2

This method has two important implications. First, Waitzman et al. estimated the costs incurred by individuals with birth defects, including all medical costs incurred, rather than the cost of the birth defect per se. These cost estimates therefore include the costs of concurrent effects (unlike the costs reported for many of the diseases in this handbook). This method yields a more comprehensive assessment of total costs than would be obtained if only individual effects were evaluated. This method is of particular use in valuing the avoidance of birth defects because they very frequently occur in clusters within an individual. As Waitzman et al. note, however, the costs of associated anomalies are included as part of the

estimate of the costs incurred by an individual with a given birth defect. These cost estimates therefore cannot be aggregated across birth defects because of the possibility of double counting.

Second, the Waitzman et al. method estimates the *incremental* costs for individuals with birth defects — that is, the costs above and beyond the average costs that would be incurred by individuals without the birth defect.

Waitzman et al. (1996) estimated three categories of costs incurred by individuals with limb reductions: direct medical costs, direct nonmedical costs, and indirect costs.[3] Direct medical costs, specifically inpatient care, outpatient care, pharmaceuticals, laboratory tests, X-rays, appliances, and long-term care are included in the cost estimates shown in this and other chapters (Chapters III.3 through III.8) based on the work of Waitzman et al. Nonmedical direct costs, specifically developmental services, and special education are also included in this handbook.

The Waitzman estimates of the costs incurred by individuals with limb reductions are based on the costs of this birth defect in California across many ages, and its occurrence in a large cohort of children born in California in 1988. California's ongoing birth defects monitoring program provides an excellent source of data. The California data sets were linked with other national data sets so that Waitzman et al. could estimate the incremental costs associated with each type of cardiac abnormality.

The method of calculating the expected lifetime incremental costs for an individual with a birth defect — i.e., the average lifetime cost per case — is the same for all the birth defects considered by Waitzman et al. The expected per capita cost at age *i*, PCC_i, for an individual born with the birth defect is the probability of surviving to age *i* (among those individuals born with the birth defect), ps_i, times the per capita cost among individuals who do survive to age *i* ($PCPREV_i$, measured in the prevalent population):

$$PCC_i = (ps_i) \times (PCPREV_i) .$$

Waitzman et al. estimate per capita costs in the prevalent population of age *i*, $PCPREV_i$, in two different ways, depending on data availability (see Chapter III.3).

Link to Chapter III.3

The present discounted value of expected per capita lifetime costs of the birth defect, PCCOBD, is just the sum of these expected age-specific per

[3] Indirect costs are not generally discussed in this handbook and so are not included in this chapter. The reader may wish to consult Waitzman et al. (1996) for information on these costs.

capita costs, appropriately discounted (as explained more fully in Chapter III.3):

$$PCCOBD = \sum_i PCC_i/(1+r)^i .$$

III.5.B.2 Results

Waitzman et al (1996) estimate the total lifetime medical costs of each of the cardiac defects according to the methodology outlined above. As outlined in Table III.3-1 in Chapter III.3, the prevalence on July 1, 1988 and the incidence in 1988 of cardiac abnormalities in the state of California was as follows:truncus arteriosus: 1,591 and 56, respectively; transposition/DORV: 7,469 and 263, respectively; tetralogy of Fallot: 5,336 and 187, respectively; and single ventricle: 1,932 and 68, respectively. The occurrence data provide an indication of the relative rate of yearly occurrence of the different anomalies discussed in this handbook.

Table III.3-1 in Chapter III.3

Table III.5-1 shows the annual per capita medical costs incurred by individuals with each type of cardiac anomaly by age group with costs updated from 1988 to 1996 dollars based on the medical care cost component of the Consumer Price Index (1996:1988=1.6465).

Table III.5-1: Annual Per-Capita Medical Costs of Heart Defects Patients by Age Group (1996$)

Condition	Age 0-1	Age 2-4	Age 5-17	Age 18+
Truncus arteriosus	$162,463	$104,225	$7,197	$5,139
Transposition/DORV	$56,296	$15,790	$3,071	$1,744
Tetralogy of Fallot	$70,729	$18,952	$5,939	$1,251
Single ventricle	$57,119	$15,727	$12,867	$10,071

The medical cost of the average population was then subtracted from these costs to obtain incremental costs. Waitzman et al. (1996) discounted these costs using three different discount rates: two percent, five percent, and ten percent. Although these discount rates do not match the standard EPA rates used in many other chapters in this handbook (zero percent, three percent, five percent, and seven percent), there is insufficient information provided in Waitzman et al. (1996) to allow a conversion to discounted costs using standard EPA discount rates. This problem exists in all chapters based on the Waitzman et al. data (i.e., Chapters III.3 through III.8).

The present discounted values of average per capita lifetime incremental costs, using discount rates of two percent, five percent, and seven percent, are listed in Table III.5-2 below. Direct medical costs and direct non-medical costs are listed separately. The sum of per-capita direct medical and nonmedical costs provides an estimate of the total per-capita costs incurred by individuals with each type of cardiac abnormality.

Children with some heart anomalies have a much lower probability of survival (see the "prognosis" descriptions in part III.5.A, under the specific descriptions above) than children with most cardiac or other anomalies discussed in this section of the handbook. This report focuses on medical costs, whereas other research often includes estimates of the value that a person would pay to save his or her life, termed "value of life" estimates. In the case of heart anomalies, survivorship is an issue for some of these children. The cost estimates presented here could therefore be dwarfed by the additional value of life associated with each estimate.

Table III.5-2: Per-Capita Net Medical Costs, Nonmedical Costs, and Total Costs of Heart Defects (1996$)			
Cost Element	**2%**	**5%**	**10%**
Truncus arteriosus			
Net medical costs	$375,394	$344,111	$316,121
Net nonmedical costs	$2,918	$2,228	$1,492
Total costs	$378,312	$346,339	$317,613
Transposition/DORV			
Net medical costs	$120,192	$113,606	$107,020
Net nonmedical costs	$4,562	$3,479	$2,323
Total costs	$124,754	$117,085	$109,343
Tetralogy of Fallot			
Net medical costs	$194,283	$179,465	$161,354
Net nonmedical costs	$5,800	$4,422	$2,954
Total costs	$200,083	$183,887	$164,308
Single ventricle			
Net medical costs	$227,212	$163,000	$123,485
Net nonmedical costs	$3,507	$2,674	$1,786
Total costs	$230,719	$165,674	$125,271
The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below. *Link to inflation factors*			

III.5.B.3 Other Studies

Several other studies have been conducted on the costs of cardiac abnormalities. In particular, two recent studies are especially useful for comparison. The first, by Pearson et al. (1991), looks at hospital use and inpatient charges for cardiac disease patients in the first year of life. The second, by Silberbach et al. (1993), predicts the hospital charges for congenital heart disease surgery. These two studies are easiest to compare to Waitzman et al. because they examine similar types of direct medical costs. Although these studies vary slightly in their methodologies, the results tend to corroborate the Waitzman et al. results. No recent studies examining the direct non-medical costs associated with cardiac abnormalities were identified.

III.5.B.3.1 Pearson et al. (1991)

The Pearson et al. study analyzes the inpatient charges for infants with cardiac disease in the first year of life. Infants admitted to The Johns Hopkins Hospital Children's Center in Maryland in 1988 were identified for the study. Complete data for 93 of these infants were available. The infants were subdivided into three groups: those with complex diseases, those with extra-cardiac anomalies, and those with both. Hospital charges were recorded, including all routine care charges, laboratory charges, medical and surgical supplies, physical therapy, operating room time and supplies, radiologic procedures, pharmacy supplies, and blood and blood related products.

Pearson et al. estimated hospital charges per infant. These charges have been adjusted to 1996 dollars using the Consumer Price Index for medical care (1996:1988=1.6465) to facilitate comparison across studies. Average hospital charges per infant were estimated at $60,506. The number is larger for infants with complex cardiac diseases.

Pearson et al.'s results are similar, in the first year of life, to those reported by Waitzman et al., particularly for transposition/DORV, tetralogy of Fallot and single ventricle (see Table III.5-1 for Waitzman et al.'s cost estimates). Waitzman et al.'s higher cost estimate for truncus arteriosus may be reflected in the upper range of costs that Pearson et al. estimated. They identified a range of $1,651 to $770,177 per patient.

III.5.B.3.2 Silberbach et al. (1993)

The Silberbach et al. study is also useful for comparison because it looks at the hospital charges for congenital heart disease surgery. Although the study is not strictly limited to children, and is on a per-surgery basis, 49 percent of the surgeries examined occurred in children less than 12 months old. The study is also useful because it breaks out costs according to ten different types of congenital heart disease, facilitating direct comparison with the Waitzman et al. study. The study was conducted between 1985 and 1989. A conservative adjustment to 1996 dollars assumes that all reported costs in the Silberbach et al. study were in 1989 dollars (Consumer Price Index for medical care (1996:1989=1.53)).

Silberbach et al. predicted the average hospital charge for a patient with congenital heart disease at $41,699. More specifically, they estimated that tetralogy of Fallot surgery costs $56,997 and surgery for transposition/DORV of the great arteries costs $44,789.

The Silberbach et al. study found similar costs to those reported in Waitzman et al., particularly in their finding that surgery for transposition/DORV is less expensive than for tetralogy of Fallot. The Silberbach et al. estimates are a bit lower. This difference in relation to Waitzman et al. and Pearson et al. is probably due to the limited nature of

the Silberbach et al. study; they calculate hospital charges for a specific surgical procedure and do not include other costs that would be incurred during the rest of the year.

III.5.C Conclusions

Because the Waitzman et al. study provides cost estimates past the first year of life, it is more appropriate for benefits evaluation than other studies reviewed. The other studies, discussed above, generally support the estimates provided by Waitzman et al.

CHAPTER III.6. COST OF SPINA BIFIDA

Clicking on the sections below will take you to the relevant text.

CHAPTER III.6. COST OF SPINA BIFIDA

III.6.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with spina bifida and the results of the analysis.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.6.A.1 Description

Spina bifida occurs when the neural tube, from which the brain and spinal cord develop (central nervous system), fails to close properly. Depending on where closure fails to occur, portions of the brain, spinal cord, and nerves connected to them will not function properly. If failure to close occurs on the lower portion of the spinal cord, then the bowel, bladder or sexual organs will be affected. Failure at mid-level may cause paralysis or malfunction of the arms and legs. Anomalies at higher levels may affect the brain. In most spina bifida cases, the normal flow of cerebrospinal fluid is also blocked (Arnold-Chiari malformation), which would result in hydrocephalus unless treated (Waitzman et al., 1996).

Some common disabilities and medical problems associated with spina bifida are:

- sight problems, including atrophy of the optic nerve in 17 percent of children and strabismus in 42 percent of children (Gaston, 1985);
- dysfunction in the arms in 45 percent of children (Turner, 1986);

[1] "Costs" in this chapter refer to direct incremental per capita medical costs, unless otherwise noted.

- epilepsy in 20 to 30 percent of children (Bartoshesky et al., 1985); and

- bladder dysfunction in most children (McLone, 1983).

III.6.A.2 Concurrent Effects

Approximately six percent of children with this anomaly have malformations outside the central nervous system. These commonly affect the diaphragm, esophagus, and kidneys. Cleft lip and palate are also associated with spina bifida (Waitzman et al., 1996). Additional malformations outside of the central nervous system include:

- pressure sores and skin problems in 70 percent of adolescents and young adults (Blum et al., 1992);

- curvature of the spine in 15 percent of children (Samuelsson and Eklof, 1988); and

- weight substantially over the norm in 30 to 50 percent of children (Thomas et al., 1987).

III.6.A.3 Causality

Spina bifida is associated with prenatal exposure to sulfonamides and antihistamines, maternal folate deficiency, and maternal diabetes. Chemicals that interfere with the development of the neural crest and fold during embryogenesis may cause spina bifida (Waitzman et al., 1996). Table III.1-1 in Chapter III.1 lists numerous chemicals associated with developmental abnormalities in human and/or animal studies.

Link to Chapter III.1, Table III.1-1

III.6.A.4 Treatment and Services

Treatment may begin before birth if diagnosis occurs during pregnancy. Lab tests are now available that provide an indication of whether spina bifida is likely. Ultrasound may be used to confirm the test results. Cesarean delivery may be used to prevent damage to the infant. The spinal canal defect is usually closed surgically shortly after birth. Approximately 90 percent of infants receive a ventriculaoperitoneal shunt to carry fluid from the head to the abdominal cavity (to prevent the occurrence of hydrocephalus noted above) (Waitzman et al., 1996).

Concurrent disorders are treated as needed, including dialysis or kidney transplant for patients with severe kidney disease, and surgery to fuse the vertebrae for patients with scoliosis (Waitzman, et al., 1996).

III.6.A.5 Prognosis

Spina bifida usually results in permanent disabilities of some type; these may be severe (e.g., paralysis). Social isolation is common, and employment prospects for adults are reduced. Even with appropriate medical treatment, children with spina bifida have a shortened lifespan. Ongoing medical treatment may be required, including replacement of shunts and treatment of kidney and urinary problems (Waitzman et al., 1996).

III.6.B Costs of Treatment and Services

III.6.B.1 Methodology

Chapters III.3 through III.8 of this handbook use cost of illness estimates developed primarily by Waitzman et al. (1996). Waitzman et al. used the same methodology to estimate the costs incurred by individuals with spina bifida as for all the birth defects for which they estimated costs. The methodology and relevant considerations are detailed in Chapter III.3, including discussions of direct and indirect costs, prevalence versus incidence, incremental costs, and concurrent effects. The analytic method, the sources of data, and the limitations of the Waitzman method are also discussed in Chapter III.3. The methodology is outlined briefly here.

Link to Chapter III.3

To estimate the lifetime medical costs incurred by an individual with a birth defect, Waitzman et al. estimated the average lifetime medical costs for an individual with the birth defect. From this value, the authors subtracted the average lifetime medical costs for an individual without the birth defect. Because they estimated lifetime costs, they used an incidence-based approach. Ideally, they would have tracked the costs of the cohort members over time, until the death of the last cohort member. Because the members of the cohort were born in 1988, however, this tracking was not possible. Instead, estimates of the costs incurred at each age were based on estimates of per capita costs in the prevalent population of that age (see Chapter III.3, Section III.3.B.1.2).

Link to Chapter III.3, Section III.3.B.1.2

This method has two important implications. First, Waitzman et al. estimated the costs incurred by individuals with birth defects, including all medical costs incurred, rather than the cost of the birth defect per se. These cost estimates therefore include the costs of concurrent effects (unlike the costs reported for many of the diseases in this handbook). This

method yields a more comprehensive assessment of total costs than would be obtained if only individual effects were evaluated. This method is of particular use in valuing the avoidance of birth defects because they very frequently occur in clusters within an individual. As Waitzman et al. note, however, the costs of associated anomalies are included as part of the estimate of the costs incurred by an individual with a given birth defect. These cost estimates therefore cannot be aggregated across birth defects because of the possibility of double counting.

Second, the Waitzman et al. method estimates the *incremental* costs for individuals with birth defects — that is, the costs above and beyond the average costs that would be incurred by individuals without the birth defect.

Waitzman et al. (1996) estimated three categories of costs incurred by individuals with limb reductions: direct medical costs, direct nonmedical costs, and indirect costs.[2] Direct medical costs, specifically inpatient care, outpatient care, pharmaceuticals, laboratory tests, X-rays, appliances, and long-term care are included in the cost estimates shown in this and other chapters (Chapters III.3 through III.8) based on the work of Waitzman et al. Nonmedical direct costs, specifically developmental services, and special education are also included in this handbook.

The Waitzman estimates of the costs incurred by individuals with limb reductions are based on the costs of this birth defect in California across many ages, and its occurrence in a large cohort of children born in California in 1988. California's ongoing birth defects monitoring program provides an excellent source of data. The California data sets were linked with other national data sets so that Waitzman et al. could estimate the incremental costs associated with spina bifida.

The method of calculating the expected lifetime incremental costs for an individual with a birth defect — i.e., the average lifetime cost per case — is the same for all the birth defects considered by Waitzman et al. The expected per capita cost at age i, PCC_i, for an individual born with the birth defect is the probability of surviving to age i (among those individuals born with the birth defect), ps_i, times the per capita cost among individuals who do survive to age i ($PCPREV_i$, measured in the prevalent population):

$$PCC_i = (ps_i) \times (PCPREV_i) .$$

Waitzman et al. estimate per capita costs in the prevalent population of age i, $PCPREV_i$, in two different ways, depending on data availability (see Chapter III.3).

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[2] Indirect costs are not generally discussed in this handbook and so are not included in this chapter. The reader may wish to consult Waitzman et al. (1996) for information on these costs.

The present discounted value of expected per capita lifetime costs of the birth defect, PCCOBD, is just the sum of these expected age-specific per capita costs, appropriately discounted (as explained more fully in Chapter III.3):

$$PCCOBD = \sum_i PCC_i/(1+r)^i .$$

III.6.B.2 Results

Waitzman et al (1996) estimate the total lifetime medical costs incurred by individuals with spina bifida according to the methodology outlined above. The following tables outline the various costs, updated from 1988 to 1996 dollars based on the medical care cost component of the Consumer Price Index (1996:1988=1.6465). Table III.6-1 shows the annual per capita medical costs incurred by individuals with spina bifida by age group.

Table III.6-1: Annual Per-Capita Medical Costs of Spina Bifida by Age Group (1996$)

Condition	Age 0-1	Age 2-4	Age 5-17	Age 18+
Spina Bifida	$34,013	$14,924	$13,208	$4,194

The medical cost of the average population was then subtracted from these costs to obtain incremental costs. Waitzman et al. (1996) discounted these costs using three different discount rates: two percent, five percent, and ten percent. Although these discount rates do not match the standard EPA rates used in many other chapters in this handbook (zero percent, three percent, five percent, and seven percent), there is insufficient information provided in Waitzman et al. (1996) to allow a conversion to discounted costs using standard EPA discount rates. This problem exists in all chapters based on the Waitzman et al. data (i.e., Chapters III.3 through III.8).

The present discounted values of average per capita lifetime incremental costs, using discount rates of two percent, five percent, and seven percent, are listed in Table III.6-2 below. Direct medical costs and direct non-medical costs, including developmental services costs and special education costs, are listed separately. The sum of per-capita direct medical and nonmedical costs provides an estimate of the total per-capita costs incurred by individuals with spina bifida.

Table III.6-2: Per-Capita Net Medical Costs, Nonmedical Costs, and Total Costs of Spina Bifida (1996$)			
Cost Element	**2%**	**5%**	**10%**
Net direct medical costs	$210,747	$163,000	$123,485
Net direct nonmedical costs			
Developmental Costs	$2,694	$1,635	$1,004
Special Education Costs	$50,719	$38,298	$25,155
Total Costs	$264,160	$202,933	$149,644
The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below. *Link to inflation factors*			

III.6.B.3 Other Studies

Waitzman et al. present a study by Lipscomb (1986) that used an incidence approach to estimate the total lifetime costs per individual of spina bifida based on data gathered from individual reviews of clinical records in North Carolina in 1985. Waitzman et al. adjust the Lipscomb estimates to account for differences in medical care prices. They deflate their California estimates by the difference in the Employee Compensation Index between California and the nation. To account for differences in the base year they adjusted the North Carolina estimates to 1988 dollars. While there is some variability in the cost distribution across age groups, the total cost estimates are strikingly similar; Waitzman et al. estimated total lifetime costs per individual of $36,529 and Lipscomb estimated total costs of $34,949 in the U.S. in 1988.

III.6.C Conclusions

The results based on the Waitzman et al (1996) work are recommended for use in benefits valuation. The Lipscomb work uses a smaller database and older data. The similarity of the two independently researched results lends credibility to the cost estimates.

CHAPTER III.7. COST OF CEREBRAL PALSY

Clicking on the sections below will take you to the relevant text.

CHAPTER III.7. COST OF CEREBRAL PALSY

III.7.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with cerebral palsy and the results of the analysis.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.7.A.1 Description

Cerebral palsy is a motor disorder appearing in early childhood that is caused by brain damage (Waitzman et al., 1996).[2] It is the most common movement disorder of childhood and affects approximately one to six children per 1,000 births. The estimate varies considerably because mild cases may not be determined in early childhood, and all cases may be obscured by other developmental disabilities, such as seizures and mental retardation. The most severe cases may result in rapid death and not be detected. When estimates of the incidence of cerebral palsy are based on evaluations in the neonatal period, the occurrence will be underestimated. It is very difficult to identify cerebral palsy during this period by clinical methods, due to the relative immaturity of the nervous system of newborn infants (Oski, 1994).

Both muscle tone and the control of movement are affected in cerebral palsy (Oski, 1994), which leads to a complex array of movement, posture, and communication problems. Various types of cerebral palsy include athetoid (15 percent of cases), spastic (70 percent), and ataxic (5 percent). Approximately 15 percent of cases are mixed (Wollack et al., 1991).

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[1] "Costs" in this chapter refer to direct incremental per capita medical costs, unless otherwise noted.

[2] Cerebral palsy is often used synonymously with static encephalopathy (Oski, 1994).

Cerebral palsy may affect one or more limbs. Athetoid cerebral palsy patients exhibit uncoordinated and uncontrolled movements. Spastic cerebral palsy patients exhibit exaggerated reflexes, increased muscle tone, weakness, and joint contractures (spasms). Ataxic cerebral palsy patients often have difficulty performing repetitive movements and have a wide-based gait (Waitzman et al., 1996).

Individuals affected with this disorder are among the most handicapped in our society. Although the incidence declined in the 1960s due to better pre- and perinatal care, the incidence has increased in recent years due to the improvement in survival among low birth weight infants. Cerebral palsy usually originates in the pre- or perinatal period; however, it can be brought on in childhood by infection, trauma, and other causes (Oski, 1994).

III.7.A.2 Concurrent Effects

Approximately 21 percent of children with cerebral palsy have malformations unrelated to cerebral palsy; however, no specific occurrence patterns have been reported for major malformations. Occurrences of hip dislocation, curvature of the spine, and poorly developed dental enamel have been frequently reported (Waitzman et al., 1996). About 50 percent of children with cerebral palsy also have strabismus. Depending on the nature of the cerebral palsy, children may have severe retardation, frequent seizures, and blindness, or have a normal intellect with minimal non-motor effects (Oski, 1994).

Other central nervous system (CNS) disorders are common in children with cerebral palsy. Epilepsy occurs in 22 to 50 percent of children with cerebral palsy, increasing with the number of limbs affected. Approximately 25 percent of the children have severe or profound mental retardation, with the degree of retardation generally related to the severity of cerebral palsy. Most children with all limbs affected are severely retarded. Other CNS disorders include severe hearing and visual impairments and speech disorders (Waitzman et al., 1996).

III.7.A.3 Causality

Risk factors for cerebral palsy include the presence of other malformations, maternal retardation, premature separation, low weight of the placenta, breech birth, and low birth weight (Waitzman et al., 1996), although these were more prominent causes in the past, when management of pregnancy and delivery were less refined. Today most cerebral palsy occurs without

identifiable risk factors (Oski, 1994). Table III.1-1 in Chapter III.1 lists numerous chemicals associated with developmental abnormalities in human and/or animal studies.

Link to Chapter III.1, Table III.1-1

III.7.A.4 Treatment and Services

Treatment of cerebral palsy focuses on improving the quality of life and function of the individual. There is no "cure". Surgery on muscles, limbs, and associated sites may be used to restore balance. Brain surgery may be used to reduce spasticity, but may have undesirable consequences. Appliances may include provision of wheelchairs, walkers, casts, or splints. In some cases, medication is used (Waitzman et al., 1996).

Treatment objectives change as the individual ages (Oski, 1994). In early childhood, improving communication abilities is often the focus because these abilities are more closely related than motor function to long-term outcome. In some cases, when speech is not possible, other supportive materials are provided to facilitate communication. Other areas of significant effort are development of the ability to perform basic daily living activities and improving motor skills (Oski, 1994). Treatment of cerebral palsy is rapidly changing and many options are usually offered, often involving multiple medical and educational specialists. Treatment plans are often complex and may require extensive non-medical care, including considerable assistance in day-to-day living activities. These are not a part of the direct medical costs, but they may contribute substantially to the overall costs associated with this disorder.

III.7.A.5 Prognosis

Among those with average or above intelligence (IQ $\geq$ 80), the limitations are not generally severe. Approximately 39 percent are able to function independently as adults, and 48 percent are partially dependent. Of those with lower intelligence, only 1 percent are independent and 17 percent are partially dependent (Cohen and Kohn, 1979). The balance of both the average and below-average intelligence groups are totally dependent. Other issues related to this disorder are low self-esteem and difficulty with sexual relationships. Among those with severe retardation (IQ $\leq$ 50) there is a mortality rate of 28 percent during the first 20 years of life. This is compared to 2 percent among those with higher IQs (Hutton et al., 1994).

III.7.B Costs of Treatment and Services

III.7.B.1 Methodology

Chapters III.3 through III.8 of this handbook use cost of illness estimates developed primarily by Waitzman et al. (1996). Waitzman et al. used the same methodology to estimate the costs incurred by individuals with cerebral palsy as for all the birth defects for which they estimated costs. The methodology and relevant considerations are detailed in Chapter III.3, including discussions of direct and indirect costs, prevalence versus incidence, incremental costs, and concurrent effects. The analytic method, the sources of data, and the limitations of the Waitzman et al. method are also discussed in Chapter III.3. The methodology is outlined briefly here.

Link to Chapter III.3

To estimate the lifetime medical costs incurred by an individual with a birth defect, Waitzman et al. estimated the average lifetime medical costs for an individual with the birth defect. From this value, the authors subtracted the average lifetime medical costs for an individual without the birth defect. Because they estimated lifetime costs, they used an incidence-based approach. Ideally, they would have tracked the costs of the cohort members over time, until the death of the last cohort member. Because the members of the cohort were born in 1988, however, this tracking was not possible. Instead, estimates of the costs incurred at each age were based on estimates of per capita costs in the prevalent population of that age (see Chapter III.3, Section III.3.B.1.2).

Link to Chapter III.3, Section III.3.B.1.2

This method has two important implications. First, Waitzman et al. estimated the costs incurred by individuals with birth defects, including all medical costs incurred, rather than the cost of the birth defect per se. These cost estimates therefore include the costs of concurrent effects (unlike the costs reported for many of the diseases in this handbook). This method yields a more comprehensive assessment of total costs than would be obtained if only individual effects were evaluated. This method is of particular use in valuing the avoidance of birth defects because they very frequently occur in clusters within an individual. As Waitzman et al. note, however, the costs of associated anomalies are included as part of the estimate of the costs incurred by an individual with a given birth defect. These cost estimates therefore cannot be aggregated across birth defects because of the possibility of double counting.

Second, the Waitzman et al. method estimates the *incremental* costs for individuals with birth defects — that is, the costs above and beyond the average costs that would be incurred by individuals without the birth defect.

Waitzman et al. (1996) estimated three categories of costs incurred by individuals with limb reductions: direct medical costs, direct nonmedical costs, and indirect costs.[3] Direct medical costs, specifically inpatient care, outpatient care, pharmaceuticals, laboratory tests, X-rays, appliances, and long-term care are included in the cost estimates shown in this and other chapters (Chapters III.3 through III.8) based on the work of Waitzman et al. Nonmedical direct costs, specifically developmental services, and special education are also included in this handbook.

The Waitzman estimates of the costs incurred by individuals with limb reductions are based on the costs of this birth defect in California across many ages, and its occurrence in a large cohort of children born in California in 1988. California's ongoing birth defects monitoring program provides an excellent source of data. The California data sets were linked with other national data sets so that Waitzman et al. could estimate the incremental costs associated with cerebral palsy.

The method of calculating the expected lifetime incremental costs for an individual with a birth defect — i.e., the average lifetime cost per case — is the same for all the birth defects considered by Waitzman et al. The expected per capita cost at age *i*, PCC_i, for an individual born with the birth defect is the probability of surviving to age *i* (among those individuals born with the birth defect), ps_i, times the per capita cost among individuals who do survive to age *i* ($PCPREV_i$, measured in the prevalent population):

$$PCC_i = (ps_i) \times (PCPREV_i) .$$

Waitzman et al. estimate per capita costs in the prevalent population of age *i*, $PCPREV_i$, in two different ways, depending on data availability (see Chapter III.3).

Link to Chapter III.3

The present discounted value of expected per capita lifetime costs of the birth defect, PCCOBD, is just the sum of these expected age-specific per capita costs, appropriately discounted (as explained more fully in Chapter III.3):

$$PCCOBD = \sum_i PCC_i/(1+r)^i .$$

[3] Indirect costs are not generally discussed in this handbook and so are not included in this chapter. The reader may wish to consult Waitzman et al. (1996) for information on these costs.

III.7.B.2 Results

Waitzman et al.'s (1996) estimates of the total lifetime medical costs of cerebral palsy are outlined in the following tables. Estimates are updated from 1988 to 1996 dollars based on the medical care cost component of the Consumer Price Index (1996:1988=1.6465). Table III.7-1 shows the annual per capita medical costs incurred by individuals with cerebral palsy by age group.

Table III.7-1: Annual Per-Capita Medical Costs of Cerebral Palsy by Age Group (1996$)

Condition	Age 0-1	Age 2-4	Age 5-17	Age 18+
Cerebral Palsy	$16,236	$9,848	$11,451	$19,349

The medical cost of the average population was then subtracted from these costs to obtain incremental costs. Waitzman et al. (1996) discounted these costs using three different discount rates: two percent, five percent, and ten percent. Although these discount rates do not match the standard EPA rates used in many other chapters in this handbook (zero percent, three percent, five percent, and seven percent), there is insufficient information provided in Waitzman et al. (1996) to allow a conversion to discounted costs using standard EPA discount rates. This problem exists in all chapters based on the Waitzman et al. data (i.e., Chapters III.3 through III.8).

The present discounted values of average per capita lifetime incremental costs, using discount rates of two percent, five percent, and seven percent, are listed in Table III.7-2 below. Direct medical costs and direct non-medical costs are listed separately. The sum of per-capita direct medical and nonmedical costs provides an estimate of the total per-capita costs incurred by individuals with cerebral palsy.

Table III.7-2: Per-Capita Net Medical Costs, Nonmedical Costs, and Total Costs of Cerebral Palsy (1996$)			
Cost Element	**2%**	**5%**	**10%**
Net direct medical costs	$461,010	$233,798	$116,899
Net direct nonmedical costs			
Developmental Services	$145,106	$68,979	$30,853
Special Education	$94,454	$71,771	$47,634
Total Costs	$700,570	$374,548	$195,386

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

III.7.B.3 Other Studies

Waitzman et al. (1996) present a study conducted in 1991 by The National Foundation for Brain Research (NFBR), using a prevalence approach, on the cost of cerebral palsy. Rather than using the primary diagnosis, however, to construct costs (as in Rice et al., discussed in Chapter III.3), cost estimates were made for cerebral palsy appearing as the first through fifth diagnosis for inpatient stays, and the first through third diagnosis for physician visits. The NFBR also estimated indirect family costs based on family income reported in the 1989 National Health Interview Survey. Waitzman et al. compare their estimate for direct medical costs of $172 million, adjusted to the nation and 1991 dollars, to the NFBR estimate for inpatient stays of $318 million. They identify two reasons for the difference in these two estimates. First, an incidence approach, such as the approach used by Waitzman et al., uses discounting, whereas a prevalence approach, such as that used by NFBR, does not. For example, Waitzman et al. calculate that the 1991 estimate of $172 million discounted at five percent would increase by over $100 million to $282 million if a two percent discount rate was used instead. Second, Waitzman et al. estimate incremental costs by subtracting the average costs of an individual without cerebral palsy, whereas the NFBR study does not subtract average costs. Waitzman et al. show that had they not subtracted the average costs, their estimate for cerebral palsy in 1991 at a five percent discount rate would be $330 million, an estimate much closer to the one produced by the NFBR study.

Link to Chapter III.3

III.7.C Conclusions

The cost estimates based on the research by Waitzman et al. (1996) are recommended for use in benefits valuation. The NFBR study does not include many relevant medical costs (including all non-hospital costs). They also do not use an incremental approach. Consequently, the NFBR cost estimates are not as closely matched to the direct medical costs which are reported in this handbook as the Waitzman et al. results.

CHAPTER III.8. COST OF DOWN SYNDROME

Clicking on the sections below will take you to the relevant text.

CHAPTER III.8. COST OF DOWN SYNDROME

III.8.A Background

This chapter contains a discussion of the methods used and the results of estimating the direct medical costs incurred by individuals with Down Syndrome and the results of the analysis.[1] It does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.8.A.1 Description

Down syndrome occurs as a result of having three, rather than two, copies of chromosome 21 (hence the name "trisomy 21"). Mental retardation and a group of physical characteristics are commonly associated with Down syndrome. In addition, a number of serious defects in critical organs (e.g., heart, digestive system) are also commonly found in people with Down syndrome. The syndrome involves clusters of external physical anomalies, learning disabilities, and organ system anomalies. Physical anomalies and their prevalence (given in parenthesis) among Down syndrome children are: unusually small head (50 percent), excess skin folds on eyelids (50-70 percent), speckled irises in eyes (30-80 percent), narrow and short palate (60-90 percent), protruding tongue (40-60 percent), broad hands (70 percent), and other relatively minor changes in physical appearance. Down syndrome children usually have a flattened nose bridge, additional skin on the back of the neck, small or anomalous ears, abnormally formed fingers, and "simian" hand creases (Pueschel and Rynders, 1982).

The severity of mental retardation associated with this disorder varies considerably. Between 3 and 12 percent of Down syndrome children are profoundly retarded. Many of these individuals are unable to walk, talk, or eat without assistance. Approximately 25 percent are severely retarded, 55

[1] "Costs" in this chapter refer to direct incremental per capita medical costs, unless otherwise noted.

percent are moderately retarded, and 14 percent are mildly retarded. Seizures occur in five to nine percent of children, increasing with age. In adulthood, memory loss and reduced cognitive abilities are usually evident after age 45 in people with Down syndrome. Pathology studies have found structural changes in the brain similar to those found in Alzheimers disease patients (Waitzman et al., 1996).

Children with Down syndrome often have very early onset Alzheimer-type changes in cognitive ability. These changes may affect their functional abilities, and are observed when comparing the abilities of Down syndrome children with other children over the range of school ages. By young adulthood, the IQ scores of Down syndrome children have progressed from the range of low-mild to high-moderate retardation seen in early school years to a range that includes severe retardation (Oski, 1994).

Down syndrome is the most common chromosomal disorder observed in the newborn period and accounts for approximately one third of all chromosomal abnormalities. Overall, chromosomal abnormalities occur in approximately 1 in 200 live births and account for a sizable fraction of the malformations and neonatal deaths that occur. The frequency of Down syndrome is estimated to range from one in 700 to one in 1,000 (Oski, 1994). With the availability of prenatal testing, not all Down syndrome fetuses are brought to term. Although the total medical costs of Down syndrome and its incidence (which is measured in terms of live births) are thereby reduced, the individual and societal costs may be very substantial.

III.8.A.2 Concurrent Effects

Associated organ system anomalies include congenital heart disease, duodenal atresia or stenosis, cleft lip or palate, fused digits, tracheoesophageal fistula, imperforate anus, failure of the testicles to descend, and incomplete development of neck vertebrae. Of these, the most common and serious are heart defects, which occur in approximately 29 percent of children with Down syndrome. Approximately 50 percent of adolescents and adults have mitral valve prolapse in the absence of symptoms of heart disease. The children usually also have poor muscle tone, increased joint flexibility, instability between the first two neck vertebrae, and an abnormally developed pelvis. Their musculoskeletal abnormalities often lead to degenerative changes in the joints. Thyroid function is often decreased (Waitzman et al., 1996).

Hearing loss affects approximately 60 percent of Down syndrome children, and 15 to 26 percent have moderate to profound hearing loss. Cataracts affect approximately 12 to 20 percent of children; strabismus affects 20 to 45 percent. Severe nearsightedness and deformity of the cornea are also common (Waitzman et al., 1996).

Down syndrome children have an increased risk of skin and lung infections, acute leukemia, and an impaired immune system function (Waitzman et al., 1996), and increased rates of testicular cancer and retinoblastoma (a childhood cancer) (Oski, 1994).

III.8.A.3 Causality

Down syndrome occurs when the egg or sperm receives an extra copy of chromosome 21. This condition is hereditary in some cases and is also associated with maternal age. Chemicals that cause chromosomal abnormalities, especially interference with normal chromosomal replication and disjunction, may cause this type of genetic abnormality (Waitzman et al., 1996). Table III.1-2 in Chapter III.1 lists chemicals associated with genotoxic effects. A review of material in the references listed in Chapter III.1 will provide information regarding those chemicals that have been shown to cause non-disjunction, and other genotoxic effects that may specifically cause an abnormal number of chromosomes.

Link to Chapter III.1, Table III.1-2

III.8.A.4 Treatment and Services

A variety of medical treatments and special services are required for Down syndrome patients. These vary widely, depending on the specific cluster of abnormalities occurring in an individual. The numerous structural abnormalities may require immediate attention in the postnatal period, or be corrected later in childhood if they are not immediately life-threatening. Some structural problems related to bone structure, muscles, and joints may require specialized equipment and physical therapy. Hearing problems and recurrent ear infections are often treated with pressure-equalization tubes and antibiotics. Due to the retardation associated with this syndrome, special education services are usually required. Many Down syndrome patients require lifelong services in the form of specialized housing and medical care.

III.8.A.5 Prognosis

Down syndrome involves a cluster of effects. While some effects, such as facial appearance, do not change over time, others become more severe over time. For example, a deterioration in memory and other cognitive functions is seen in most Down syndrome patients over the age of 45 (Waitzman et al., 1996). Laxity in the ligaments often leads to degenerative changes in the joints, especially in the knees and spine (Semine et al., 1978; Mendez et al., 1988). The prevalence of seizures, which occur in approximately five to nine percent of Down syndrome patients (Waitzman et al, 1996), increases with age (McVicker et al., 1994). In addition to

increased morbidity over time, the lifespan of Down syndrome patients is likely to be shortened, due to the multitude of serious effects associated with this disease.

III.8.B Costs of Treatment and Services

III.8.B.1 Methodology

Waitzman et al. (1996) provide an estimate of the direct medical and non-medical costs of treating Down syndrome. They used the same methodology to estimate the costs incurred by individuals with Down syndrome as for all the birth defects for which they estimated costs. The methodology and relevant considerations are detailed in Chapter III.3, including discussions of direct and indirect costs, prevalence versus incidence, incremental costs, and concurrent effects. The analytic method, the sources of data and the limitations of the Waitzman method are also discussed in Chapter III.3. The methodology is outlined briefly here.

Link to Chapter III.3

To estimate the lifetime medical costs incurred by an individual with a birth defect, Waitzman et al. estimated the average lifetime medical costs for an individual with the birth defect. From this value, the authors subtracted the average lifetime medical costs for an individual without the birth defect. Because they estimated lifetime costs, they used an incidence-based approach. Ideally, they would have tracked the costs of the cohort members over time, until the death of the last cohort member. Because the members of the cohort were born in 1988, however, this tracking was not possible. Instead, estimates of the costs incurred at each age were based on estimates of per capita costs in the prevalent population of that age (see Chapter III.3, Section III.3.B.1.2).

Link to Chapter III.3, Section III.3.B.1.2

This method has two important implications. First, Waitzman et al. estimated the costs incurred by individuals with birth defects, including all medical costs incurred, rather than the cost of the birth defect per se. These cost estimates therefore include the costs of concurrent effects (unlike the costs reported for many of the diseases in this handbook). This method yields a more comprehensive assessment of total costs than would be obtained if only individual effects were evaluated. This method is of particular use in valuing the avoidance of birth defects because they very frequently occur in clusters within an individual. As Waitzman et al. note, however, the costs of associated anomalies are included as part of the estimate of the costs incurred by an individual with a given birth defect. These cost estimates therefore cannot be aggregated across birth defects because of the possibility of double counting.

Second, the Waitzman et al. method estimates the *incremental* costs for individuals with birth defects — that is, the costs above and beyond the average costs that would be incurred by individuals without the birth defect.

Waitzman et al. (1996) estimated three categories of costs incurred by individuals with Down syndrome: direct medical costs, direct nonmedical costs, and indirect costs.[2] Direct medical costs, specifically inpatient care, outpatient care, pharmaceuticals, laboratory tests, X-rays, appliances, and long-term care are included in the cost estimates shown in this and other chapters (Chapters III.3 through III.8) based on the work of Waitzman et al. Nonmedical direct costs, specifically developmental services, and special education are also included in this handbook.

The Waitzman estimates of the costs incurred by individuals with Down syndrome are based on the costs of this birth defect in California across many ages, and its occurrence in a large cohort of children born in California in 1988. California's ongoing birth defects monitoring program provides an excellent source of data. The California data sets were linked with other national data sets so that Waitzman et al. could estimate the incremental costs associated with Down syndrome.

The method of calculating the expected lifetime incremental costs for an individual with a birth defect — i.e., the average lifetime cost per case — is the same for all the birth defects considered by Waitzman et al. The expected per capita cost at age i, PCC_i, for an individual born with the birth defect is the probability of surviving to age i (among those individuals born with the birth defect), ps_i, times the per capita cost among individuals who do survive to age i ($PCPREV_i$, measured in the prevalent population):

$$PCC_i = (ps_i) \times (PCPREV_i) .$$

Waitzman et al. estimate per capita costs in the prevalent population of age i, $PCPREV_i$, in two different ways, depending on data availability (see Chapter III.3).

Link to Chapter III.3

[2] Indirect costs are not generally discussed in this handbook and so are not included in this chapter. The reader may wish to consult Waitzman et al. (1996) for information on these costs.

The present discounted value of expected per capita lifetime costs of the birth defect, PCCOBD, is just the sum of these expected age-specific per capita costs, appropriately discounted (as explained more fully in Chapter III.3):

$$PCCOBD = \sum_i PCC_i/(1+r)^i .$$

III.8.B.2 Results

Waitzman et al. (1996) estimate the total lifetime medical costs of Down syndrome as outlined in the following tables, updated from 1988 to 1996 dollars based on the medical care cost component of the Consumer Price Index (1996:1988=1.6465). Table III.8-1 shows the annual per capita medical costs associated with Down syndrome by age group.

Table III.8-1: Annual Per-Capita Medical Costs of Down syndrome by Age Group (1996$)

Condition	Age 0-1	Age 2-4	Age 5-17	Age 18+
Down syndrome	$27,265	$5,577	$2,231	$7,529

The medical cost of the average population was then subtracted from these costs to obtain incremental costs. Waitzman et al. (1996) discounted these costs using three different discount rates: two percent, five percent, and ten percent. Although these discount rates do not match the standard EPA rates used in many other chapters in this handbook (zero percent, three percent, five percent, and seven percent), there is insufficient information provided in Waitzman et al. (1996) to allow a conversion to discounted costs using standard EPA discount rates. This problem exists in all chapters based on the Waitzman et al. data (i.e., Chapters III.3 through III.8).

The present discounted values of average per capita lifetime incremental costs, using discount rates of two percent, five percent, and seven percent, are listed in Table III.8-2 below. Direct medical costs and direct non-medical costs, including developmental services costs and special education costs, are listed separately. The sum of per-capita direct medical and nonmedical costs provides an estimate of the total per-capita costs incurred by individuals with Down syndrome.

Table III.8-2: Per-Capita Net Medical Costs, Nonmedical Costs, and Total Costs of Down syndrome (1996$)			
Condition	**2%**	**5%**	**10%**
Net direct medical costs	$141,596	$90,556	$64,212
Net direct nonmedical costs			
Developmental services	$67,645	$35,439	$19,089
Special education	$144,138	$109,622	$72,854
Total Costs	$353,379	$235,617	$156,155

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

CHAPTER III.9 COST OF REDUCING HIGH BLOOD LEAD LEVELS IN CHILDREN

Clicking on the sections below will take you to the relevant text.

CHAPTER III.9 COST OF REDUCING HIGH BLOOD LEAD LEVELS IN CHILDREN

III.9.A Background

This analysis focuses solely on the medical costs associated with efforts to reduce blood lead (PbB) levels in children under the age of six. Information is provided regarding treatment, source reduction and education prescribed in response to elevated PbB levels. The chapter does **not** include medical costs of treating health effects that result from lead exposure. Cost estimates may be developed for lead-induced effects in the future (concurrent effects are discussed in more detail below). The chapter also does not include information on elements such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, etc. The reader is referred to Chapter I.1 for a discussion of the cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter III.1 contains information regarding the special characteristics of developmental defects, and a list of chemicals that may cause developmental abnormalities.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and III.1
Link to inflation factors

III.9.A.1 Description

Elevated PbB levels in young children occur when children are exposed to lead via any media (i.e., air, water, food, soil). Elevated PbB in children is a considerable public health concern, due to the potential adverse effects of lead on multiple organ systems and the particular susceptibility of young children to many of these effects, including neurological damage. Lead is toxic to the kidneys and is associated with low birth weight, male sterility, cancer, and a wide array of neurological disorders. Elevated PbB may lead to neurological impairment, behavioral abnormalities, and damage to the cardiovascular, kidney, liver, gastrointestinal, blood-forming, reproductive, and endocrine systems. Lead is also a suspected carcinogen and mutagen (EPA, 1987), and impairs the immune system, causing increased susceptibility to infectious agents (ATSDR, 1997).[1]

[1] This analysis used data provided in EPA, 1985 and 1987, which contain a cost-benefit analysis of reducing lead in gasoline.

Children are particular susceptibility to neurological impairment. Lead damages the developing neurons in the brain by damaging the protective coating of myelin on nerve cells; it is suspected of causing irreversible limitations in brain function. A relationship between a decrease in cognitive functioning (as measured by IQ tests) and lead exposure in young children has been reported in numerous studies.

Elevated PbB levels are used to evaluate the level of risk and determine treatment. The Centers for Disease Control (CDC) have developed a classification system for risks to children, based on their PbB levels and a related measure of lead exposure, erythrocyte protoporphyrin (EP). Their classification system was modified in EPA (1987) and is shown in Table III.9-1. This system is used in Section B to determine treatment costs.

Table III.9-1

Condensed Version of CDC Risk Classification Table

Blood Lead Level (µg/dl)	Erythrocyte Protoporphyrin Level (EP) (µg/dl)		
	0-32	33-53	>53
0-20	I	Ia	Ia
21-40	Ib	II	III
>40	*	III	IV

* = not generally observed
Source: U.S. EPA (1987)

III.9.A.2 Concurrent Effects

As noted above, lead exposure may lead to a variety of adverse health effects. The occurrence of effects will depend on the levels of PbB (as reflective of exposure throughout the body), the health status of the individual (e.g., poor nutritional status is especially problematic), and individual factors. Most children in the U.S. today do not experience severe adverse health effects that are measurable. Damage to the nervous system is very difficult to quantify, especially in young children. Aside from IQ loss, this damage not usually identified except in severe lead poisoning cases. Severe lead poisoning may lead to coma and death. The form of lead is important; and organic lead, such as tetraethyl lead (TEL), has caused deaths in children.

III.9.A.3 Causality and Special Susceptibilities

Children absorb considerably more lead than adults when ingesting the same contaminated media. Adults absorb five to ten percent of dietary lead and retain little of it; young children absorb 40 to 50 percent of dietary lead and retain 20 to 25 percent of it (Oski et al., 1994). Demographic and cultural factors affecting nutrition and dietary patterns may be considered when evaluating risks and costs. As noted above, the occurrence of adverse effects depends, in part, on the health status of the individual and individual factors. Both the uptake of lead into the body (which impacts the PbB levels) and the severity of health impacts may be exacerbated by various factors including poor health and nutritional status. Elevated EP (an indicator of lead poisoning) is often associated with iron deficiency (EPA, 1987). Diets high in fat and low in calcium, magnesium, iron, zinc, and copper increase the absorption of lead (Oski et al., 1994). Lead is stored in the body primarily in bone and may be released, causing toxicity, over many decades.

III.9.A.4 Treatments and Services

The treatments and services provided for children with elevated PbB depend on their risk classification, as shown in Table III.9-1. Detailed treatment descriptions are provided in Section B of this chapter along with cost data, and so are not presented here.

Link to Table III.9-1

III.9.A.5 Prognosis

Elevated PbB levels can always be brought down over time. The prognosis for health effects related to the elevated levels is more serious. The prognosis for full and unimpaired recovery depends on the degree of lead poisoning that occurred (e.g., the risk classification), the amount of time during which the PbB levels were elevated, the age of the child, general health and nutrition status, the degree of intervention (including special education strategies provided), and individual factors. It is not possible to predict the outcomes for individual children, due to the variety of factors which impact the final outcome. High risk children (as determined by the CDC classification system) are generally more likely to experience permanent damage than children with moderate or low risk levels.

PbB levels greater than 10 to 15 ug/dL sustained during early childhood carry a substantial risk for long-lasting but subtle injury to the nervous system, even if no clinical symptoms are detected. Attention deficits and reading disabilities have been observed in cohorts of young children with elevated PbB levels. In adults with elevated PbB as children, increased

rates of dropping out and having long-term reading disabilities have been observed. When levels are very high and encephalopathy has resulted, serious sequelae may occur in later years that include seizure disorders, mental disorders, and (in some rare cases) blindness and hemiparesis. In some cases, residential care is required (Oski et al., 1994).

III.9.B Costs of Treatments and Services

III.9.B.1 Methodology

To estimate the average costs of testing and treating children with high PbB levels, this analysis relies heavily on methodologies developed for the benefit-cost analysis of reducing lead in gasoline (U.S. EPA, 1985) and later applied by the EPA's Office of Air Quality Planning and Standards (U.S. EPA, 1987).

The average direct cost per child with high PbB levels was calculated in four steps:

- a typical treatment profile was developed for each risk level,
- the costs of relevant treatments were determined,
- the costs of treatments were combined with the treatment profiles to produce an estimate of the average cost per child, and
- the costs were reduced to reflect the fact that only a portion of children with high PbB levels will be screened.

III.9.B.2 Treatment Profile and Costs by Risk Level

The costs of relevant treatment elements (e.g., chelation therapy, neuropsychological evaluation, family education) were estimated by U.S. EPA (1985) and adjusted in U.S. EPA (1987). These costs are based on the CDC's (1978) recommended clinical management program and are linked to the risk level by determining PbB and EP levels (See Table III.9-1).

Link to Table III.9-1

The treatment profile is developed at the age at which the child is first screened. This analysis considers the cost of follow-up through age five regardless of the age of the child at the initial screening. Consequently, the actual costs for children initially screened at older ages may differ from those estimated in this chapter. They may be greater or lesser, depending on the medical consequences of later screening. In addition, treatment is

still likely to take place when screening occurs later in childhood, so overall costs may not be reduced regardless of the screening results. It was assumed that the distribution of the ages of children screened is uniform over the ages one through five. The cost of follow-up tests are adjusted accordingly.

Regardless of the age of initial screening, follow-up testing of children is assumed to continue through age five. A child initially screened at age one will therefore have follow-up tests for five years (ages one to five, including the initial screening year), while a child initially screened at age five will have follow-up tests only in the year of screening. The cost estimates presented below, given in 1996$, are averages for all screened children in the risk group regardless of the age at which they were initially screened.

Risk Level I. Children in this risk group are considered to be at low risk. Because screening is concentrated on children in areas with high-risk factors, follow-up treatment and family education are recommended. The estimate of the average (undiscounted) cost per child at this risk is $522.

Risk Level Ia. Children in this risk group do not have elevated PbB levels. They do have elevated EP levels, which may be indicative of iron deficiency or other medical problems. In addition to initial testing, all children at this risk level are tested for iron deficiency, at a cost of $39. The cost of medication for anemia is estimated as $127. With a mean population PbB of 20, 23.8 percent of those classified in risk level Ia will receive the medication, resulting in an average cost of $29 per child. The percentage of the children testing positive for anemia will vary with the mean population PbB concentration; a higher mean population would increase the percentage of children testing positive, and would therefore increase the average treatment costs per child. Health education, stressing nutritional needs, is assumed to be provided to 50 percent of the families with children in this risk group. The average (undiscounted) costs per screened child at this risk level is $692.

Risk Level Ib. In addition to the initial screening, children in risk category Ib receive periodic follow-up tests and limited family education. Table III.9-2. shows an estimated average (undiscounted) cost for this risk group of $623.

Risk Level II. As can be seen from Table III.9-2, children at moderate risk receive no chelation therapy. Also, no neuropsychological evaluation is performed and family education is limited. The major cost for this group comes from follow-up tests. The estimated average (undiscounted) cost for screened children in risk level II is $1,205.

Risk Level III. The treatment for children in risk level III is similar to treatment for children in risk level IV. For risk level III, however, a $CaNa_2$-EDTA provocation test is included. This test is used to evaluate the responsiveness of the child to chelation therapy. Also, the costs of chelation treatment fall sharply compared with children in risk level IV, due to the decreased percentage of children estimated to need this therapy. Only 0.43 percent of risk level III children are assumed to require this therapy, as compared with 37 percent of children in risk level IV. The cost of follow-up tests also decreases, since the frequency of follow-up tests is higher for children who have received chelation therapy than for children who have not. The estimated average (undiscounted) cost for screened children who are in risk level III is $2,632.

Risk Level IV. As can be seen from the table, the major cost element for children in the urgent risk group is chelation therapy. The probability of requiring chelation therapy increases with PbB concentrations. EPA (1987) estimated that 37 percent of the children in this risk group would require chelation therapy, based on a mean population PbB level of 20 μg/dl. Note that the cost of treatment for children in this risk group depends on this assumption regarding mean population PbB levels. A higher mean population PbB level would result in a greater percentage of children in this risk group requiring chelation therapy. Cost estimates for this risk group would therefore increase.

EPA reports that in some cases, an initial chelation therapy may be followed by a rebound in PbB levels as the body attempts to equilibrate between lead in soft tissue and lead in blood. A second and sometimes a third chelation treatment is therefore necessary. Fifty percent of children who receive one chelation treatment are assumed to require a second treatment. Fifty percent of children requiring a second chelation treatment are assumed to require a third. The total average (undiscounted) cost of treating a child in risk level IV is estimated to be $5,200.

Typical treatment for children in each risk level is shown in Table III.9-2, along with the associated average costs per screened child in each risk level.

Table III.9-2
Average Direct Cost of Treatment per Screened Child

Year	Treatment	Cost Per Child (1996 $) Level IV	Level III	Level II	Level Ib	Level Ia	Level I
Year of screening	Chelation, inpatient	1,486	13	0	0	0	0
	2nd chelation, inpatient	743	5	0	0	0	0
	3rd chelation, inpatient	372	3	0	0	0	0
	Initial lab test	61	61	61	61	61	61
	$CaNa_2$ provocation test	0	221	221	0	0	0
	Iron deficiency test	0	0	0	0	39	0
	Medication for anemia	0	0	0	0	29	0
	Follow-up tests	570	481	481	120	120	120
	Neuropsychological evaluation	1,204	1,204	0	0	0	0
	Family education	401	401	200	200	200	101
	Total	4,837	2,390	964	382	450	281
2nd year	Follow-up tests	145	97	97	97	97	97
3rd year	Follow-up tests	108	72	72	72	72	72
4th year	Follow-up tests	72	48	48	48	48	48
5th year	Follow-up tests	36	25	25	25	25	25
TOTAL		5,200	2,632	1,205	623	692	522

Totals may not add due to rounding.
Sources: U.S. EPA, 1987, Bureau of Labor Statistics.

III.9.B.3 Average Treatment Costs

To determine the average costs per child it was first necessary to estimate what percent of children in each risk category are screened. The percent of children who are placed in each risk category based on the screening results were then estimated. The risk level was used to determine the percent of patients receiving each type of treatment.

For children in risk levels III and IV, it was assumed that the lead exposure would result in behavioral symptoms; therefore, all children in these risk levels would be screened. The average cost per screened child in risk levels III and IV was assumed to equal the average cost per child in these risk groups.

Children in the lower risk categories may not develop obvious symptoms and may not receive treatment. U.S. EPA (1987) has estimated that 20 percent of children are screened for blood lead levels in any one year. A probability analysis could be performed to estimate the likelihood of a child being treated between disease onset and the age of six. Costs could then be adjusted based on the predicted average years past onset that screening occurs, but the level of detail of the information available on frequency of screening does not warrant this detailed analysis. As a simple and approximate method of accounting for the fact that not all children with high PbB levels are screened, the treatment costs for children in risk categories II, I, IA, and IB are multiplied by 0.2. The estimated costs for each risk level are shown in Table III.9-3.

Table III.9-3

Average Direct Costs per Child With High Blood Lead Levels--All Risk Groups[a] (1996 $)

Risk Level Per Child	Cost per Disease Year (1996 $) 1	2	3	4	5	Total Cost (1996 $)
IV	4,837	145	108	72	36	5,200
III	2,390	97	72	48	25	2,632
II[b]	193	19	14	10	5	241
Ib[b]	77	19	14	10	5	125
Ia[b]	90	19	14	10	5	138
I[b]	56	19	14	10	5	105

[a] Assuming uniform distribution of the tested children over ages 1 through 5.

[b] As explained in the text, cost estimates for these risk categories have been multiplied by 0.20 to reflect the percentage of children expected to be screened. If it is assumed that all children who need services will receive them, then the values reported in Table III.9-3 for Levels I and II should be used.

Source: U.S. EPA, 1987.

III.9.B.4 Survival

No data linking survival rates to elevated blood lead levels were found. This analysis assumes, therefore, that survival rates match typical survival rates in the entire U.S. population. The calculated survival rates for disease years one through five for children ages one to five, however, are 100 percent, as reported in *Vital Statistics of the United States* (U.S. Department of Health and Human Services, 1985). Survival rates therefore have no impact on the cost estimates.

III.9.B.5 Present Value Costs

Table III.9-4 shows the discounted direct cost estimates in Table III.9-3. Estimates of the present value costs per child with high PbB levels are shown in Table III.9-4, using discount rates of zero, three, five, and seven percent. Using a five percent discount rate, estimates of the net present value of medical costs per child with high blood levels are $5,162 for risk level IV, $2,610 for risk level III, $237 for risk level II, $120 for risk level Ib, $134 for risk level Ia, and $101 for risk level I. The discount rates have only a minor impact on the present value cost estimates, due to the fact that the majority of costs are incurred in the year of screening and are therefore unaffected by the discount rates.[2]

[2] Screening may not be coincident with onset of high PbB levels; no information was located regarding a typical time period between onset of high PbB levels and screening. If such information was available, then the costs of the disorder could be discounted over this lag period.

Table III.9-4

Discounted Average Direct Costs per Child Age One to Five Years with High Blood Lead Levels (1996 $)

Risk Level	Discounted Per Patient Costs (Discount Rate %)			
	0	3	5	7
IV	5200	5185	5162	5135
III	2632	2623	2610	2591
II	241	240	237	234
Ib	125	123	120	117
Ia	138	137	134	132
I	105	104	101	97

Sources: U.S. EPA, 1987, Bureau of Labor Statistics.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking below.

Link to inflation factors

Lead exposure analyses can produce estimates of the distribution of PbB levels and EP levels among the population, and therefore the distribution of the population among the risk levels shown in Table III.9-1. This distribution can be compared to levels of PbB and EP in the population under various regulatory options to estimate the change in the number of individuals in each of the risk categories. By multiplying the change in the number of individuals in each risk category by the costs of screening and treating an individual in that risk category and summing over all risk categories, the benefits of the regulations may be calculated.

Link to Table III.9-1

III.9.B.6 Limitations

There are numerous limitations to the cost estimates provided in this chapter. Foremost is the restriction of the information to those costs associated directly with the reduction of lead levels in blood. As discussed in Section III.9.A, numerous serious concurrent effects occur as a result of elevated blood lead levels. These effects are the reason that time and money are spent to reduce blood lead level in children. The costs of their treatment may be substantial. Some children may not experience measurable (or any) consequences of elevated blood lead levels, particularly if the elevations are very small, the children are healthy, and they have a good nutritional status.

Another major limitation is the assumption that only 20 percent of children are tested, valued when the chapter was originally written in 1993. There has since been an increased awareness of the risks associated with lead poisoning in children and a concurrent increase in the testing of young

children, which will lead to an increase in both testing and treatment costs. The costs presented in this chapter are therefore an underestimate of actual costs.

Another limitation is the lack of data regarding the age at which testing is performed. As stated in the text, testing may not be done at the age of one year. If it is done later, the costs of treatment may be greater or less than those estimated here. Costs would be lower if only minimal treatment were required because they would extend over a shorter period. If a delay in testing led to higher levels requiring more complex treatment and long-term impairment, then the costs could be much higher.

Finally, the cost estimates in this chapter are based largely on a methodology and data that were collected in the 1980s. These data may be outdated if new protocols are in place, and the costs may therefore differ from those presented here.

CHAPTER IV.1 INTRODUCTION TO THE COST OF RESPIRATORY ILLNESS AND SYMPTOMS

Clicking on the sections below will take you to the relevant text.

CHAPTER IV.1 INTRODUCTION TO THE COST OF RESPIRATORY ILLNESS AND SYMPTOMS

IV.1.1 Overview

Section IV of the Cost of Illness Handbook provides direct medical cost estimates for respiratory illness and symptoms, excluding cancers of the respiratory system. Cancers are discussed in Section II, and at the time of this writing includes one respiratory illness, lung cancer.

This introductory chapter contains a brief summary of respiratory illness definitions and duration that are relevant to estimating the costs of respiratory illness and symptoms (referred to subsequently as "illness" for simplicity).[1] The illnesses included in this section are those that were being evaluated by EPA in a manner that required cost estimates (e.g., for policy evaluations, benefits assessments, comparative illness reduction strategies). Although the specific applications of the cost data vary, basic cost information is provided for each illness. There is considerable variation in both the level of detail that was required for the illness in this section and the type of information that was available for the illness.

IV.1.2 Illness Definition and Duration

Respiratory illnesses involve the upper or lower respiratory system, which usually includes the nose, tonsils, throat, mouth, trachea (wind pipe), and all the structures of the lungs (bronchi, alveoli, etc.). Respiratory illnesses also are usually defined to include ear infections, sinusitis, and related illnesses (Oski et al., 1994). Often the illnesses involve multiple parts of the respiratory system.

A characteristic of the respiratory illnesses that are discussed in this section is that they are commonly treated by primary care physicians. This is in contrast to the illnesses discussed in Sections II and III, which were more likely to be treated by a physician or team of physicians with subspecializations, such as oncology and pediatric surgery, neonatal pediatrics, etc. The illnesses in this section may be very serious and even life-threatening. They usually are not, however, and are often treated with medications and minimally invasive procedures. Most illnesses of this type can be treated on an outpatient basis, rather than requiring hospitalization. Consequently, the costs of the illnesses, which are estimates of the average costs, are generally much lower, on an annual basis, than costs for illnesses that require more intensive treatment.

[1] "Cost" refers to direct medical costs unless otherwise noted.

All direct medical costs presented in the Handbook are estimates of the "average" cost for patients, so that the extremely high and low cost treatments that may be required in a small number of cases have been averaged into the overall distribution of care costs to yield an average cost. For most illnesses, the circumstances that would lead to unusually high or low costs are noted in the individual illness chapters.

This section includes cost estimates for both acute and chronic illnesses. An acute illness generally has a rapid onset (hours or days) and is sufficiently intense to cause someone to seek medical treatment. A chronic illness, such as asthma, is also assumed to require medical attention, but may continue over months and years, with a requirement for continuous or intermittent medical supervision and care. Symptoms are observed pathological responses in the body that may be associated with numerous causes, including illnesses or other stimuli (e.g., a cough in response to smoke).

CHAPTER IV.2: COST OF ASTHMA

Clicking on the sections below will take you to the relevant text.

CHAPTER IV.2: COST OF ASTHMA

IV.2.A. BACKGROUND

This chapter contains a discussion of the lifetime incremental direct medical costs incurred by asthma patients, and methods used to estimate those costs. Asthma is of particular concern to EPA because there are many pollutants that may cause or exacerbate this disease. Regulation of primary and toxic air pollutants may result in a reduced number of cases of chronic airway diseases, including asthma. Programs to reduce indoor air pollutants, such as environmental tobacco smoke (ETS), are also crucial in reducing the impacts of this disease. The benefits of such activities can be estimated in part, by evaluating the direct medical costs avoided. A full measure of the costs of asthma would also include direct non-medical costs and indirect costs. This chapter does not include information on elements of willingness-to-pay (WTP), such as indirect medical costs, pain and suffering, lost time of unpaid caregivers, lost productivity of patients, etc. The direct medical costs presented in this chapter may be useful in providing a lower-bound measure of WTP. The reader is referred to Chapter I.1 for a discussion of direct cost estimation methods and cost elements that are relevant to all benefits estimates. In addition, Chapter IV.1 contains general information regarding respiratory illnesses.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and IV.1
Link to inflation factors

This chapter uses the Guidelines for Diagnosis and Management of Asthma developed by the National Heart, Lung, and Blood Institute (NHLBI, 1997), which provide disease definition and clinical practice guidelines. The guidelines were developed by clinicians and researchers and provide information on current approaches to treating asthma. Current Medicare reimbursements and journal articles were used to obtain cost estimates. The medical and economics literature was consulted to obtain supporting information. A cost estimate was developed for the average patient and an upper bound value was estimated based on patients with moderate or severe asthma who had a high use rate of acute care services.

IV.2.A.1 Description

IV.2.A.1.1 Definition

Asthma is a chronic inflammatory disorder of the airways, designated as ICD9-CM-493 in the International Classification of Diseases (ICD-9).

Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and the chronic nature of the disease. Airflow limitation and the narrowing of airways can be manifested as acute bronchoconstriction, airway edema, mucus plug formation, and remodeling of the airway walls. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Asthma patients are usually categorized as having mild persistent, mild intermittent, moderate persistent, or severe persistent asthma, based on symptoms and the results of diagnostic tests. Their care depends, to some extent, on this categorization (NHLBI, 1997). Asthma episodes (also referred to as exacerbations or acute symptoms) are periods when bronchial constriction restricts airflow and causes the symptoms described above. The episodes can be triggered by allergens, irritants such as cigarette smoke, odors, pollution, sulfite preservatives, weather changes, and emotions. Prolonged severe attacks may be precipitated by common colds (e.g., influenza, rhinovirus). Some drugs cause short severe attacks (e.g., aspirin, nonsteroidal anti-inflammatory drugs). Responses are typically triggered within a few hours and may persist as a hypersensitive response to stimuli for two to three weeks (Eggleston, 1994).

In recent years the importance of inflammation in asthma has been further substantiated by research. When inflammation occurs, it is usually associated with airflow obstruction that is often reversible spontaneously or with treatment. The inflammation also causes an increase in the existing bronchial hyperresponsiveness to the triggers listed above. At the physiological level, asthma results from complex interactions among inflammatory cells, mediators, and other cells and tissues in the airways (NHLBI, 1997).

Although asthma may affect individuals throughout their life, the disease has certain age-specific characteristics and differential diagnosis issues. These issues need to be considered in the etiology and treatment of asthma (NHLBI, 1997). This chapter focuses on asthma that is diagnosed in childhood because that is the most common period of diagnosis, and much of the care provided for asthmatics is provided during childhood. In addition, the Agency has a particular interest in costs associated with childhood asthma. Most of the information provided is relevant to patients of any age, however, and information is provided to allow the reader to calculate costs associated with asthma onset at any age.

Asthma is a leading cause of morbidity among children and is the most commonly cited reason for school absenteeism, accounting for one-third of all school days lost. It is the most common cause for hospitalization of children. The median age of onset of asthma is four years; however, more than 20 percent of children who are diagnosed with asthma develop symptoms during the first year of life (Eggleston, 1994).

IV.2.A.1.2 Sources of Health Statistics Data

Although asthma is one of the most common chronic diseases in the U.S. and has increased in importance over the past 20 years, surveillance of asthma trends was very limited until recently. CDC provided summary data in 1998 for the overall period 1960 to 1995 that described some of the trends in asthma occurrence (CDC, 1998a). These data include asthma prevalence(for the years 1980-1994).[1] They also include asthma office visits (1975-1995), emergency room visits (1992-1995), hospitalizations (1979-1984), and deaths (1960-1995). The CDC report noted that the overall trend has been toward an increase in asthma prevalence and asthma deaths, with substantial differences in death rates within a single geographic region. Asthma hospitalizations have increased in some areas and decreased in others. Surveillance data are not available at the state or local levels, with the exception of asthma mortality (CDC, 1998a).

The National Center for Health Statistics (NCHS) collected much of the basic information on which the 1998 CDC surveillance summary was based (CDC, 1998a). They used the National Health Interview Survey which provides data on prevalence supplied by patients.[2] They also used the National Ambulatory Medical Care Survey which provides physician office visit data; the National Hospital Ambulatory Medical Care Survey, which provides emergency room visit data; and the National Hospital Discharge Survey, which provides data on in-hospital stays. Mortality data were also collected from each state (CDC, 1998a). Information is expressed both as the absolute value (e.g., number of cases) and the rate in the population (e.g., 2 per 10,000 people).[3] Age groupings used in the CDC surveillance summary are 0 to 4, 5 to 14, 15 to 34, 35 to 64, and >64 years (CDC, 1998a).

Mortality data from CDC (1998a) were limited, so additional information was also obtained from NCHS's FASTATS (CDC, 1999a). Multiple areas within this large database were used; they can be accessed through the website listed in the References section.

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[1] Prevalence is a measure of how many people have a disease, rather than how many were newly diagnosed in a particular year.

[2] The prevalence of a chronic disease is often determined through patient surveys.

[3] It is useful to consider both values because neither value alone can fully express trends and potential impacts. Rates provide information on changes, standardized to a specific size population. Absolute values reflect a combination of changes in the rate, along with changes in the underlying population size. For example, a rate could stay the same, but if the population increased by 20 percent, then the absolute number of cases would need to increase by 20 percent to maintain the same rate.

CDC also published a forecast estimate of self-reported asthma prevalence for the U.S. in 1998 (CDC, 1998b). This estimate was developed using 1995 survey data, 1998 census data, and linear extrapolations of region-specific increases in asthma prevalence over previous years (CDC, 1998b).

Another report by CDC contains an evaluation of the number and rate of ambulatory care visits for various diagnostic categories for the period 1993 to 1995 for children under 15 years of age (CDC, 1998c). The National Hospital Ambulatory Medical Care Survey provided hospital outpatient data used in this analysis. There are age restrictions in the data (only ages 0 to 14 are covered); however, other data sources were not located for hospital outpatient visits. The survey data are therefore used both as the source of the rate for those patients aged 0 to 14, and to estimate the visits for patients 15 years and older.

Data from the various government statistical summaries are provided below. In addition, some statistics are calculated using existing data. Most calculated statistics are for 1994 because this is the most current year for which prevalence data are available. Prevalence is important because it is a commonly used denominator in calculating statistics in this analysis, such as the rates of various services per asthmatic.

An important consideration when reviewing the asthma statistics is the way the rates are presented. Data on rates are provided in the CDC reports using the entire general population in the group of interest as a denominator (e.g., all people, all people aged zero to four, all blacks, etc). This division gives a somewhat distorted sense of the utilization of services by asthmatics because both the prevalence of asthma in the population and the size of the overall population have increased. The rate of service use could therefore appear to increase in the general population, while it actually decreased *among asthma patients*. Consequently, many statistics are presented using two types of rates for this discussion:

- rate per number in the population — denominator is total number of people in group of interest (e.g., children aged zero to four), and

- rate per number of asthmatics — denominator is number of asthmatics in the group of interest.

The rates are important because they are used to estimate the proportion of asthmatics using various services in the cost section of this chapter, which follows. Because the rates are not generally provided in the CDC reports, most rates *per asthmatic* were calculated for this analysis using the CDC statistics.

IV.2.A.1.3 Prevalence of Asthma

The self-reported prevalence of asthma increased 75 percent from 1980 to 1994 to 13.7 million people during the period from 1993 to 1994, and the trend was observed among all races, sexes, and age groups (CDC, 1998a). Estimates of asthma prevalence in 1998 by CDC, based on population trends and the pattern of increasing incidence, yielded a CDC-estimated total of 17,229,000 asthmatics of all ages in the U.S. (CDC, 1998b). This section focuses on the actual reported values (CDC, 1998a), rather than on the estimated prevalence (CDC, 1998b).

The increase in asthma prevalence was the greatest for children aged 0 to 4 (160 percent) with a rate increase during the period 1980 to 1994 from 22.2 per 1,000 (2.2 percent) to 57.8 per 1,000 (5.8 percent).[4] The current rate indicates that more than 1 in every 20 very young children have asthma, with approximately 1.3 million children in this age group having asthma during the most recent survey period (1993-4), in contrast with 360,000 in 1980 (CDC, 1998a). As noted above, the average age of diagnosis is four years, so half of all children will be diagnosed with asthma after the age of four. There was a 74 percent increase in prevalence in the age group 5 to 14 from 1980 to 1994. By the age of 18, the prevalence is 7.5 percent. This is in contrasts to the general population (all ages), with a prevalence of 5.7 percent. The prevalence rates are near or below 5 percent among age groups over 18 (CDC, 1998b). Among adults 35 years and older, the asthma rate was 44.6 per 1,000 (4.5 percent) in 1993-4. Asthma prevalence is 14 percent higher among blacks than whites, with rates of 57.8 versus 50.8 per 1,000 (5.8 versus 5.1 percent) during the most recent survey period (CDC, 1998a).

Asthma is most commonly diagnosed in children by the age of five and in adults in their thirties, although onset of symptoms can occur at any age. About ten percent of patients are first diagnosed with asthma after age 64 (AAFA, 1999).

Family income is related to asthma incidence, with those under the age of 45 having a prevalence of eight percent when family incomes were less than $10,000 compared to six percent for those with incomes greater than $35,000 (CDC, 1999a).[5]

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[4] All rates are expressed in terms of the entire population rather than just asthma patients, unless otherwise stated. For example, 10 per 1,000 indicates 10 cases among all the population, of whom some are asthma patients. This standard is used for all rates expressed in this section, unless otherwise noted.

[5] NCHS does not provide much detail on the age group of most interest to this analysis in their summary statistics (they group all those under the age of 45 together for many statistics). Consequently, the data are reported for this group, although those under 18 are of most interest.

Many studies have reported an association between urban residence and asthma. The NCHS aggregate statistics (not provided by individual age group) support this association, with a rate of 5.8 percent in metropolitan statistical areas compared with 5.1 percent in non-metropolitan areas. The rate is slightly higher in central city areas compared to non-central city areas within a metropolitan area (CDC, 1999a). Some areas have reported much higher rates, including Chicago, Bronx, and an area in Louisiana (CDC, 1998b).

There is substantial variation in asthma rates among states, although data are limited. In three states where surveys of adults were recently carried out, self-reported medically diagnosed active asthma in the previous year occurred in 6.6 percent and 7.4 percent of the population in Oregon in the years 1995 and 1996 respectively. Of those, 9 percent received emergency care for asthma in the preceding year. In New Hampshire, 11 percent of respondents reported having medically-diagnosed active asthma, and 19.9 percent of males and 44.6 percent of females had used medication (CDC,1998a). In Washington state, 10.8 percent of adults reported having asthma at some point in their life and 12.8 percent of children had asthma. Family incomes below $20,000 per year were associated with an approximately two-fold increase in asthma prevalence among children (MMWR, 1999). More state data will be available in the future, allowing national patterns to be evaluated.

IV.2.A.1.4 Office Visits

Use of office visits has increased in approximate correspondence to the prevalence of asthma. From 1975 to 1995, the estimated annual number of office visits for asthma increased from 4.6 to 10.4 million. The lowest rate of office visits was among people aged 15 to 34 years. The annual rate of office visits for asthma during the period 1993 to 1995 was 39.6 for whites and 43.8 for blacks per 1,000. The rate was higher for pediatric cases: 50.3 for ages 0 to 4 and 51.5 for ages 5 to 14 (CDC, 1998a).

The rates of office visits *among asthmatics* was calculated for this analysis using the prevalence statistics and the number of office visits reported by CDC (1998a). In 1994 there were 1,024,000 office visits for asthma among children aged 0 to 4 and a population of 1,300,000 children aged 0 to 4 with asthma. These statistics yield a rate of 780 per 1,000 asthmatic children for age 0 to 4, yielding an average annual office visit rate of 0.78 per patient. Using the same calculation for the age group 5 to 14, the rate was 720 per 1,000, yielding an annual average visit rate of 0.72 per patient.

As with all services discussed in this section (e.g., hospitalization, emergency room use), it was not possible to determine what percentage of patients had more than one office visit more in a year, nor the distribution of visits among patients. However, it was possible to estimate the average number of visits per patient (CDC,1998a). For costing purposes, the rates

make it possible to calculate an average cost per patient, even though some patients will have much higher or lower costs, depending on actual utilization of medical services.

IV.2.A.1.5 Hospital Outpatient Visits

There is a trend toward increasing provision of outpatient services by hospitals. These may function as clinics, or be more similar in practice to a group medical practice within a hospital. These outpatient visits provide the same kind of care that is provided in a physician's office; it is therefore anticipated that the costs will be the same (discussed in Section IV.2.B, below). It is important to determine the number of these visits that occur annually, to estimate the total number of medical visits and to determine the number of visits per year by a patient.

The CDC report "Ambulatory Health Care Visits by Children: Principal Diagnosis and Place of Visit" provides information on the number of children and rate per 100 children for ambulatory visits to physicians' offices, hospital outpatient departments, and emergency rooms (CDC, 1998c). Other sources of information for physicians' visits and emergency room visits are preferable for most statistics because they cover all ages, while this report covers patients only up to age 14. This report is useful, however, for evaluating patient utilization of hospital outpatient services, which the other sources do not describe.

CDC (1998c) reports an outpatient visit rate of 0.8 per 100 children aged 0 to 14 per year, during the 1993 to 1995 period, with 469,000 visits per year. Dividing the number of visits by the total number of asthmatic children in this age group of 4,090,000 children yields an average annual visit rate of 0.115 per asthmatic child. To evaluate the use of outpatient hospital care among those over 14 years of age, it was assumed that the relationship between this type of care and physician's office visits would be the same across ages. The ratio of hospital outpatient visits to office visits among children aged 5 to 14 is 0.115/0.72 = 0.159. The rate of office visits among all asthmatics in 1994 was estimated to be 0.607 per year (including adults and children). By applying the outpatient/office visit ratio determined for children (0.159) to the office visit rate for all ages (0.607), the rate of outpatient use per patient can be estimated as: $0.159 \times 0.607 = 0.10$.

IV.2.A.1.6 Combined Medical Visit Rate

When the hospital outpatient visit rate is added to the office visit rate, the total annual physician visits per patient can be estimated. As described above, the per patient rate of office visits among all asthmatics in 1994 was estimated to be 0.607 per year and the rate of outpatient use was estimated to be 0.10. Summing these two values yields an overall patient visit rate of 0.707 for the average patient. In subsequent discussions, the outpatient and physicians' office visits are discussed together as physician's office

visits, due to their similarity and to the fact that a physician is usually seen in either location.

An estimate of the medical visit rate for children can also be calculated. CDC (1998c) reports a physician visit rate of 5.3 per 100 children (similar to that reported in CDC 1998a), with 3,029,000 visits per year. Combining the hospital outpatient visits with the office visits yields 3,498,000 visits per year. This total yields an overall rate of 0.855 per patient aged 0 to 14 (2,498,0000/4,090,000). An annual visit rate can be calculated for the two childhood age divisions. For zero- to four-year-olds, the office visit rate listed above was 0.78 per patient. Adding the rate of 0.115 from above yields 0.895 per year. For five- to fourteen-year-olds, the office visit rate of 0.72 per patient was combined with the rate of 0.115 to obtain a rate of 83.5 per patient (taken directly from or calculated from statistics provided in CDC, 1998a).

IV.2.A.1.7 Emergency Room Use

Only recent data (1992-1995) are available on emergency room use, so longitudinal trend analysis is limited.[6] In 1994 the overall rate was 6.3 per 1,000 and 0.117 per asthmatic. There was not a statistically significant change in use over the four-year period among all patients (CDC, 1998a), but the rate of use by black asthmatics increased by 50.1 percent. Among white asthmatics the increase was 4.1 percent (calculated from statistics provided in CDC, 1998a and CDC, 1998c). Blacks had consistently higher rates of use than whites with a rate in 1995 (the most recent year with data) of 22.9 per 1,000 (population) versus 4.9 in whites. In 1994, the likelihood of an asthma patient visiting an emergency room was 0.337 for blacks and 0.087 for whites (taken directly from or calculated from statistics provided in CDC, 1998a).

Rates were higher for younger than for older patients. In 1994, the rate for children aged 0 to 4 was 14.5 per 1,000 people. For ages 5 to 14 the rate was 8.0 per 1,000 people. Rates of emergency room use in 1994 *among asthmatic children* were 239 per 1,000 (23.9 percent) for ages 0 to 4, and 112 per 1,000 (11.2 percent) for ages 5 to 14. Rates per 1,000 in the general population were very similar among the age groups within the span from 15 to 64 (approximately 7 per 1,000) and much lower for the elderly (65+ years) at 3.0 per 1,000. Rates *among asthmatics* in those age groups were lower than the rates for children (taken directly from or calculated from statistics provided in CDC, 1998a).

As discussed above under office visits, it was not possible to determine what percentage of patients used an emergency room more than once in a given year, so the values provided are an average across all patients. As

[6] Use is defined by CDC as admission for asthma listed as first diagnosis.

discussed in Section IV.2.B below, some patients have a much higher rate of emergency room use and hospitalization than the average patient.

IV.2.A.1.8 Hospitalization

Asthma is the ninth leading cause of hospitalization nationally (CDC, 1998b). Although the number of hospitalizations has increased substantially during the period 1980 to 1994 from 386,000 to 466,000, the rate of hospitalizations has not changed significantly (17.6 to 18.1 per 10,000 people). When the increase in asthma prevalence is considered, the hospitalization rate *among asthma patients* has actually decreased over the years considered. The hospitalization rate among asthmatics in 1994 was 0.034 per patient (calculated from data on prevalence and hospitalization provided in CDC, 1998a)

There have been dramatic shifts in hospitalization usage by whites and blacks during the period of study (1980 to 1994). While overall hospitalization rates for asthma patients have decreased by approximately 25 percent during that period, hospitalization among blacks has increased by 37 percent from 26.0 to 35.5 per 10,000. During the most recent observation period (1994) blacks had a hospitalization rate that was more than three times greater than whites, even though blacks have only a 14 percent greater prevalence of the disease (see prevalence discussion above) (CDC,1998a).

Hospitalization of patients of different ages has also changed during the observation period. Hospitalization of patients aged 35 and older has declined, but the number (not rate) of hospitalizations of very young children has increased dramatically. Among zero- to four-year-olds there has been a 45 percent increase in the hospitalization rate, from 34.3 to 49,7 per 10,000. This rate should be compared with an overall rate increase in the prevalence of asthma among this age group (discussed above) of 160 percent, which is substantially greater than the rate of hospitalization. (The total number of children in this age group with the disease in 1980 was 360,000 versus 1,280,000 in 1994). Using these numbers with the number of hospitalizations in 1980 (56,000) and 1994 (97,000), the hospitalization rates were estimated. In 1980, the rate of hospitalization among young asthma patients was approximately 16 percent, and in 1994 it was approximately 8 percent.[7] The hospitalization rate *among asthma patients* in this age group is therefore approximately one-half of what it was in 1980 (taken directly from or calculated from statistics provided in CDC, 1998a).

There has been a very modest increase among older children and young adults in the hospitalization rate per 10,000 people. For ages 5 to 14, the

[7] There is no way to determine which patients were hospitalized more than once in a given year, but these overlaps are not expected to occur more frequently in 1994 than in 1980. Due to this uncertainty, the percents provided are approximate values.

increase has been from 15.9 to 18.0 per 10,000; for the age group 15 to 34, the increase has been from 8.7 to 10.0 per 10,000 (taken directly from or calculated from statistics provided in CDC, 1998a). As with very young children discussed above, the overall asthma hospitalization rate *among asthma patients* in this age group has declined substantially.

Evaluating the reasons behind trends observed in hospitalization of asthma patients is difficult because many factors impact hospitalization, including:

- changes in the health status of patients (e.g., severity of the disease, management of the disease),
- changes in guidelines for admission to hospitals due to managed care,
- cost containment efforts or other considerations,
- a shift to emergency room use without admission rather than admitting patients,
- patient preferences,
- more self-administered therapy, or
- other factors.

The reduction in hospitalizations should *not* be interpreted as an improvement in the health status of patients, without additional information on the causes of the decreases in admissions.

There are regional differences in hospitalization; however, these are not discussed in this analysis. The differences may be reviewed in the summary provided by CDC (CDC,1998a)

IV.2.A.1.9 Mortality

Mortality from asthma is relatively rare and directly impacts the medical costs only by reducing the medical costs for those patients who die. Mortality is a sentinel event, however, as infant mortality is, in expressing the overall health or sickness of a population or population subgroup. Mortality is usually preceded by considerable medical treatment for illness (although not in every case for asthma). As such, it is useful to evaluate the patterns of mortality to gain some insight into medical care. Because mortality has little direct effect on the cost of medical care for asthma, limited data are provided below.

The CDC has provided a summary of mortality numbers and rates, by five-year increments over the past two decades (CDC, 1998a). They note that changes in the ICD codes and diagnosis during that period complicate the analysis of trends (CDC,1998a). Asthma-related deaths vary considerably by age group, with 85 percent of deaths occurring among people over 34 years of age. This rate may be due to the overlap of asthma with chronic

obstructive pulmonary disease (COPD), which usually occurs in older individuals. Decreases in airway function, which is reversible in asthma, is not reversible with COPD (CDC,1998a).

During the 1993 to 1995 observation period, the annual death rate from asthma was 17.9 per 1,000,000 population (CDC, 1999b). Using the total asthma population of 13,690,000, and 5,429 deaths (both from 1994), the death rate *among asthmatics* was 397 per 1,000,000 (an annual probability of dying of 0.0004). Among whites the mortality rate was 15.1 per 1,000,000 general population; among blacks the rate was 38.5 per 1,000,000 general population (CDC, 1999b). In light of the fact that the prevalence rate of asthma among blacks and whites is very similar (50.8 versus 57.8 per 1,000 general population, respectively (CDC, 1998a)), the difference in death rates is striking.

In addition to the source used above, CDC also provides a more detailed age-, race-, and sex-specific summary of mortality related to asthma, as well as other diseases (CDC, 1999b). These data can be used to determine the age- and race-specific mortality rates. There is no rate listed (numbers are too small to estimate reliably) for the first year of life. For ages 1 to 4 and 5 to 9, the rate is 0.2 per 100,000 general population. For ages 10 to 14 and 15 to 19, the rate is 0.4 per 100,000. The rate very gradually increases as age increases for subsequent ages (taken directly from or calculated from statistics provided in CDC, 1998a).

There are clear racial differences in deaths due to asthma among children. Among blacks, the numbers are too small to estimate reliably under age five. From that age forward, the rates are substantially higher than for whites. The black/white ratio for children is as follows:

Age	Black Rate/White Rate
5 to 9	0.8 per thousand / too small to estimate
10 to 14	1.2 / 0.2 = 6-fold difference
15 to 19	1.0 / 0.3 = >3-fold difference

The differences in mortality persist through adulthood. The overall mortality rate due to asthma is 3.86×10 (-4) among whites and 6.31×10 (-4) among blacks with asthma.

A number of studies have evaluated differences in medical care, hospitalization, emergency room use, and mortality between blacks and whites. A discussion of the hypotheses offered for these differences is beyond the scope of this chapter, which is focused on direct medical costs. One frequently offered observation is that better patient outreach and education reduces severe episodes and resulting emergency room visits and

hospitalizations by improving control of the disease. This improvement is likely to have an impact on mortality. (A subset of these patients is discussed below as "high-use" patients).

IV.2.A.1.10 Summary of Asthma Statistics

Table IV.2-1 contains information on prevalence and some aspects of medical care for asthma. Most notable statistics in the table were discussed in preceding sections. Statistics that are used later in cost calculations are bolded with an * at the beginning of the entry.

Table IV.2-1: Asthma Statistics: Data on overall population statistics, age, and racial characteristics [a, b, c, d]

Characteristic	Statistic	Source
Prevalence		
number 1994	13,700,000	CDC, 1998a
number forecast 1998	17,200,000	CDC, 1998b
number of blacks 1994	1,880,000	CDC, 1998a
number of whites, 1994	10,700,000	CDC, 1998a
overall rate per 1,000	57 (5.7%)	CDC, 1998a
overall rate under 18 years per 1,000	75 (7.5%)	CDC, 1998a
number of children aged 0 to 4 in 1980	360,000	CDC, 1998a
number of children aged 0 to 4 in 1994	1,300,000	CDC, 1998a
rate for ages 0 to 4 per 1,000 in 1980	22.2 (2.2%)	CDC, 1998a
rate for ages 0 to 4 per 1,000 in 1994	57.8 (5.8%)	CDC, 1998a
increase in prevalence rate in children 0 to 4 from 1980 to 1994	160%	Calculated from statistics provided in CDC, 1998a
number of children aged 5 to 14 in 1980	1,520,000	CDC, 1998a
number of children aged 5 to 14 in 1994	2,790,000	CDC, 1998a
increase in prevalence rate in children 5 to 14 from 1980 to 1994	74%	Calculated from statistics provided in CDC, 1998a
Office Visits [e]		
rate 1994 all ages per 1,000	34.1	CDC, 1998a
rate 1994 per asthmatic patient	0.607	Calculated from statistics provided in CDC, 1998a
rate 1994 ages 0 to 4 per 1,000	50.3	CDC, 1998a
rate 1994 per asthmatic patient	0.78	Calculated from statistics provided in CDC, 1998a
rate 1994 ages 5 to 14 per 1,000	51.5	CDC, 1998a
rate 1994 ages 5 to 14 per asthmatic patient	0.72	Calculated from statistics provided in CDC, 1998a
rate 1994 among blacks per 1,000	43.8	CDC, 1998a
rate 1994 among whites per 1,000	39.6	CDC, 1998a

Table IV.2-1: Asthma Statistics: Data on overall population statistics, age, and racial characteristics [a, b, c, d]		
Characteristic	**Statistic**	**Source**
Outpatient Hospital Visits		
rate 1994 among children aged 0 to 14 per 100 children	0.8	CDC, 1998c
rate 1994 among children aged 0 -14 per asthmatic child	0.115	Calculated from data provided in CDC, 1998c and 1998a
rate 1994 extrapolated to patients over age 14 (see text for method)	0.10	Calculated from data provided in CDC, 1998c and 1998a
Combined Office/Outpatient Visits		
rate 1994 for children 0 to 4 per asthmatic patient	**0.855**	**Calculated from data provided in CDC, 1998c and 1998a**
***rate 1994 extrapolated to all asthmatics expressed per asthmatic patient (see text for method)**	**0.707**	**Calculated from data provided in CDC, 1998c and 1998a**
Emergency Room (ER) Visits (no historical data were available) [f]		
rate 1994 all ages per 1,000	6.3	CDC, 1998a
***rate 1994 of ER visits per asthmatic**	**0.117**	**Calculated from data provided in CDC, 1998c and 1998a**
rate 1994 ages 0 to 4 per 1,000	14.5	CDC, 1998a
rate 1994 ages 5 to 14 per 1,000	8.0	CDC, 1998a
rate 1994 among blacks per 1,000	19.1	CDC, 1998a
rate 1994 among whites per 1,000	4.6	CDC, 1998a
rate of admissions among black asthmatics 1994 (635,000 admissions per 1,880,000 cases)	0.337	Calculated from statistics provided in CDC, 1998a
rate of admissions among white asthmatics 1994 (927,000 admissions per 10,700,000 cases)	0.087	Calculated from statistics provided in CDC, 1998a
increase in rate among blacks during period 1992 to 1995 (4 years) per 1,000 general population (228.9 in 1995/151.9 in 1992) [h]	50.1%	Calculated from statistics provided in CDC, 1998a
increase in rate among whites during period 1992 to 1995 (4 years) per 1,000 general population (48.8 in 1995 versus 46.8 in 1992)	4.2%	Calculated from statistics provided in CDC, 1998a
Hospitalization (described as number of discharges) [g]		
number 1980	386,000	CDC, 1998a
number 1994	466,000	CDC, 1998a

Table IV.2-1: Asthma Statistics: Data on overall population statistics, age, and racial characteristics [a, b, c, d]

Characteristic	Statistic	Source
rate per 1,000 in 1980	1.76	CDC, 1998a
rate per 1,000 in 1994	1.81	CDC, 1998a
***rate of hospitalization among asthmatics all ages in 1994**	**3.4%**	**Calculated from statistics provided in CDC, 1998a**
change in rate per asthma patient for all patients	-25%	Calculated from statistics provided in CDC, 1998a
rate of hospitalization among asthmatic children aged 0 to 4 in 1980	16%	Calculated from statistics provided in CDC, 1998a
rate of hospitalization among asthmatic children aged 0 to 4 in 1994	8%	Calculated from statistics provided in CDC, 1998a
change in rate among asthmatic children aged 0 to 4 from 1980 to 1994	-50%	Calculated from statistics provided in CDC, 1998a
change in rate per 10,000 for children aged 0 to 4 from 1980 to 1994	+45%	Calculated from statistics provided in CDC, 1998a
change in rate per 1,000 for blacks from 1980 to 1994	+37%	Calculated from statistics provided in CDC, 1998a
Mortality		
rate 1994 per 1,000 general population	0.0179	CDC, 1999b
rate 1994 among asthmatics per patient	0.0004	Calculated from data provided in CDC, 1998a
rate 1994 among whites per 1000	0.0151	CDC, 1999b
rate 1994 among blacks per 1,000	0.0385	CDC, 1999b
rate 1994 among asthmatic blacks per patient	$6.31 \times 10^{(-4)}$	Calculated from data provided in CDC, 1998a and 1999b
rate 1994 among asthmatic whites per patient	$3.86 \times 10^{(-4)}$	Calculated from data provided in CDC, 1998a and 1999b

Table IV.2-1: Asthma Statistics: Data on overall population statistics, age, and racial characteristics [a, b, c, d]

Characteristic	Statistic	Source

a. All numbers and rates are annual. See text for additional detail.

b. All rates are per person in the general population unless otherwise noted. When rates are expressed per asthmatic, the number of asthmatics is the 1993-4 value, unless otherwise noted.

c. The study period 1993-1994 is listed as 1994, while the study period 1979-1980 is listed as 1980.

d. Age- and race-related statistics are presented only when there are differences across the ages or races. If the values are very similar (e.g., as with overall prevalence of the disease among whites and blacks), no data are listed. Data are not provided on the racial designation "other," which comprises a very small portion of asthmatic patients and represents a diverse group of individuals who are categorized as neither black or white (e.g., Hispanic, Native American, Asian).

e. It was not possible to determine the percentage of patients with more than one office visit per year. The statistics presented do not indicate the total number of persons treated, but rather the number of visits that occurred.

f. It was not possible to determine the percentage of patients with more than one visit to the ER. The statistics presented do not indicate the total number of persons treated, but rather the number of visits that occurred.

g. It is important to note the differences in rates when expressed per population versus per asthmatic patient. The overall number of asthmatic patients has increased substantially, as well as the rate of asthma in the population. Increases in use of services (e.g., office visits, ER visits, hospitalizations) must therefore be considered in light of the number of asthmatics, rather than just the overall population.

h. The percentage change is calculated as: $\{ (y2 - y1)/y1\} \times 100$, where y1 = the number in earlier years and y2 = the number in the most current year considered.

* Statistics that are bolded (but not italicized) with an * are used in calculating costs later in this chapter.

IV.2.A.1.11 Variations in the Management and Use of Medical Services Among Asthmatic Patients.

Variations in disease management and the use of medical services occur on the basis of individual patient characteristics, including the severity of the disease. Considerable variation also results from the degree to which a patient has, and follows, an adequate asthma management plan. Under optimal circumstances, most patients would have a long-term asthma management plan that managed the symptoms of asthma sufficiently well that they did not have asthma episodes requiring medical intervention in emergency rooms or as inpatients in hospitals. Theoretically, the management plan would control inflammation sufficiently well with long-acting therapies so that short-acting therapies in response to airway restrictions were not routinely required. NHLBI has issued guidelines designed to address this issue. In practice, many patients either do not receive drug plans, or do not follow drug plans that manage asthma at this level of control.

Considerable evidence supports the contention that many, if not most, patients do not receive or follow treatment plans that are consistent with NHLBI guidelines, although the degree of compliance varies. Recent studies suggest that many patients who are seen in emergency rooms report not having treatment plans or not taking anti-inflammatory medication on a regular (proactive) basis. It has also been estimated that over one half of all people who use inhalers do not use them properly (AAFA, 1999).

It has been suggested, anecdotally, that it will take some time for NHLBI guidelines to become familiar and comfortable to most primary care physicians. In addition, there is not consensus among all physicians that they should prescribe according to NHLBI guidelines. Another factor is constraints on medical providers' time for patient education (due to cost containment or other reasons). This factor may be an important contributor to the seemingly high percentage of patients who do not use drug therapies that are optimal. Patients may also resist or not remember treatment plans. Regardless of the reasons behind the noncompliance with NHLBI guidelines, the fact of its occurrence is a reality. This noncompliance poses problems in evaluating both treatment of and costs for asthma.

One approach to this problem is to evaluate the studies that have been done on patients before and after training in optimal asthma management. Such an evaluation can provide information that can be used to estimate variations in management and services that occur and their costs. Studies of educational interventions have focused mainly on populations that have had a high level of acute care (e.g., emergency room use or hospitalization) in the recent past. Although these populations are not representative of the cross-section of asthma patients, the studies provide insight into both 1) the

high level of costs incurred by some patients, and 2) the savings in medical services and costs that may be gained through patient compliance with asthma management plans.

It has been estimated that the costs of hospitalizations and emergency room (ER) visits for asthma together comprise about 73 percent of the total direct expenditures on asthma for children (age 17 and under) in the United States (Weiss et al., 1992). It is also generally believed that most hospitalizations and ER visits for asthma could be avoided by following an asthma management protocol, such as NHLBI guidelines (see, for example, Weiss et al., 1992; Coventry et al., 1996; and Higgins et al., 1998). Although there are no national statistics on the costs of asthma for those asthmatics who do *not* follow such guidelines, several studies of the cost savings resulting from asthma management education programs support the hypothesis that the asthma-related medical costs for those asthmatics who do not follow an asthma management protocol are likely to be substantially greater than the costs for those who do follow such a protocol – largely due to increased utilization of hospitals and emergency rooms, which are relatively more costly than physician and pharmaceutical services.

Several prospective studies have compared utilization and the corresponding costs of medical services by asthma patients for a period of time (usually a year) before an intervention program to those for the same period of time after the program. These studies focused on patients who had used acute care services (e.g., hospitalizations or emergency room visits) recently, and most evaluated patients who had a relatively high rate of utilization and a moderate or severe form of asthma. These studies therefore do not represent the experiences of the average patient. The data from these studies can be used to evaluate the costs of patient services before and after intervention for patients with a high use of services at the outset. By multiplying the average cost of utilization (e.g., for hospitalization) by the number of occurrences of utilization, before and after an intervention, and for each type of medical service considered, the average per-patient cost before the intervention can be compared to the average per-patient cost after the intervention. Each study thus affords an estimate of the extent to which complying with an asthma management protocol may reduce asthma-related medical costs — or, conversely, the extent to which failure to comply may increase these costs for some patients.

There are several factors, including the exact nature of the intervention, the utilization categories considered, and the severity of asthma in the study subjects, that would likely affect the ratio of before-intervention costs to after-intervention costs; these factors vary from study to study. Moreover, because these studies (some of which are pilot studies) were often based on relatively small samples and may not necessarily be representative of the population of asthmatic children as a whole, their results should not be

taken as definitive. They do, however, afford a rough idea of the magnitude and range of the extent to which the asthma-related costs of the "noncompliant" population of asthmatic children may exceed those of the "compliant" population of asthmatic children. The results of these studies are summarized in Table IV.2-2.

Table IV.2-2: Summary of Asthma Intervention Studies

	Higgins et al., 1998	Westley et al., 1997	Greineder et al., 1995	Gaioni et al., 1996
Utilization categories included in study:				
Hospitalization	x	x	x	x
ER visits	x	x	x	x
Office (clinic) visits	x	x		
Chest radiographs	x			
Inhaled anti-inflammatory drugs	x			
Beta-2 agonists	x			
Considered children separately?	yes	yes	yes	no
Number of subjects (children)	61	43	53	207
Were the estimated savings net of the costs of the intervention?	no	no	yes	yes
Ratio of before-intervention to after-intervention costs	7.62	3.60	3.84	2.01

These studies suggest that the asthma-related medical costs of children in the "noncompliant" population could be from twice to over seven times the costs of children in the "compliant" population. As noted above, however, several factors are likely to affect these ratios. First, the intervention programs differed from one study to another. Second, some studies took into account the cost of the intervention program itself, and considered the savings net of those costs, while other studies did not. Third, these studies generally selected asthmatics whose asthma was more severe than average, focusing primarily on patients with considerable hospitalizations and emergency room use prior to the study. Both their "before intervention" and "after intervention" acute care use rates are much higher than the national average. This frequency suggests that they would be categorized as patients with moderate or severe asthma. Fourth, these patients may have had much poorer compliance with management plans (or a lack of a plan) than other patients, leading to their very high acute care use rate at the outset of study participation.

The results of these studies shed light on the cost impacts that the variations in treatment may have. No single study fully illustrates national patterns of treatment, but the information in these and other studies is used later in this analysis as the basis for estimating medical costs for some patients. Additional detail is provided on the studies in Section IV.2.B.

IV.2.A.2. Concurrent Effects

Asthma usually occurs concurrently with allergies (as described above), although this is not always the case with adult-onset asthma. In the elderly it is often associated with other respiratory diseases such as chronic obstructive pulmonary disease (COPD). It has also been linked to other upper and lower respiratory tract diseases (e.g., sinusitis, rhinitis). It is not clear in most cases whether one disease triggered another.

As with most pharmaceuticals, those that are used to treat asthma have adverse side effects. Long-term use of corticosterioids have been associated with growth retardation in children and other serious health effects. There are also potential health risks listed for most other drugs used to control asthma. It is beyond the scope of this analysis to evaluate the health risks and potential direct medical costs of these secondary illnesses. These illnesses, however, are likely to occur in some patients and lead to an underestimate of medical costs when not considered.

Asthma may exacerbate cardiac and other problems. Asthma often leads to restricted activities in patients and a sedentary lifestyle that has been associated with numerous health problems. Asthma is a leading cause of activity restriction in children (NCHS web site, 1999). Perhaps most significantly, asthma during childhood has been associated with permanent structural changes in the lungs that are associated with adult respiratory diseases. This is one reason for the current focus in medical services on reducing episodes of asthma and the severity of the disease. Quantitative data were not obtained on the concurrent effects that result from the adverse physiological impacts of asthma. Due to the lack of information on these impacts, however, the cost estimates provided in this chapter, which focus solely on costs associated directly with asthma treatment, will underestimate total medical costs.

IV.2.A.3 Causality and Special Susceptibilities

Asthma usually begins in childhood and is often associated with atopy — the genetic susceptibility to produce IgE (an immune response) in response to exposure to common environmental allergens. Atopy occurs in 30 to 50 percent of the asthmatic population, and occurs in the absence of asthma in some individuals. It is the strongest predisposing factor for the

development of asthma. In young children who wheeze in response to viral infections, the presence of allergy in the child or their family is very strongly associated with asthma throughout childhood (NHLBI, 1997).

Other risk factors are neonatal lung disease, especially in infants with reduced lung volumes, and respiratory infections. Respiratory syncytial virus (RSV) has been particularly highlighted in association with asthma. Approximately half of all children with RSV bronchiolitis develop chronic asthma (Eggleston, 1994).

In adults asthma occurs both with and without IgE responsiveness. Without it, asthma is often associated with sinusitis, nasal polyps, and sensitivity to aspirin. Although the genesis may differ, the inflammatory process is similar to that seen in atopic asthma. Workplace exposures to some materials can also cause clinical signs of asthma, which may persist after the workplace exposure has ceased (NHLBI, 1997). Because asthma is often associated with atopy in response to exposure to common environmental allergens (NHLBI, 1997), these allergens are important asthma triggers. In adults asthma occurs both with and without IgE responsiveness and has been linked to numerous environmental agents.[8]

Numerous studies have identified air pollutants (e.g., particulate matter and ozone) as contributors to asthma (EPA, 1996). Hospitalizations for asthma have been shown to increase during air pollution episodes. Passive cigarette smoke (ETS) is also a strong instigator of asthma, with multiple studies showing associations between parental smoking and childhood asthma. EPA has provided a detailed summary of literature related to ETS through 1992 (EPA, 1992).

There has been an increase, as shown in the statistics presented earlier, in the incidence of asthma, asthma hospitalizations, and asthma deaths in recent decades. The specific causes of this increase are not known, although it has been hypothesized that air pollution and smoking in the home may be contributing factors.[9]

Appendix IV.2-A contains a list of many of the chemicals known or suspected of causing asthma that have been reported in the EPA Hazardous Substances Data Base (HSDB). High quality human dose-response studies are uncommon because non-pharmaceutical chemicals are rarely tested on

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[8] The medical literature on asthma usually refers to external agents that can trigger asthma as "environmental factors," although they do not necessary mean "environmental" in the sense in which it is used in this Handbook. The environmental factors referred to in the literature include any aspects of the environment that are external to the body and include, but are not limited to, environmental pollutants.

[9] Maternal versus paternal smoking is a stronger risk factor for childhood asthma, and more women smoke now than in the first half of the century.

humans, which limits the information that can be obtained directly from human studies. Animal studies provide an additional source of information for links between a pollutant and disease. Potential causality of asthma as indicated by the HSDB toxicity excerpts was the only requirement for including a chemical in this table.

Regarding special susceptibility, it is difficult to determine whether an increase in the occurrence of a disease within a population group is due to genetic susceptibilities of the group, or a common characteristic that is unrelated to their genetic predispositions. That is the case with asthma, which affects a disproportionate number of socioeconomically disadvantaged minority children who often live in urban areas. It is likely that a combination of factors are at work in this case, including nutritional status, the presence of numerous pollutants in the environment, the greater likelihood that someone in the home smokes, less prenatal care, and other factors.

In addition to a greater likelihood of the occurrence of asthma, there is a greater likelihood that the same populations will be hospitalized for asthma, and that they will die of the disease (as shown in Table IV.2-1). Both of these endpoints indicate a much more severe case of asthma than what is routinely observed and can be treated through periodic office visits and self-medication with physician-prescribed treatments. At present there are clearly higher risks of the disease associated with the characteristics described above. These have environmental justice implications for benefits evaluations that focus on asthma.

Although socioeconomic and geographic factors may be the primary factors in the observed differences in asthma rates in the national population, genetic differences may also play an important role. This has recently been found to the case with some types of cardiovascular disease; African-Americans appear to have higher risks in some studies even when socioeconomic and other factors are carefully controlled. The rapid increase in asthma incidence and serious consequences has made careful evaluation of the risk factors for this disease difficult, and it has yet to be determined whether there are large differences within the U.S. population in the inherent (genetic) susceptibility to the disease (NHLBI, 1997).

IV.2.A.4 Treatment and Services

This chapter provides cost estimates that are based on a description of specific treatments and services provided to asthma patients. It is unlike chapters that use cost estimates obtained from journal articles or other sources. Because the cost estimates are generated for each specific service, very detailed treatment information is provided along with the costs of each

service. Consequently, treatment is more appropriately discussed in Section IV.2.B on cost. This section provides only a brief description of asthma treatment and services.

Treatment of asthma involves three phases: 1) initial diagnosis of the disease with efforts directed at immediate stabilization of the patient, 2) ongoing care to minimize episodes and maximize the quality of life of the patient, and 3) acute care for treatment of asthma episodes.

Depending on the severity of the asthma episode at initial diagnosis, a variety of treatment strategies are employed and may be provided on either an inpatient or outpatient basis. Follow-up care and long-term management of the disease involves multiple strategies. A major goal of asthma treatment is to enable patients to control their symptoms through the use of medications that they self-administer, and to control their exposure to situations that trigger their asthma episodes. This patient-centered focus requires determining the best long-term disease management approach and considerable training by medical personnel to achieve the objective of enabling the patient to live a life as free from asthma symptoms as possible (NHLBI, 1997).

Most asthma is managed through the use of drugs and avoidance of asthma triggers (e.g., allergens, irritants, behavior such as exercise in cold environments). When management is not adequate, asthma episodes occur that require more aggressive care, either provided at home or by a medical professional. These two scenarios, long-term management and acute episodic treatment, are reflected in the drug therapies offered to patients. Two major types of drugs are used to address these two circumstances: 1) long-term control agents: anti-inflammatory drugs that are self-administered;[10] and 2) acute control agents: bronchodilators that relieve acute symptoms (also self-administered, except in crisis). The drug therapies comprise the majority of costs in well-managed long-term asthma care. When long-term management is inadequate, as it often is for some groups of patients, episodes occur that require the use of acute control agents (and in some cases hospitalization, emergency room use, and mortality).

As the above paragraph indicates, this disease is largely a manageable disease for most patients. In practice, there are large differences in how well the disease is managed due to differences in treatment by medical care providers and the patient. As a result of this variation, the cost section of this chapter (Section IV.2.B) contains a discussion and cost evaluations based on differences in the use of medications and resulting medical services.

[10] Self-administered includes administration by a parent or non-medical care provider.

IV.2.A.5 Prognosis

Asthma is a chronic disease that is commonly observed in childhood, but it may be diagnosed or persistent at any age. Approximately 60 percent of asthmatic children undergo remission in young adult life, but 50 percent of those (30 percent of the original population) become symptomatic again as young adults. Among those who are asymptomatic as adults, some studies have shown that they retain airway hyperresponsiveness. Based on the above statistic, it is assumed in this analysis that 30 percent of asthmatic children will become permanently asymptomatic at age 18 and incur no additional medical costs for asthma treatment. Tests of airway hyperactivity show that the airways have not returned to normal among asymptomatic young adults who were previous asthma patients. As a general rule, children whose asthma is resolved are those with:

- less severe intermittent asthma;
- few positive skin tests to inhalant allergens;
- no persistent wheezing or rhonchi; or
- no heavy exposure to pollution, allergens, or cigarette smoke (Eggleston, 1994).

The assumption that 30 percent of children will undergo remission is based on observations made in the past. It is not known if the remission rate at this time is the same as it was when the 30 percent statistic was observed. It is also not known which percentage of asthmatics in any severity category (discussed below), will undergo remission. In this analysis it was assumed that the severity mix among asthmatics who became asymptomatic was the same as the mix in the original asthma population. This assumption introduces uncertainty to this cost analysis.

Although many children see a gradual lessening of symptoms as they progress toward adulthood, this is not universally the case. In some cases, the disease becomes more severe and in rare cases is fatal. As discussed under Concurrent Effects above, damage that is done to lung tissue and structure during asthma episodes may lead to adverse long-term or permanent changes in the lung. Current treatment strategies are designed to minimize the inflammatory processes that occur during an asthma episode, in part to avoid long-term damage to the respiratory system (NHLBI, 1997).

The long-term disease course and effects of asthma differ among individuals. In some patients fibrosis of the subbasement membranes in the respiratory system may occur, and this may contribute to persistent abnormalities in lung function in these individuals (NHLBI, 1997). Due to concerns regarding the irreversible damage that can occur, effort is being

focused on early diagnosis, limiting the severity of the disease, and drug therapy that minimizes the inflammation causing structural changes in the respiratory system (NHLBI, 1997).

When considering the prognosis for asthma patients, it is necessary to take into account both the recurrence of asthma episodes and the effects that treatment of asthma may have on overall health. Inflammation is an early and persistent component of asthma and therapy to suppress it is long term. Greater asthma control achieved with high doses of inhaled corticosteroids causes less airway inflammation. The drug therapies used to control asthma episodes are not without side effects, as discussed previously. There are a variety of products on the market and each has specific advantages and disadvantages. There is some evidence that some of the most effective asthma treatments also lead to growth retardation in children. Consequently, the prognosis for this disease must take into account both the long-term nature of asthma in many individuals and potential damage to the patient that results from control of asthma symptoms. Quantitative data on long-term prognosis is not available for newly-diagnosed patients because many new drugs have been introduced recently.

Urban residence and poverty are major risk factors for asthma morbidity and mortality. There are areas of increased mortality in cities, especially among people in lower socioeconomic groups (Eggleston, 1994).

Mortality due to asthma is a rare event. The mortality rate for asthmatics is 0.0004 (see Table IV.2-1 above).[11] Some population subgroups have much higher rates than average (for example, teenagers in lower socioeconomic groups). Increased mortality among young and otherwise healthy patients has been associated with an inability to understand or comply with the sometimes demanding drug and activity regimens required to control asthma episodes. They may also be less likely or able to obtain timely health care for acute episodes.

Link to Table IV.2-1

As discussed in the section IV.2.A.4 above, there are differences in how individual patients manage their disease. These differences can lead to major differences in the prognosis among patients. Self- or parental management of the disease is much more important for asthma than for most diseases discussed in the Handbook. This distinction places a large burden on the medical community regarding outreach, education, patient tracking, and follow-up care. Ultimately, the prognosis for asthma patients depends largely on their ability and interest in managing their disease

[11] The value of a statistical life (VSL) can be computed for those patients who die of the disease when asthma avoidance is being considered in a benefits analysis.

through complying with treatment plans. Asthma deaths have occurred among patients with mild, moderate, and severe asthma, and so are not strictly related to the severity of the disease. Both hospitalizations and mortality are strongly related to the degree of control of inflammation and a timely response to acute asthma episodes. Patient (or caregiver) education, access to medical care, and appropriate use of drug therapies are very strong determinants in the overall prognosis for asthma patients.

Link to Section IV.2.A.4

IV.2.B. Costs of Treatment and Services

This section contains a description of the methodology used to estimate cost, followed by a description of the services provided for the three main components of care: diagnosis, long-term management and acute care management, and a presentation of the costs of these services. Costs are presented on an annual and lifetime basis for both the average and high services use patient.

IV.2.B.1. Methodology Summary

Estimates of the direct costs of asthma are constructed using national data on asthma medical services, utilization, reimbursement by Medicare, and national recommendations and private sector costs regarding drug therapy. The probabilities of patients utilizing various services are multiplied by the cost per service. The methodology by which estimates of the lifetime incremental costs are developed proceeds in four steps:

1) Develop treatment descriptions and probabilities,
2) Estimate the cost of each treatment component,
3) Estimate the annual costs of treatment, and
4) Sum costs over the lifetime of an average patient and apply discount rates.

After initial diagnosis, asthma management can be considered as two separate activities: long-term management and management of acute episodes. Long-term management includes the establishment of an appropriate treatment program, education for the patient and for family members to allow them to manage the disease, and office visits to evaluate the patient's ongoing health and use of medications. It also includes the drug therapy that is used to manage the disease. Acute episode management focuses on reducing symptoms of an acute asthma attack and preventing further damage to the patient's health. This section is organized according to the treatment components listed above, with diagnosis described first, followed by long-term management and then acute episode management.

IV.2.B.1.1 Treatments and Services Evaluated

The first step in estimating the cost of the disease is to model the typical course of the disease and the corresponding treatment. Three main sources were used to construct disease course and treatment profiles for asthma in this chapter: NHLBI Guidelines (NHLBI, 1997 — primary source), data from the literature, and, to a limited degree, data from a physician panel convened in 1991.[12]

Asthma treatments and costs have three main components:

1) diagnosis,
2) long-term management, and
3) acute episode management.

Diagnosis is required for all patients, and the types of diagnostic tests and evaluations conducted are assumed to be the same for all patients (although differences may exist among care providers). Long-term management consists of office or outpatient visits and self-administered drug therapy. Acute care results from immediate health emergencies that require emergency room use and/or hospitalization. These components of health care are first described (in Sections IV.B.2, 3, and 4) and then the costs of the services are presented and discussed (in Section IV.B.5).

IV.2.B.1.2 Evaluation of Differences in Asthma Management [13]

IV.2.B.1.2.1 Overview of Issues

As discussed in Section IV.2.A.1.11 above, under optimal circumstances all patients would have a long-term asthma management plan that managed the symptoms of asthma sufficiently well that they did not have asthma episodes requiring medical intervention. In practice, many patients either do not receive drug plans, or do not follow drug plans that manage asthma at this level of control. The lack of adequate medication often leads to higher costs for office visits and acute care (emergency room use and hospitalization).

Link to Section IV.2.A.1.11

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[12] A panel of three physicians (two pulmonologists and an internist) was convened in 1991 to determine a standard treatment protocol and the percentage of patients receiving various types of treatments. The purpose of the panel was to supply information that was used to develop the first asthma COI chapter in 1991. These physicians, all from New England, did not represent a cross-section of primary care physicians who treat most asthma cases. Aware of these limitations, they reviewed Medicare treatment records and other materials and attempted to provided useful information on overall treatment patterns. The information they provided has been largely superseded by NHLBI guidelines and other information.

[13] All referrals to asthma management acknowledge that this process involves both the medical community and the patient, due to the importance of self-medication and other activities in asthma treatment.

As discussed in Section IV.2.A.1.11 above, some patients use services at a much higher rate than the average patient, suggesting that substantial differences exist in the utilization of medical services and the resulting costs among asthma patients. In addition to obtaining a cost estimate for the "average" patient, it would be useful to obtain cost estimate for patients with two different patient profiles: one in compliance with treatment plans (such as those specified by NHLBI guidelines), and one that does not have well-managed asthma and has health problems related to the management plan. There are limited data on the variations in treatment that preclude providing highly reliable national estimates for these two patient groups, but there are some studies of high-use patients (as discussed in Section IV.2.A.1.11). These studies were used to describe a hypothetical patient who is not following an optimal treatment plan and incurs the associated higher medical costs.

IV.2.B.1.2.2 Patient Types Evaluated in this Cost Analysis

Descriptions of treatments and costs are provided for two types of patients:

1) the average patient: a profile was developed using national statistics on office and outpatient visits, emergency room use, and hospitalization, as described in Section IV.2.A, Table IV.2-1. No data are available on drug therapy use, so NHLBI guidelines are assumed to be relevant. Issues related to drug therapy are discussed below.

Link to Table IV.2-1

2) the high-use patient: a profile was developed using studies of patients who have difficulty managing their asthma with a larger number of acute episodes than average. The estimate of their hospital and emergency room use is based on studies that evaluated the experiences of patients before they had training on how to follow their management plans. These patients tend to have moderate or severe asthma. Their costs provide a type of reasonable upper bound on costs.

Ideally, data would be available on patients with mild asthma who are in compliance with treatment plans and have a resulting low utilization of acute care services. These data, which could provide a lower-bound cost estimate, are not available. The studies that evaluated "before" and "after" intervention included mainly patients who had serious acute care problems and were not likely to include mild asthma cases.[14] Consequently, although

[14] Mild asthma is estimated to comprise 70 percent of all asthma cases, as discussed below.

data are available on the impact of intervention on high-use patients, there are no data on a cross section of asthma patients.

As discussed above, asthma treatments and costs have three main components (diagnosis, long-term management, and acute episode management). Diagnostic methods and costs are likely to be similar regardless of the subsequent decisions of patients or their physicians. Long-term management and acute episode services will vary, depending on the factors discussed above. Although the number of hospitalizations and emergency room visits are assumed to vary for the two patient types, the level of services provided during hospitalization and emergency room visits are *not* assumed to differ. (There is no basis on which to assume that the services would differ.)

IV.2.B.1.2.3 Quantitative Data on Treatment and Services for Two Patient Types

The Average Patient. National statistics listed in Section IV.2.A Table IV.2-1 on treatment and services were used (office/outpatient visits, emergency room use, and hospitalization).

Link to Table IV.2-1

The High-use Patient. Table IV.2-3 lists the frequency of use of various services before and after the intervention of an asthma management program. The "before" statistics have been used to develop a hypothetical "high-use" patient profile, to provide an indication of the high costs that can be associated with asthma in the absence of adequate disease management. (The data in this table expand on information provided in Table IV.2-2.) The "after" data are used in the sensitivity analysis presented in Section IV.2.C.

Although studies indicate that inadequate disease management is a relatively common problem, data were not located that adequately describe the percentage of asthma patients with this problem or its extent. Consequently, this analysis does not assign the "high-use" costs to a specific proportion of asthma patients. It is likely that these patients' use of acute care services comprises a substantial portion of the overall national acute care services use reflected in the "average" patient costs referred to above.

Table IV.2-3: Acute Care Utilization Rates for "High-use" Asthmatics Before and After Participation in an Asthma Management Program									
Study	Utilization Rate Per "High-use" Asthmatic per Year								
	Hospitalization			Emergency Room Visits			Office (Clinic) Visits		
	Before Intervention	After Intervention	Ratio	Before Intervention	After Intervention	Ratio	Before Intervention	After Intervention	Ratio
Higgins et al., 1998	0.149	0.070	2.13	0.498	0.316	1.58	2.587	3.724	0.70
Westley et al., 1997	0.530	0.190	2.79	3.670	1.350	2.72	4.395	2.442	1.80
Greineder et al., 1995	0.660	0.094	7.00	1.358	0.283	4.80	—	—	
Gaioni et al., 1996	0.758	0.169	4.49	1.126	0.304	3.70	—	—	
Mayo et al., 1990	1.560	0.480	3.25	—	—	—	—	—	
Average Across Studies:	0.732	0.201	3.93	1.663	0.563	3.20	3.491	3.083	1.25
Average Asthmatic (for Comparison)	0.034			0.117			0.707		

IV.2.B.1.3 Duration of Treatment and Services

Although patients can be diagnosed with asthma at any point in their lives, most people are diagnosed as children. As noted earlier, the average age of diagnosis is four years (Eggleston, 1994) and that is the age that is used as the average onset of the disease for this analysis.. As noted above, asthma patients are assumed to live a normal lifespan due to the minimal mortality due to asthma. An average life expectancy of 75 years was assumed for purposes of estimating care duration and cost.[15] This lifespan is recommended in EPA's Exposure Factors Handbook for general use (EPA, 1997), which yields an overall lifespan with asthma of 72 years (from age 4 through age 75). There is an assumption that 30 percent of patients with mild asthma become asymptomatic and no longer require treatment at age 18. (See discussion in Section IV.2.A.5.).

Link to Section IV.2.A.5

Life expectancy increases as individuals survive through each year of their life, so that by the average age of diagnosis (four years) life expectancy is longer than 75 years for the average person in the United States. This figure is balanced by the likelihood that people with chronic illnesses, such as asthma, have a decreased life expectancy due to asthma and related illnesses or the side-effects of treatment. The average duration of treatment is uncertain for asthmatics, and the actual duration and associated costs may be greater or lesser than the value estimated in this analysis.

IV.2.B.2 Diagnosis

IV.2.B.2.1 Medical Evaluation During Diagnosis

The diagnosis of asthma usually occurs in response to the observation of symptoms that prompt a visit to a physician's office or emergency room (ER). It may also occur when a routine physical is scheduled, especially in the case of children. Treatment in an ER does not imply a severe medical condition; rather, it indicates an acute problem and may be the medical location of choice for some patients who do not have a regular physician, or when an asthma episode occurs outside of usual office hours. NHLBI does not distinguish among diagnoses in different settings when describing the diagnostic protocol (NHLBI, 1997).

Medical evaluation needed to diagnose asthma is not complex in most cases. Asthma is indicated by an appropriate array of symptoms, an acute

[15] There may be mortality due to therapy or other aspects of asthma that are not well-described at this time. In the absence of information to the contrary, it was reasonable to assume a normal lifespan for asthmatics.

reaction to asthma-related stimuli, and quick relief by appropriate therapy. Other supporting evidence may include family history, an elevated IgE level, and eosinophilia (Eggleston, 1994).

When considering a diagnosis of asthma, NHLBI recommends the following:

- careful history-taking (specific questions can be viewed at the NHLBI web site),
- physical examination, and
- spirometry to evaluate air flow.

Beyond the above activities, NHLBI discusses some specific procedures that may be dictated by the patient's characteristics and history, but that are not required for most patients. These may include:

- additional pulmonary function tests (lung volume, inspiratory and expiratory flow loops, diffusion capacity test (primarily in older patients));
- diurnal variation in PEF over one to two weeks;
- bronchoprovocation with methacholine, histamine, or exercise;
- chest X-ray;
- allergy testing;
- screening for nasal polyps and sinus disease;
- evaluation of gastrointestinal reflux;
- evaluation of biomarkers of inflammation (in development); and
- other tests to rule various diseases suggested by patient symptoms.

Many of the above additional evaluations have specific and narrow indicators for their use and are not needed for most patients. It is not possible to determine the percentage of patients that are evaluated for each of the above. Some of the evaluations would be done during a second diagnostic visit to a specialist (e.g., allergy testing) or may be characteristics observed by the patient and reported back to the physician (e.g., diurnal variation in PEF over one to two weeks). Second diagnostic visits are considered below. The other evaluations listed above are beyond the scope of this analysis, but their inclusion would increase costs. Thus, their exclusion leads to an underestimate of costs.

Diagnosis of asthma is difficult in young children. They are often diagnosed as having bronchitis, bronchiolitis, or pneumonia. In infants there are two patterns of wheezing (a critical observation in asthma), allergic and nonallergic. As children develop, the nonallergic infants no longer wheeze during colds and other minor illnesses because their airways

enlarge. Allergic children continue to have episodes when their airways constrict and may be diagnosed with asthma (AAFA, 1999).

Diagnoses of asthma are not frequently made in children under the age of one year. When wheezing and related symptoms occur prior to that age, they are generally diagnosed as bronchiolitis or other diseases that cause wheezing, with the understanding that they may later be diagnosed as asthma. The symptoms that occur prior to one year may be "asthma" in the pragmatic, if not clinically defined, sense of the term. When asthma is diagnosed in much older children, it may be because their symptom onset occurs later or because there is a delay in diagnosis beyond the onset of symptoms, which can lead to more severe forms of asthma when diagnosis occurs. Numerous studies have suggested that an underdiagnosis of asthma is a public health problem.

IV.2.B.2.2 Services Provided During the Diagnostic Visit

Based on NHLBI guidelines and the 1991 panel recommendations, components of the diagnostic visit (that are costed individually for Medicare reimbursement) are listed in Table IV.2-4. As discussed previously, services will vary depending on patient characteristics, the physician's practice methods, and other factors.[16] X-rays were included in this list because they appear as a possible procedure in NHLBI guidelines and were listed by the 1991 physician panel as a diagnostic procedure.

Table IV.2-4: Diagnostic Procedures

Chest X-Ray, Two Views
Blood Gases: pH, pO2, pCO2
Automated Hemogram
Breathing Capacity Test
Office Visit, Level 5, New Patient
Drawing Blood for Specimen

Diagnosis may occur at a physician's office, in a hospital outpatient clinic, or in an emergency room. It is assumed in this analysis that an outpatient clinic would provide essentially the same services for the same cost as a physician's office. When diagnosis occurs in an emergency room, it may be that the patient is experiencing symptoms that require immediate attention or that medical care is unavailable via other means (e.g., they do not have a personal physician. Due to the potentially more serious nature of their symptoms, there *may* be additional services provided. These services may include: a complete blood count (CBC), theophylline administered

[16] The NHLBI does not recommend different evaluations during diagnosis based on severity (severity category is determined during diagnosis, not at the onset of the process).

intravenously, nebulizer therapy, or other services that are medically required (as described by the 1991 physician panel). These added services will lead to increased costs not considered in this analysis. (A description of services and the costs for an emergency room visit are described below.)

Emergency room staff often do not have information available on the medical history of a patient, so may treat each patient entering the emergency room with asthma as a new diagnosis (Physician panel, 1991). That was the assumption made when developing the description of services and costs for the emergency room services discussed below. This description and the associated costs may be relevant for both initial diagnosis in an emergency room and visits to the emergency room that occur after diagnosis. Whether this is the case will depend on the specific hospital's practices, and whether the patient was referred to the emergency room by a physician who provided the patient's medical history to the hospital.

IV.2.B.2.3 Asthma Severity Level

When diagnosed with asthma, the severity of the patient's disease is evaluated and a severity category is assigned. These categories are subsequently used to develop an asthma management plan for the patient. The National Heart, Lung, and Blood Institute (1997) has developed a classification scheme for asthma by severity of disease. Patients are diagnosed at their initial visit (or a subsequent visit to a specialist) with either mild intermittent, mild persistent, moderate persistent, or severe persistent asthma based on this classification scheme. Treatment plans and costs vary depending on the severity of the asthma. The classification scheme, shown in Table IV.2-5, shows symptoms and lung function measures that are used to categorize asthma (NHLBI, 1997).

Recent information was not located in the literature regarding the distribution of patients into the various categories listed above. Estimates are available from the 1991 physician panel: approximately 70 percent of asthmatics have mild asthma, 25 percent have moderate asthma, and 5 percent have severe asthma. In their 1997 publication, NHLBI separated mild asthma into two components, intermittent and persistent (NHLBI, 1997). For purposes of this analysis, it is assumed that half of those with mild asthma are in each diagnostic category.

It is also assumed that the 1991 panel's estimate of the percentage of patients in each category is currently accurate. Due to increases in the occurrence and acute services use by asthmatics in recent years, it is possible that more patients are now in the moderate and severe asthma categories than in the past. Uncertainty exists regarding this distribution because data on the current severity distribution are not available. This uncertainty does not impact service utilization, which is not based on severity in this analysis (it is based on national statistics and the results of

studies of service utilization). Severity categories are used, however, to estimate drug therapy use and cost. Consequently, if the severity distribution among asthma patients is currently more severe than it was in 1991, the costs of drug therapy will be underestimated. As better information becomes available and/or practices change, the percentages can be modified to reflect current knowledge.

In this analysis, patients were assumed to retain the severity level that they were originally diagnosed up to age 18. Beyond that age it was assumed that 30 percent become symptom-free (Eggleston, 1994; see discussion in Section IV.2.A.5). The remaining 70 percent continue to require treatment at the severity level at which they were originally diagnosed. As with the severity distribution, the percentage of patients becoming symptom-free may differ from estimates made in the past.

Link to Section IV.2.A.5

Table IV.2-5: Classification of Asthma Severity			
Clinical Features Before Treatment*			
	Symptoms**	**Nighttime Symptoms**	**Lung Function**
STEP 4 Severe Persistent	• Continual symptoms • Limited physical activity • Frequent exacerbations	Frequent	• FEV_1 or PEF $\leq$ 60% predicted • PEF variability > 30%
STEP 3 Moderate Persistent	• Daily symptoms • Daily use of inhaled short-acting $beta_2$-agonist • Exacerbations affect activity • Exacerbations $\geq$ 2 times a week; may last days	> 1 time a week	• FEV_1 or PEF > 60%-<80% predicted • PEF variability > 30%
STEP 2 Mild Persistent	• Symptoms > 2 times a week but < 1 time a day • Exacerbations may affect activity	> 2 times a month	• FEV_1 or PEF $\geq$ 80% predicted • PEF variability 20-30%
STEP 1 Mild Intermittent	• Symptoms $\leq$ 2 times a week • Asymptomatic and normal PEF between exacerbations • Exacerbations brief (from a few hours to a few days); intensity may vary	$\leq$ 2 times a month	• FEV_1 or PEF $\geq$ 80% predicted • PEF variability < 20%

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

** Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

IV.2.B.2.4 Drug Therapy During Diagnosis

A patient is initially diagnosed with asthma may receive two types of drug therapies that are consistent with the two aspects of managing asthma:

1) *Long-term care*. The patient will receive a management plan that includes long-term drug therapy for control of their disease. If this management plan adequately controls symptoms, the patient will be maintained on that plan, with subsequent review to determine if dosages can be "stepped down" and still maintain control over the disease.

2) *Episodic care*. A patient diagnosed in response to an asthma episode will receive drugs during the visit to address current symptoms. These will be short-acting drugs that are used in response to asthma episodes rather than for long-term disease management.

In both cases, the drug regimens do not differ from those that would be used under similar circumstances after initial diagnosis. Consequently, they are discussed below under the two relevant headings: Long-term Management and Management of Acute Episodes. The specific therapeutic drugs that are recommended for use when asthma is initially diagnosed vary, depending on the disease symptoms, patient characteristics, and the physician's prescribing habits. There are two main groups of drugs used to treat asthma, one for long-term management of the disease and one for quick relief of symptoms.

In the cost section below, drug costs are assumed to begin when the diagnosis is made at age four. The drugs prescribed or given in the physician's office at diagnosis will be the same as those used during the subsequent long-term management and quick-relief management. Consequently, the specific drugs are discussed below under those two headings. Separate drug costs are not assigned to the diagnostic process because they are the same as those itemized under the Drug Therapies section below.

IV.2.B.2.5 Referral to Specialists During Diagnosis

Most people with asthma are diagnosed by and receive care from a primary care physician. NHLBI does not suggest that diagnostic procedures vary depending on the severity category in which the patient may be ultimately diagnosed. Consequently, it is assumed that all patients will undergo similar diagnostic procedures, although NHLBI recommends referral to specialists in asthma treatment (e.g., a pulmonologist) under specific circumstances. The conditions leading to referal are related to ongoing care and meeting treatment goals unrelated to the initial diagnosis; consequently, they are not discussed in this section. Some criteria are relevant at diagnosis, and one (criterion 5) is related to the severity category of the patient. The criteria are:

1) signs and symptoms are atypical or there are problems in differential diagnosis;

2) other conditions complicate asthma or its diagnosis;

3) additional diagnostic testing is indicated (e.g., allergy testing, complete pulmonary function studies, rhinoscopy, provocative challenge, bronchoscopy);

4) patient is being considered for immunotherapy;

5) patient has severe persistent asthma (Step 4, as shown in Table IV.2-5), or is under age three and has moderate or severe persistent asthma (Step 3 or 4) and in some cases mild persistent asthma (Step 2); and

6) patient has significant psychiatric, psychosocial, or family problems that interfere with asthma therapy. (NHLBI, 1997, refer to this source for additional detail)

Link to Table IV.2-5

Referral to a specialist occurs when a patient's asthma or some other health characteristic is complex and requires more sophisticated investigation and/or treatment. This analysis does not attempt to speculate on what specialized treatment would be provided because the reasons for referral and the resulting treatments vary widely. The analysis assumes that the cost of treatment by a specialist would be the same as the cost of the initial office visit for diagnosis. This is a conservative assumption, because it is likely that the treatment would be at least as complex (and costly) as the initial office visit for diagnosis.

It is not known what percentage of patients may experience any of the above, but an estimate can be made for criterion 5. As discussed previously, the 1991 physician panel provided an estimate of the percentage of individuals who fall into each severity category. Using this information, the percentage of patients who would be referred to a specialist based on criterion 5 can be estimated. It was estimated in 1991 that 70 percent of asthmatics have mild asthma (35 percent persistent, 35 percent intermittent), 25 percent moderate, and 5 percent severe asthma. Using this information with criterion 5, an estimate of the number of patients who will see a specialist following their initial visit with a primary care physician was made as follows:

For severe asthma: the 5 percent of patients with severe asthma will all be assumed to consult a specialist.

For moderate asthma: the criterion is age-related. There is not a distribution of ages of diagnosis available; however, if four years is the median age of diagnosis (50 percent above and 50 percent below), then it will be assumed that half of all patients were diagnosed at age three or younger. Thus, one half of the 25 percent of patients with moderate asthma, or 12.5 percent of all asthma patients, will be assumed to consult with a specialist.

For mild asthma: there is not quantitative guidance provided for those with mild asthma. Based on the numerous criteria for referral to specialists, the substantial number of very young children who have asthma (and are more difficult to evaluate and treat) and the statement that some cases of mild persistent asthma will require referral to a specialist, it was assumed that one half of those with mild asthma, or 35 percent of all asthma patients, will consult a specialist. ***Aggregating the three categories above, the total percentage of patients who are assume to consult with a specialist***

following initial consultation with a primary care physician is 52.5 percent.

It was assumed that patients meeting this criterion would meet with a specialist after the first diagnostic visit, for additional diagnosis and planning evaluations. As noted above, the specific additional evaluations that are performed in this visit will vary depending on the reason for referral and patient characteristics. Consequently, the specific activities cannot be estimated. It is reasonable to assume that they will be at least as complex (and as costly) as those provided by the primary care physician in the first diagnostic visit.

IV.2.B.2.6 Level of Visit and Number of Visits for Diagnosis

To estimate the costs of office visits, it is necessary to specify the level of visit (1 to 5), which is determined by the length of the visit. Visits for asthma include a number of activities related to the initial diagnosis, including the determination of the appropriate treatment plan through tests, history taking, physical exam and evaluation, explanation of the disease and management plan to the patient (or parent), and patient education regarding drugs and equipment. A second visit follows shortly after diagnosis to determine if the treatment plan is managing the disease adequately; additional patient education may also be provided.

NHLBI has emphasized the importance of education and the management of asthma by the patient and physician as key elements of care. Emphasis is also placed on quality of life issues, which is closely tied to adequate disease management (NHLBI, 1997). These foci require considerable time be spent by medical staff on training and education of patients. This is particularly true due to the daily need for self-medication for many asthmatics and the use of inhalers and peak flow meters. The result of all this is a requirement that more time be spent during office visits than is spent for many other chronic diseases.[17] Due to the time requirements, this analysis assumes that a single maximum duration (level 5) office visit would be used for the initial diagnostic consultation.

[17] Consultation with one pediatrician who treats many asthma cases suggests that considerable time is required for adequate patient education. He routinely spent one hour or more explaining the disease and training the patient, which was followed by later consultations with nurse practitioners. It was felt that this time investment was necessary to ensure that patients understood their treatment plans, how to avoid asthma triggers, how to use inhalers and peak flow meters, and other aspects of their disease.

NHLBI guidelines indicate that the first diagnostic visit is followed shortly by another visit to determine if the management plan is adequate for the patient, and to make any necessary adjustments. Additional patient education may also be provided.[18] This analysis assumes that a second visit will follow the first within a short time frame as part of the diagnostic process. Within the set of those patients who require adjustment of their treatment plans at this visit, there may be a subset that require another visit to determine if the modified plan was optimal. The percentage of patients requiring this third visit is not known. Consequently, this visit and any subsequent planning visits related to initial diagnosis are not included. The assumption that only two visits are required will cause an underestimate of medical cost in this analysis.

IV.2.B.3 Long-term Management

Long-term management of asthma involves ongoing use of medications and asthma trigger avoidance by patients. It also requires periodic assessments and monitoring by medical care providers. For purposes of cost evaluation the focus of this discussion is on:

1) the office visits or hospital outpatient visits that occur, and
2) the drug therapy regimen that is prescribed for the patient.

No skilled nursing or therapeutic services are typically provided to asthmatics in their homes, so costs for such services are not included in this analysis. It is assumed that severe asthmatics will use a nebulizer with compressor in the home on an ongoing basis. This cost (which is minimal) is listed with drug therapy, since it is self-administered and is more closely related to drug therapy than to medical services.

As discussed above, the frequency and complexity of long-term care depends substantially on the patient receiving an adequate treatment plan, understanding it, and complying with it (particularly self-administered drug regimens). Consequently, an estimate of the patient's use of treatment and services and their cost is provided for an average patient, as well as for high-use patients. When a patient is managing their exposures to asthma triggers adequately and self-administers drugs that prevent asthmatic crises, the course of their therapy and resulting costs for many patients may be fairly predictable. When management is inadequate, there will be asthma episodes requiring different self-administered drugs, more office and emergency room visits, and potential hospitalization (discussed in the following section). In either case, there will be office visits and self-medication.

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[18] It has been observed that many patients need to be checked for use of their asthma therapy equipment. At one children's asthma camp, it was observed that as few as ten percent of patients appeared to be using their inhalers correctly (Aligne, 1999).

IV.2.B.3.1 Long-term Management for the Average Patient

IV.2.B.3.1.1 Office Visits

The number of office visits an average asthma patient makes per year was estimated using CDC data reported in Section IV.2.A to be 0.707 (see Table IV.2-1). The services provided during office visits are shown in Table IV.2-4 (based on information from the 1991 physician panel and a review of information in NHLBI guidelines). The categories of services shown in the table below are those specified for Medicare reimbursement and do not provide detailed descriptions of services. For example, the activities of the physician (e.g., history taking, discussion of symptoms, education of the patient, etc.) are not specifically listed in the table, but are assumed to fall under the category of "office visit."

Link to Table IV.2-1
Link to Table IV.2-4

Table IV.2-6: Asthma: Description of Follow-Up Care by Severity Level

Chest X-Ray, Two Views
Assay for Theophylline
Breathing Capacity Test
Office Visit, Level 5, Established Patient
Drawing Blood for Specimen

For some patients who have difficulty managing their asthma through treatment plans, NHLBI recommends additional evaluations and activities that are similar to those listed under Section IV.A.2.5, above(e.g., allergy testing, immunotherapy). These additional steps will result in additional costs that are not considered in this analysis, due to a lack of detailed information on their use, and will cause an underestimate of total costs.

Link to Section IV.A.2.5

IV.2.B.3.1.2 Drug Therapies

As noted above, no data are available on the actual practices of asthmatics regarding drug use. Consequently, NHLBI guidelines were used as an estimate of drug use and costs. Aside from drugs administered during acute episodes in a medical care setting, most asthma drugs are self-administered, following directions provided by a physician. NHLBI recommends that most patients be treated with self-administered long-term asthma medications to reduce inflammation. All patients but those with

mild intermittent asthma (approximately 35 percent of patients) are encouraged to have daily anti-inflammatory medication. NHLBI also recommends the self-administration of "quick-relief" medications to deal with asthma episodes. The type of drugs, their quantity, and their frequency of use depends on the severity of the asthma and specific characteristics of the patient. Pharmaceutical usage is discussed by level of asthma severity in this analysis because it is not possible to determine the distribution of specific patient characteristics. Both the costs of various drug alternatives, and drug costs for different management plans, will vary.

Although NHLBI drug therapy guidelines were used in this analysis to estimate drug costs, the distribution of drugs between long-term management and quick relief medications may differ among patients. Among patients whose asthma is not well managed, there may be a greater use of quick-relief medications for acute episodes and less use of drugs used for long-term management among many patients. Study data (discussed below) suggest that many patients do not manage their disease in a manner that provides long-term low-level care, but rather use medication when they experience symptoms. As described in Section IV.2.A, a lack of disease management causes asthma attacks. Consequently, those who don't use preventive long-term care drugs are likely to need a greater amount of short-term relief medications. Given this trade-off, the drug costs are not expected to differ substantially among patients in the average versus high-use categories considered in this analysis (although hospitalization and emergency room use are, as discussed below).

The NHLBI recommends the therapies shown in Table IV.2-5 for initial management planning for children age five and under, and those shown in Table IV.2-6 for patients older than five years of age.

Table IV.2-7: Stepwise Approach for Managing Asthma in Infants and Children under 6 Years of Age
Adapted from NHLBI, 1997. Sections dealing with education and cautions are not included.

	Long-term Control	**Quick Relief***
STEP 4 Severe Persistent	Daily medications: • Daily anti-inflammatory medicine — High-dose inhaled corticosteroid with spacer/holding chamber and face mask — If needed, add systemic corticosteroids 2 mg/kg/day and reduce to lowest daily or alternate-day dose that stabilizes symptoms *beclomethasone dipropionate*	• Bronchodilator as needed for symptoms (see step 1) up to 3 times a day *albuterol* .
STEP 3 Moderate Persistent	Daily medication: • Daily anti-inflammatory medication. Either: — Medium-dose inhaled corticosteroid with pacer/holding chamber and face mask OR, once control is established: — Medium-dose inhaled corticosteroid and medocromil OR — Medium-dose inhaled corticosteroid and long acting bronchodilator (theophylline) *beclomethasone dipropionate*	• Bronchodilator as needed for symptoms (see step 1) up to 3 times a day *albuterol*
STEP 2 Mild Persistent	Daily medication: Daily anti-inflammatory medication. Either: — Cromolyn (nebulizer is preferred; or MDI) or nedocromil (MDI only) — Infants and young children usually begin with a trial of cromolyn or nedocromil OR — Low-dose inhaled corticosteroid with spacer/holding chamber and face mask *cromolyn*	• Bronchodilator as needed for symptoms *albuterol.*
STEP 1 Mild Intermittent	• No daily medication needed.	• Bronchodilator as needed for symptoms $\leq$ 2x / week Inhaled short-acting beta2-agonist by nebulizer or face mask and spacer/holding chamber *albuterol*
Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.		**Step up** If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control (avoidance of allergens or other factors that contribute to asthma severity).

Table IV.2-7: Stepwise Approach for Managing Asthma in Infants and Children under 6 Years of Age

Adapted from NHLBI, 1997. Sections dealing with education and cautions are not included.

	Long-term Control	Quick Relief*

NOTE:

- The stepwise approach presents general guidelines to assist clinical decision making; it is not intended to be a specific prescription. Asthma is highly variable; clinicians should tailor specific medication plans to the needs and circumstances of individual patients.
- Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition or starting at a higher level of therapy (e.g., a course of systemic corticosteroids or higher dose of inhaled corticosteroids).
- A rescue course of systemic corticosteroids may be needed at any time and at any step.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may be especially common with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- At each step, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diagnosis and education.
- Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be considered if the patient requires step 3 care.

* In all quick relief cases, the “intensity of treatment depends on severity of exacerbation” (NHLBI, 1997).

Table IV.2-8: Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age: Treatment
Adapted from NHLBI, 1997. Sections dealing with cautions are not included.

	Long-term Control	Quick Relief	Education
STEP 4 Severe Persistent	Daily medications: • Anti-inflammatory: inhaled corticosteroid (high dose) AND • Long acting bronchodilator: either long acting inhaled $beta_2$ -agonist, sustained-release theophylline, or long acting $beta_2$ -agonist tablets AND • Corticosteroid tablets or syrup long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids) *beclomethasone dipropionate*	• Short-acting bronchodilator: inhaled $beta_2$ -agonists as needed for symptoms. *albuterol* .	Steps 2 and 3 actions plus: • Refer to individual education/counseling
STEP 3 Moderate Persistent	Daily medication: • Either Anti-inflammatory: inhaled corticosteroid (medium dose) OR Inhaled corticosteroid (low-medium dose) and add a long acting bronchodilator, especially for nighttime symptoms; either long acting inhaled $beta_2$ -agonist, sustained-release theophylline, or long acting $beta_2$ -agonist tablets. *beclomethasone dipropionate*	• Short-acting bronchodilator: inhaled $beta_2$ -agonists as needed for symptoms. *albuterol*	Step 1 actions plus: • Teach self-monitoring • Refer to group education if available • Review and update self-management plan

Table IV.2-8: Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age: Treatment
Adapted from NHLBI, 1997. Sections dealing with cautions are not included.

	Long-term Control	Quick Relief	Education
STEP 2 Mild Persistent	One daily medication: • Anti-inflammatory: either inhaled corticosteroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil). • Sustained-release theophylline to serum concentration of 5-15 mcg/mL is an alternative, but not preferred, therapy. Zafirlukast or zileuton may also be considered for patients ≥12 years of age, although their position in therapy is not fully established. *cromolyn*	• Short-acting bronchodilator: inhaled $beta_2$ -agonists as needed for symptoms. *albuterol.*	Step 1 actions plus: • Teach self-monitoring • Refer to group education if available • Review and update self-management plan
STEP 1 Mild Intermittent	• No daily medication needed.	• Short-acting bronchodilator: inhaled $beta_2$ -agonists as needed for symptoms. *albuterol*	• Teach basic facts about asthma • Teach inhaler/spacer/holding chamber technique • Discuss roles of medications • Develop self-management plan • Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations • Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants
Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.		**Step up** If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control (avoidance of allergens or other factors that contribute to asthma severity).	

Table IV.2-8: Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age: Treatment
Adapted from NHLBI, 1997. Sections dealing with cautions are not included.

	Long-term Control	Quick Relief	Education

NOTE:

- The stepwise approach presents general guidelines to assist clinical decision making; it is not intended to be a specific prescription. Asthma is highly variable; clinicians should tailor specific medication plans to the needs and circumstances of individual patients.
- Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition, or starting at a higher level of therapy (e.g., a course of systemic corticosteroids or higher dose of inhaled corticosteroids).
- A rescue course of systemic corticosteroids may be needed at any time and at any step.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may be especially common with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- At each step, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diagnosis and education.
- Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be considered if the patient requires step 3 care.

The tables list drug options for each severity category. Data were not available on which drugs, of the many options, were actually used by a specific percentage of patients. Consequently, drugs were selected for purposes of cost estimation in this analysis because they were referred to or recommended frequently in the literature reviewed for this work. The selected drugs are listed in italics following each recommendation in the tables. Specific drug options in each drug category (e.g., beta2- agonists) are shown in Appendix IV.2-B with recommended doses for different ages and weights.

Some drugs are specified as "if needed" by NHLBI. Because they are not prescribed for all patients and information is lacking on the percentage of patients receiving these discretionary drugs, it was assumed that they were not prescribed for the average patient and they are not listed in the tables.[19] This is a cost-conservative assumption.

IV.2.B.3.2 Long-term Management for the High-use Patient

Patients who are not in compliance with NHLBI guidelines or other management plans are likely to spend less effort and money "managing" their disease through long-term drug therapy, and have a higher frequency of emergency room visits, hospitalizations, and sick visits to doctors' offices or clinics. Although actual practices are not well documented nor known at the national level, a number of studies have been carried out to evaluate specific intervention programs for "high-use" patients. These studies indicate that the frequency of visits to emergency rooms, hospitals, and doctors' offices or clinics to treat acute episodes can be substantially greater than for the average asthmatic. Some of these study results were summarized in Tables IV.2-2 and IV.2-3.

Link to Tables IV.2-2
Link to Table IV.2-3

IV.2.B.3.2.1 Office Visits

Two of the studies listed in Table IV.2-3 above (Higgins et al., 1998; and Westley et al., 1997) examined the rate of office visits among "high-use" patients before and after an intervention program. These studies suggest that the frequency of visits to doctors' offices or clinics among these "high-use" patients may be substantially greater than the frequency for the average asthmatic. The average frequency of visits (averaged over the two studies) was almost five times the frequency for the average asthmatic (3.491 per year versus 0.707 per year). Based on this information, the hypothetical high-use patient is estimated to visit a physician's office (or outpatient clinic) 3.491 times per year. Although these visits are listed under "long-term management" they are likely to be used mainly to address short-term medical needs rather than for checkups, planning, or education,

[19] Refer to NHLBI for additional information on these medications and recommendations.

due to the nature of the asthma management approach taken by these patients and their caregivers. The proportion of each type of office visit is not known.

IV.2.B.3.2.2 Drug Therapies

As discussed above, NHLBI guidelines regarding drug therapy are used for estimating treatment and costs for all asthma patients. Section IV.2.B.3.1.2 above provides details on drug therapy, and additional detail is provided in Appendix IV.2-B. Patients who are not in compliance with NHLBI guidelines are expected to use medication when they experience symptoms rather than use long-term management. Those who do not use long-term care drugs are likely to need a greater amount of short-term relief medications. There is not sufficient information in the literature to quantitatively determine the trade-offs in drugs used or costs incurred. Given the lack of data and the likelihood that underuse of preventive medication will result in greater use of short-acting medications, this analysis assumes that drug costs do not differ substantially among patients with different management strategies (although office visits, hospitalization, and emergency room use differ, as discussed below).

Link to Section IV.2.B.3.1.2

IV.2.B.4 Acute Care

IV.2.B.4.1 Acute Care for the Average Patient

IV.2.B.4.1.1 Emergency Room Visits

As discussed above, emergency room visits result when asthma episodes cannot be managed by the patient or family members sufficiently well to provide relief to the patient. The patient may be experiencing a life-threatening episode, or a relatively mild episode on arrival to the emergency room. Care will therefore vary widely. As discussed in Section IV.2.A, the likelihood of an asthma patient vising an emergency room is 0.117 annually. The procedures anticipated to occur, based on the 1991 physicians panel and NHLBI guidelines, are shown in Table IV.2-9. The emergency room services are not assume to be related to severity category because mild or severe exacerbations can occur among asthma patients in any severity category (NHLBI, 1997).

Table IV.2-9: Services provided in Hospitals to Asthma Patients
Chest X-Ray, 2 Views
Assay for Theophylline
Blood Gases: pH, pO2, pCO2
Automated Hemogram
IV Infusion Therapy, 1 Hour
Breathing Capacity Test
Airway Inhalation Treatment
ER Visit, Level 5
Drawing Blood for Specimen

IV.2.B.4.1.2 Hospitalization

Hospitalization occurs when the patient requires care beyond what can be provided in the emergency room — either specific therapies or observation and care that requires a longer period to provide. As discussed in Section IV.2.A, the likelihood of an average asthma patient being hospitalized is 0.034 annually. Hospital cost reimbursements are specified by Medicare, based on the patient's diagnosis in a diagnostically related group (DRG). This system is used widely by many medical cost reimbursement systems. Due to the use of this system, it is not necessary to list specific services provided in the hospital to estimate the costs of hospitalization, and they are not described in this analysis.

IV.2.B.4.2 Acute Care for High-use Patients

Failure to properly manage relatively severe asthma results in a much greater occurrence of acute episodes and greater utilization of more expensive acute care facilities. Utilization rates of acute care facilities (i.e., emergency rooms and hospitals) among "high-use" asthmatics can be many times the rates among the general population of asthmatics. Using the average of the "before intervention" rates in the studies listed in Table IV.2-3, the average rate of hospitalization in this group was estimated to be over 20 times the average rate among all asthmatics (0.732 per patient per year versus 0.034 per patient per year). The average rate of emergency room visits was estimated to be 1.663 per patient per year, over ten times the rate in the general population of asthmatics of 0.117. These higher values are used in the cost analysis below to estimate the annual and lifetime costs for the hypothetical high-use patient.

Link to Table IV.2-3

IV.2.B.5 Annual Cost of Treatment and Services

IV.2.B.5.1 Overview

The goal of this analysis is to determine the lifetime incremental direct medical cost of asthma. This section aggregates the annual costs for the following:

- office visits,
- drug therapy,
- emergency room care, and
- hospitalization.

The cost of diagnosis is also described, although that is incurred only once, rather than annually.

The medical costs are estimated for the average patient and for hypothetical high-use patients. Most costs for treatments and services were estimated using the Medicare reimbursements system. This system provides support for care for the elderly and the disabled. Consequently, recipients span all ages. There are specific reimbursements for many services for children (ages 0 to 17), which are used in this analysis. Medicare reimbursements charges generally fall between Medicaid reimbursement and self-pay or private insurance reimbursement. The use of Medicare data has both advantages and disadvantages, discussed in Chapter I.1.

Link to Chapter I.1

Although the arguments for and against using Medicare data to estimate costs are complex, these data are used in this case primarily because they are national cost data that have been judged, for this application, to be a reasonable proxy for the direct medical costs of services for asthma. Medicare payments are thought to be reasonably representative of the national costs of medical care because the Medicare program is the largest national payer for health care services. The Health Care Financing Administration (HCFA), which administers the Medicare program, has conducted a considerable amount of research into the actual resource costs of providing medical services, and has used this research in establishing Medicare payment rates. Moreover, Medicare payment methodologies and payment rates are often used by private payers and state Medicaid programs as a starting point in establishing their own methodologies and rates, and Medicare payment rates usually fall somewhere between Medicaid payment rates and private payer payment rates. Finally, data regarding Medicare payment rates are readily available from HCFA.

The services described for diagnosis, long-term management and management of acute episodes were mapped to actual CPT/HCPCS codes, which are used by the Medicare program to identify and pay for physician services and outpatient services.[20] Hospital costs are based on the admitting diagnosis and any subsequent diagnoses.

IV.2.B.5.2 Costs of Diagnosis

The cost of diagnosis is assumed to be the same for all patients and to occur only once during a lifetime. It was assumed that diagnosis occurred in a physician's office for this analysis. Diagnosis can also occur in an emergency room, which may lead to higher costs. Those costs would be best represented by the emergency room costs discussed in the next section. As discussed above, emergency room care usually does not rely on previous medical diagnosis and care; the patient goes through essentially the same procedures as diagnosis of a new case of asthma.

Medicare payment for most services provided in a physician's office is determined under the Medicare physician fee schedule. One exception to the Medicare physician fee schedule is made for clinical laboratory services, for which payments are determined under a separate fee schedule. Both the Medicare physician fee schedule and the Medicare clinical laboratory fee schedule used for the purposes of this analysis are effective for Calendar Year 1999. The treatments and services discussed above are included in Table IV.2-10 below, with relevant codes to link to Medicare's reimbursement system.

[20] The services identified in the tables represent one possible treatment profile. Actual practice patterns are variable across physicians, across specialties, and even across geographic areas. The cost estimates provided in the following tables should therefore be regarded with an understanding of this limitation.

Table IV.2-10: Costs of Diagnosis					
CPT Code	CPT Description	Source	1999 RVUs	1999 Physician Conversion Factor	1999 Medicare Payment
71020	Chest X-Ray, Two Views	Physician Fee	1.00	$34.73	$34.73
82803	Blood Gases: pH, pO2,	Clinical Lab Fee			$26.74
85025	Automated Hemogram	Clinical Lab Fee			$10.74
94010	Breathing Capacity Test	Physician Fee	0.88	$34.73	$30.56
99205	Office Visit, Level 5, New	Physician Fee	4.00	$34.73	$138.93
G0001	Drawing Blood for	Carrier Manual			$3.00
Total					$244.70

Under the Medicare physician fee schedule, the payment for a given service is determined using relative value units (RVUs), geographic practice cost indices (GPCIs), and a conversion factor (CF). RVUs measure the relative time, effort, and expense that physicians incur when providing services. The Resource Based Relative Value Scale (RBRVS) used by HCFA for the Medicare program expresses the RVUs for all services on a single scale. Under the RBRVS, there are separate RVUs for physician work (PW), practice expense (PE), and malpractice expense (ME). GPCIs are used to adjust RVUs for regional cost variations. There are separate GPCIs for physician work, practice expense, and malpractice expense RVUs. Finally, a CF quantifies the dollar value of one relative value unit and converts the RVUs associated with each service into a fee amount. Hence, the general formula for determining payment under the Medicare physician fee schedule for a given service is expressed as follows:

$$\text{Allowed Charge} = [(RVU_{PW} \times GPCI_{PW}) + (RVU_{PE} \times GPCI_{PE}) + (RVU_{ME} \times GPCI_{ME})] \times CF$$

As shown in Table IV.2-10, the 1999 Medicare payment for CPT codes 99203, 99204, 99205, 71020, and 94010 are determined under the Medicare physician fee schedule. CPT codes 99203, 99204, and 99205 describe office visits of increasing complexity for new patients; CPT code 71020 describes a two view chest X-ray; and CPT code 94010 describes spirometry, a breathing capacity test. National cost estimates were developed in this analysis; the GPCIs were not used to adjust the RVUs for these services. The 1999 Medicare payment for CPT codes 82803 (arterial blood gases) and 85025 (an automated complete blood count) are determined under the Medicare clinical laboratory fee schedule. Again, national cost estimates were developed, so the national limits under the Medicare clinical laboratory fee schedule were used in Table IV.2-10.

Finally, there is a nominal payment for HCPCS code G0001, routine venipuncture. The total Medicare payment for a patient diagnosed in the physician's office with asthma is $244.70 for the initial visit.

As discussed above, there is a second visit to confirm that the management plan is working properly. This visit is assumed to involve the same diagnostic procedures. Like the initial visit it involves time to discuss issues with the patient and do additional training. Consequently, the cost of this second visit is assumed to be the same as for the first visit. The total cost of diagnosis for patients who do not see a specialist is estimated as the cost of two visits, which equals $489.40.

As discussed in Section IV.2.B.2.5, 52.5 percent of all patients are assumed to be referred to a specialist during the initial diagnostic process. This referral will add a single additional office visit to the cost above for 52.5 percent of patients. This yields a total cost of:

$244.70 × 2 + .525 ($244.70) = $617.87

The average total cost for diagnosis is estimated to be $617.87

Link to Section IV.2.B.2.5

There are likely to be drugs provided by the physician at the time of diagnosis. Those costs are incorporated into the drug therapy costs discussed below under long-term management.

V.2.B.5.3 Cost for the Average Patient

IV.2.B.5.3.1 Office Visits

Table IV.2-11 provides the 1999 Medicare payment for follow-up care provided in a physician's office for patients with mild asthma, moderate asthma, and severe asthma. As discussed earlier, the Medicare payment for services provided in a physician's office is determined by the Medicare physician fee schedule and the Medicare clinical laboratory fee schedule.

As shown in Table IV.2-11, the 1999 Medicare payment for CPT codes 99215, 71020, and 94010 are determined under the Medicare physician fee schedule. CPT code 99215 describes an office visit of level 5 for established patients; CPT code 71020 describes a two-view chest X-ray; and CPT code 94010 describes spirometry, a breathing capacity test. The 1999 Medicare payment for CPT code 80198 (assay for theophylline) is determined under the Medicare clinical laboratory fee schedule. The national limit under the Medicare clinical laboratory fee schedule was used in Table IV.2-11. Finally, there is a nominal payment for HCPCS code G0001, routine venipuncture.

Table IV.2-11: Asthma: Cost of Office Visit					
CPT Code	CPT Description	Source	1999 Medicare RVUs	1999 Medicare Conversion Factor	1999 Medicare Payment
71020	Chest X-Ray, Two Views	Physician Fee	1.00	$34.74	$34.74
80198	Assay for Theophylline	Clinical Lab Fee Schedule			$19.56
94010	Breathing Capacity Test	Physician Fee	0.88	$34.73	$30.56
99215	Office Visit, Level 5, Established Patient	Physician Fee Schedule	2.82	$34.73	$97.94
G0001	Drawing Blood for Specimen				$3.00
					$185.80

The total Medicare payment for follow-up care provided in a physician's office to a patient with asthma is estimated to be $185.80. ***Using the average patient rate of 0.707 visits per year, the average annual cost of office visits per patient is estimated to be $131.36.***

IV.B.5.3.2 Cost of Drug Therapy

As discussed previously, the NHLBI recommends specific drug therapies for children five years and younger and for those older than five, for each severity category. These therapies were listed in Tables IV.2-5 and IV.2-6 in Section IV.2.B.3 above. As discussed in that section, data were not available on which drugs were actually used by a specific percentage of patients, so drugs were selected from the numerous options that were referred to or recommended frequently in the literature reviewed for this work. The selected drugs are listed in italics following each recommendation in the above-cited tables.[21]

Link to Table IV.2-5
Link to Table IV.2-6

The selected drugs are listed in Table IV.2-12 with the dose and frequency of use. Their use is then converted to units (e.g., one inhaler) and the unit cost is listed, followed by the annual cost. The final column contains the weighted cost calculated as the percentage of patients in the severity category (listed in column 1) times the annual cost.

Drug costs were taken from the 1998 Red Book, a reference book used by the pharmacies to obtain prices (Red Book, 1998). The relationship between pharmaceutical average wholesale prices (AWP) cited in the Red

[21] Specific drug options in each drug category (e.g., beta-2 agonists) are shown in Appendix IV.2-B with recommended doses for different ages and weights.

Book and the average retail price has fluctuated dramatically over the last few years. Historically, retail prices were based on a percentage markup over wholesale prices. In some cases, however, the Red Book AWP actually exceeds retail rates. A quick review of prices charged by national pharmacy chains for the most common asthma medications indicated that Red Book prices are very close to those charged by the chains. There are numerous companies marketing the most common drugs, and their prices vary somewhat.

For this analysis, an average cost was estimated by reviewing the spectrum of costs listed in the Red Book . When the HCFA price was provided and it was lower than the average price (e.g., in the case of albuterol tablets) that price was used. (The HFCA price is the maximum price limit determined for payment by the federal government.) When prices were provided for various sizes of packaging, the largest size, which was invariably the least expensive, was used to estimate costs. These prices are likely to vary over time as new products are introduced and market forces continue to play a role in pricing.

Drug therapy costs differ for the youngest patients (ages four and five), and older patients, as shown in the table above. The drug costs per year for each age are used in the lifetime cost analysis, based on the costs incurred at each specific age.

Additional information, not used in the lifetime cost analysis on the average annual cost across all ages, is provided here. The average cost per patient was calculated as a weighted average cost per year. If diagnosis occurs at age four (the average age of diagnosis) and the patient has asthma throughout his or her life (through age 75), then the full lifespan of the disease is 72 years. Two of those years are at the lower cost for drug therapy of $471.40, and 70 are at the higher cost of $615.14. The average annual cost per patient is calculated as:

$$[2 \times \$471.40 + 70 \times \$615.14] / 72 = \$611.15$$

Table IV.2-12: Drug Costs for Asthma Therapy: Long-term and Acute Management (Adapted from NHLBI, 1997. Additional detail provided in Tables IV.2-5 and 6 above.)							
Severity (% in Category)	**Drugs**	**Dose**	**Frequency**	**Units per Year**	**Cost per Unit in $**	**Annual Cost in $**	**Proportional Annual Cost (cost * % in category)**
Children age 5 and under							
1 (35%)	albuterol	2 puffs	2 × /week	1 inhaler	25	25	8.75
2 (35%)	albuterol	2 puffs	2 × /week	1 inhaler	25	25	8.75
	cromolyn	2 puffs	1 × /day	3.7 inhalers	70	259	90.65
3 (25%)	albuterol	2 puffs	3 s /day	10.95 inhalers	25	274	68.50
	beclomethasone dipropionate	8 - 16 puffs (assume 12)	over the day	21.9 inhalers	40	876	219.00
4 (5%)	albuterol	2 puffs	3 × /day	10.95 inhalers	25	274	13.70
	beclomethasone dipropionate	> 16 puffs (assume 17)	over the day	31.03 inhalers	40	1241	62.05
Total Annual Average Cost : $471.40							
Children Over age 5 and Adults							
1 (35%)	albuterol	2 puffs	2 × /week	1 inhaler	25	25	8.75
2 (35%)	albuterol	2 puffs	2 × / week	1 inhaler	25	25	8.75
	cromolyn	2 puffs	1 × /day	3.7 inhalers	70	259	90.65
3(25%)	albuterol	2 puffs	3 × /day	10.95 inhalers	25	274	68.50
	beclomethasone dipropionate	12 - 20 puffs (assume 16)	over the day	29.2 inhalers	40	1168	292.00
4(5%)	albuterol	2 puffs	3 × /day	10.95 inhalers	25	274	13.70
	beclomethasone dipropionate	>20 (assume 21)	over the day	38.33 inhalers	40	1533	76.66
	methyl prednisolone	24 mg/day = 6 tablets	over the day	2190 tablets	.50	1095	54.75
	albuterol	4 mg tablets	2 × /day	730 tablets	.0378	28	1.38
Total Average Annual Cost: $615.14							
Cost for both age groups, assuming age of diagnosis of four years (at beginning of year) and death at age 75.							

In addition to the cost of drugs discussed above, patients with severe asthma are urged to have a nebulizer at home as part of their asthma therapy. A nebulizer costs approximately $80.00, and comes with a five-year warranty, yielding an annual cost of approximately $16.00. This cost is assumed to be applicable only to the five percent of patients who are estimated to have severe asthma. The average cost per patient is therefore estimated to be 16 × 0.05 = $0.80. This cost is added to the annual drug cost listed in Table 2-12, yielding a total annual average cost of $472.20 for children under 5 years of age and $615.94 for children five and over and for adults.

Using the assumptions and sources above, the estimated drug therapy cost for the average asthma patient is $611.95.

When lifetime costs are calculated, the stream of costs incurred each year is summed. The costs for ages four and five 4 and 5 are added to the costs for ages 6 through 75, yielding the same average annual cost. This analysis also provides discounted costs (at three, five, and seven percent). When costs are discounted, the average annual cost will differ slightly because the discounting applied to later years yields much lower costs than those incurred in the current or proximal years.

IV.2.B.5.3.3 Costs of Emergency Room Care for the Average Patient

Currently, Medicare payment for outpatient hospital services is determined under multiple methodologies. For example, payment for ambulatory surgical services is determined on the basis of a blend of aggregate hospital outpatient costs and the ambulatory surgical center (ASC) payment methodology, while payment for diagnostic radiology services is determined on the basis of a blend of aggregate hospital outpatient costs and the Medicare physician fee schedule. Medicare payments for most outpatient hospital services are based in part on aggregate hospital outpatient costs; payment rates for individual outpatient services do not exist.

Beginning in 2000, however, Medicare payment for most outpatient hospital services will be determined using a prospective payment system (PPS) based on Ambulatory Payment Classification (APC) groups. A proposed rule for this system was published in the September 8, 1998 *Federal Register* and revised in the June 30, 1999 *Federal Register*. We used these proposed payment rates to develop the cost estimates provided in Table IV.2-8 because the proposed Medicare hospital outpatient PPS assigns payment rates to individual outpatient services. Once again, however, clinical laboratory services will be exempt from the proposed PPS and will continue to be paid under the Medicare clinical laboratory fee schedule. It also should be noted that the proposed PPS applies only to the

facility fee paid to a hospital. Professional services provided by physicians will therefore continue to be paid under the Medicare physician fee schedule.

Link to Table IV.2-8

Under the proposed PPS, each service provided in a hospital outpatient department will be assigned to an APC. An APC represents a group of services with similar resource requirements and clinical characteristics. The payment for the service will be determined as the product of the relative weight for the APC group to which the service is assigned and a CF. The labor-related portion of the CF will be adjusted by the Medicare wage index for inpatient hospital services based on the metropolitan statistical area in which the hospital is located. We did not adjust the national standardized operating amounts because we are developing national cost estimates. Although the proposed PPS will become effective sometime in 2000, the proposed CF published in the *Federal Register* is expressed in 1999 dollars.

Table IV.2-13 provides the 1999 Medicare payment for treating patients with asthma in a hospital emergency room. As shown in Table IV.2-5, the 1999 Medicare payment for CPT codes 99283, 99284, 99285, 90780, 94640, and 71020-TC are determined under the Medicare hospital outpatient PPS. CPT codes 99283, 99284, and 99285 describe emergency department visits of increasing complexity, CPT code 90780 describes one hour of IV infusion therapy, CPT code 94640 describes nebulizer therapy, and CPT code 71020-TC describes the technical component of a two-view chest X-ray. The 1999 Medicare payment for the physician's interpretation of the X-ray (71020-26) is determined under the Medicare physician fee schedule, and the 1999 Medicare payment for CPT codes 80198 (assay for theophylline), 82803 (arterial blood gases), and 85025 (automated complete blood differential) are determined under the Medicare clinical laboratory fee schedule. Finally, there is no payment for HCPCS code G0001 in a hospital setting. The total Medicare payment for a patient diagnosed in a hospital emergency room with asthma is $442.84. The average patient uses an emergency room 0.117 times per year. ***This yields an average annual cost of $51.81 per patient for emergency room visits.***

Link to Table IV.2-5

Table IV.2-13: Cost of Emergency Room Care											
Procedure	CPT Code	CPT Description	Status	Source	APC	APC Description	Proposed APC Relative Weight	Proposed APC Conversion Factor	1999 RVUs	1999 Physician Conversion Factor	1999 Medicare Payment
Chest Radiological Examination	71020-PC	Chest X-Ray, 2 Views, Professional		Physician Fee Schedule					0.33	$34.73	$11.00
Routine Venipuncture	71020-TC	Chest X-Ray, 2 Views, Technical	X	Hospital Outpatient PPS	700	Plain Film	0.80	$51.42			$41.00
Blood Gas Oximetry	80198	Assay for Theophylline	A	Clinical Lab Fee Schedule							$19.56
Blood Theophylline	82803	Blood Gases: pH, pO2, pCO2	A	Clinical Lab Fee Schedule							$26.74
Spirometry	85025	Automated Hemogram	A	Clinical Lab Fee Schedule							$10.74
Complete Blood Count	90780	IV Infusion Therapy, 1 Hour	X	Hospital Outpatient PPS	906	Infusion Therapy Except Chemo	1.93	$51.42			$99.00
Emergency Room Charge	94010	Breathing Capacity Test	X	Hospital Outpatient PPS	971	Level I Pulmonary Tests	0.98	$51.42			$50.00
Theophylline IV	94640	Airway Inhalation Treatment	S	Hospital Outpatient PPS	976	Pulmonary Therapy	0.44	$51.42			$23.00
Nebulizer Therapy	99285	ER Visit, Level 5	V	Hospital Outpatient PPS	95533	High Level ER Visits/Respiratory	3.13	$51.42			$161.00
Physician Charge	G0001	Drawing Blood for Specimen	A	Not Paid in Hospital							$0.00
Total											$442.84

IV.2.B.5.3.4 Cost of Inpatient Hospital Care for the Average Patient

Hospitalization costs are determined by the specific diagnosis that is provided for the patient. The standard form of these diagnoses is the International Classification of Disease codes: ICD-9. Medicare payment for inpatient hospital services is determined under the Medicare hospital inpatient prospective payment system. Under this system, reimbursement is based on the principal and secondary ICD-9-CM diagnosis and procedure codes, and the age and sex of the patient.

1999 Medicare payment reimbursement values are provided for hospital patients with the following principal ICD-9-CM diagnoses:

493.00—Extrinsic Asthma Without Status Asthmaticus
493.01—Extrinsic Asthma With Status Asthmaticus
493.10—Intrinsic Asthma Without Status Asthmaticus
493.11—Intrinsic Asthma With Status Asthmaticus
493.90—Unspecified Asthma Without Status Asthmaticus
493.91—Unspecified Asthma With Status Asthmaticus

There are three DRGs for patients diagnosed with asthma:

DRG 96—Bronchitis & Asthma Age > 17 With Complications
DRG 97—Bronchitis & Asthma Age > 17 Without Complications
DRG 98—Bronchitis & Asthma Age 0-17

Information was not available on the percentage of patients admitted with asthma complications that are directly related to asthma. Those that are unrelated would not have costs attributable to asthma. For this analysis, it is assumed that "asthma without complications" as listed above is relevant (DRG 96). Costs for DRG 97 are provided to demonstrate the cost range that may occur with complications. For children (ages 0 to 17) the Medicare reimbursement system does not make a distinction between patients with and without complications.

As shown above, the reimbursements also differ for children (ages 0 to 17) and adults. The distribution of hospitalizations between children and adults was estimated using the data from CDC (1998a) regarding the number of hospitalizations for different age groups for the years 1993-1994. The percentage of hospital visits made by children (through age 17) was 37.71 percent (rounded to 38 percent), with the balance of admissions for adults (62 percent).

Generally, payment is determined as the product of the relative weight for the DRG to which the patient is assigned and a national standardized operating and capital amount. There are separate national standardized operating amounts for large urban areas and other areas. The labor-related portion of the national standardized operating amount is usually adjusted

by the Medicare wage index for inpatient hospital services, based on the MSA in which the hospital is located. We did not adjust the national standardized operating amounts because we are developing national cost estimates. Medicare does not provide a single national value, but instead provides two values, one for urban areas (metropolitan statistical areas) and one for non-urban areas. Although information is not available on the distribution of asthma hospitalizations geographically, the problem of asthma hospitalizations in urban areas is well-recognized. The values for urban hospitals are therefore used in this analysis.

Table IV.2-14 lists the 1999 Medicare payment for a patient assigned to DRGs 96, 97, or 98 as $3,531.13, $2,648.68, or $3,111.38, respectively, in large urban areas; and $3,338.59, $2,504.26, or $2,941.73, respectively, in other areas. Using the urban area values, an age-weighted cost based on the percentage distribution discussed above can be calculated:

38% × $3111,38 + 62% × $2648.68 = $2824.50.

The average hospitalization cost is estimated to be $2,824.50. This cost is combined with the average rate of hospitalizations for asthma patients of 0.034 per year to yield an ***estimated annual hospitalization cost of $99.43 per patient.***

Table IV.2-14: Asthma: Cost of Inpatient Hospital Care

DRG	DRG Description	ICD-9 Diagnosis Codes	DRG Relative Weight	National Standardized Operating Amount for Large Urban Areas	National Standardized Capital Amount	DRG Payment for Operating and Capital for Large Urban Areas	National Standardized Operating Amount for Other Areas	National Standardized Capital Amount	DRG Payment for Operating and Capital for Other Areas
96	Bronchitis & Asthma Age > 17 With Complications	493.00, 493.01, 493.10, 493.11, 493.90, 493.91	0.7891	$4,096.83	$378.05	$3,531.13	$3,852.83	$378.05	$3,338.59
97	Bronchitis & Asthma Age > 17 Without Complications	493.00, 493.01, 493.10, 493.11, 493.90, 493.91	0.5919	$4,096.83	$378.05	$2,648.68	$3,852.83	$378.05	$2,504.26
98	Bronchitis & Asthma Age 0-17	493.00, 493.01, 493.10, 493.11, 493.90, 493.91	0.6953	$4,096.83	$378.05	$3,111.38	$3,852.83	$378.05	$2,941.73

IV.2.B.5.3.5 Annual Costs for the Average Patient

The total annual medical costs for the average asthma patient sum the costs of office visits, drug therapy, emergency room use, and hospitalizations. These costs, as discussed in the text above, are summarized in Table IV.2-15. The are derived by multiplying the cost of each service times the rate of utilization per patient in a given year. Note that the costs for drug therapy and hospitalization change during childhood; the differing costs are presented at the end of the table.

IV.2-15: Summary of Average Annual Costs for the Average Patient (undiscounted)

Treatment and Service	Cost (1999$)*
Office Visits	131.36
Drug Therapy**: ages 4 and 5 ages 6 to 75	 472.20 615.94
Emergency Room Use:	51.81
Hospitalization: ages 4 to 17 ages 18 to 75	 105.79 90.06
Total: ages 4 to 5 ages 6 to 17 ages 18 to 75	 761.16 904.90 889.17

* The costs are as listed in previous tables The costs for all services are in 1999 dollars, based on Medicare reimbursement amounts. The drug costs are taken from the 1998 Red Book (Red Book, 1998) and were not adjusted because the CPI for this year is not yet available.

**Includes an average annual $0.80 for use of a nebulizer.

IV.2.B.5.4 Costs for the High-use Patient

The cost categories for the high-use patient are the same as those for the average patient: office visits, drug therapy, emergency room use, and hospitalizations. As discussed above, the annual cost of drug therapy for high-use patients is assumed to be the same as for the average patient, even though the actual use of specific drugs (long-term versus short-acting) is expected to differ. The cost of nebulizers are higher, on average, than for average patients, because the proportion of severe asthmatics in the high-use group is higher than among all asthmatics (1 in 6 versus 1 in 20). The annual average cost of a nebulizer, used only by severe asthmatics, is greater than for the average asthmatic ($2.66 per year, averaged over all high-use asthmatics, versus $0.80 per year averaged over all asthmatics), yielding an annual estimated drug cost of $474.06 for children ages four and five and $617.80 for those over age five.

The costs per service in the other categories (e.g., emergency room visit) are assumed to be the same for the average patient and for the high-use patient. The frequency of utilization of each type of service is different, as discussed above and as shown in Table IV.2-3. The costs of a hospitalization are calculated for two separate age categories (ages 0-17, and ages over 17), as are the costs of drug therapy (ages 4 and 5, and ages over 5). As discussed above, the annual cost in each category is derived by multiplying the cost of each service by the rate of utilization of the service (i.e., the average number of times the service is used per year per high-use patient). The utilization rates used in these calculations are given in Table IV.2-3. The total annual costs for the high-use patient are shown in Table IV.2-16.

Link to Table IV.2-3.

Table IV.2-16: Total Annual Costs for the High-use Asthma Patient

Treatment and Service	Cost (in 1999$)
Office Visits	648.66
Drug Therapy* ages 4 to 5 ages 6 to 75	 474.06 617.80
Emergency Room Use	736.45
Hospitalization ages 4 to 17 ages 18 to 75	 2,276.18 1,937.69
Total ages 4 -5 ages 6 to 17 ages 18 to 75	 4,135.35 4,279.09 3,940.60
*Includes an annual average $2.66 for use of a nebulizer.	

The costs for each age group among high-use patients are more than five times the corresponding costs for the average patients described in the previous section. This difference reflects the much higher use of expensive services, such as emergency rooms and hospitals, and the increased number of office visits.

IV.2.B.6. Summary of Lifetime Costs

Lifetime costs are those direct medical costs incurred by the patient from the average age of diagnosis of the disease (four years in this case) to the average age of death of 75 years. The medical costs relevant to each age were summed over the ages 4 to 75 to calculate the estimated lifetime direct medical costs.

As discussed in the prognosis section (Section IV.2.A.5), approximately 30 percent of asthma patients become asymptomatic as they move into adulthood. For this analysis it is assumed that these patients will not incur costs beyond their seventeenth year, although in practice there is a range of ages entering adulthood when people become asymptomatic. The remaining 70 percent of asthma patients are assumed to have the disease throughout their life. It is not assumed that high-use patients will go into asthma remission because : 1) they are based on a higher risk group (moderate and severe asthmatics), and 2) their disease has not been carefully managed (by definition) and their increased use of acute services indicates a higher number of asthma episodes. As discussed in Section IV.2.A, the repeated episodes that occur when asthma is not carefully managed are likely to lead to permanent adverse structural changes in the respiratory system, which is likely to cause this group to have a higher requirement for ongoing medical care.

Link to Section IV.2.A.5

The death rate among asthma patients in 1994 was 0.0004 per patient. Mortality from asthma occurs primarily among the elderly. The impact of deaths on costs is not considered in this analysis due to the very small percentage of patients who die of this disease, the advanced age at which people typically die of asthma (and therefore the very small reduction in cost associated with death), and the impact that discounting has in minimizing costs attributable many decades in the future.[22] Unfortunately, there are also deaths that occur among children and young adults. A precise age distribution is not available for asthma-associated deaths, and asthma mortality was not evaluated in this analysis due to its rarity.

Table IV.2-17 shows the lifetime costs estimated to occur for asthmatic patients both as an undiscounted cost and at discount rates of three, five, and seven percent.

Table IV.2-17: Lifetime Direct Medical Costs for Asthma (in 1999$)

Patient Category	Undiscounted	3%	5%	7%
Average patient	$49,099	$22,447	$15.974	$12.242
High-use Patients	$220,026	$101,459	$72,342	$56,411

[22] While the impact of mortality and an associated reduction in medical costs is small on an individual basis, there are a substantial number of deaths when the rate is considered in light of the entire asthmatic population. Consequently, it would be useful to consider the VSL with the mortality statistics if benefits evaluations were being carried out.

The undiscounted costs for the average patient are approximately $50,000 over the average lifespan. For the hypothetical high-use patient, the lifetime costs are approximately $220,000.

Data reviewed for this analysis suggest that high-use patients are likely to be people in lower socioeconomic groups, in urban areas, and often minorities. The need for acute care and the medical costs borne by these people is considerably higher than for the average asthmatic. Conversely, improvements in their disease management and reductions in the occurrence or severity of disease will result in substantial reductions in costs, as well a concurrent reduction in pain and suffering, disability, and lost school time. The sensitivity analysis that follows is an evaluation of the potential impacts on costs of interventions designed to improve asthma management.

IV.2.C. Sensitivity Analysis

Many aspects of this cost analysis for asthma could be considered in a sensitivity analysis. A single aspect has been selected for evaluation at this time (additional evaluations may be done at a future date).[23] As discussed previously, there are substantial costs associated with acute care required by patients who are not able to follow an optimal management plan for the disease. This difficulty in following an optimal plan may be due to the medical care provided, access to care, patient understanding, or other factors. Studies of service utilization among high-use patients cited in the preceding sections evaluated the impact of education and guidance designed to improve asthma management by patients. These interventions had a substantial impact on service utilization (as shown in Table IV.2-3 above). This sensitivity analysis considers the medical costs incurred by those patients after intervention. This analysis provides an alternative cost estimate for moderate and severely affected patients, as well as demonstrating the potential efficacy of programs that assist asthma patients in managing their disease.

Link to Table IV.2-3

The data from Table IV.2-3 were used as a source of utilizations rates, taking the average values across studies from the "after intervention" columns for office visits, emergency room visits, and hospitalizations. It was assumed that drug therapy costs would not change (although the use of specific drugs is likely to change).

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[23] Numerous parameters that could be evaluated in a sensitivity analysis are presented in the Uncertainty Analysis section that follows (IV.2.D). Feedback is sought from reviewers on which specific parameters would be of interest. The calculation of costs is carried out through spreadsheets that can be modified easily for most parameters to evaluate sensitivity to altering assumptions and other inputs.

Table V.2-18: Total Annual Costs for the High-use Asthma Patient After Intervention	
Treatment and Service	**Cost (1999$)**
Office Visits	572.81
Drug Therapy* ages 4 to 5 ages 6 to 75	 474.06 617.80
Emergency Room Use	249.47
Hospitalization ages 4 to 17 ages 18 to 75	 624.41 531.55
Total ages 4 -5 ages 6 to 17 ages 18 to 75	 $1,920.75 $2,064.48 $1,971.63
*Includes an annual average $2.66 for use of a nebulizer	

Using the same approach as described above, the costs over the lifespan were summed to obtain an estimated total lifetime medical cost. The undiscounted value is $109,281. The various discounted costs are shown in Table IV.2-19 below.

Table IV.2-19: Lifetime Direct Medical Costs for Asthma Among High-use Patients After Intervention (in 1999$)				
Patient Category	**Undiscounted**	**3%**	**5%**	**7%**
High-use Patients After Intervention	$109,281	$50,041	$35,569	$27,678

As a comparison of Tables IV.2-18 and IV.2-19 shows, there is a substantial decrease in costs resulting from interventions that reduce the use of acute care medical services. There is an approximately $110,000 savings in lifetime medical costs using undiscounted medical cost estimates. Even using highly discounted values (at 7%) the savings is approximately $30,000.

Additional information on the specific methods used to improve patients' asthma management can be obtained from the five papers cited in Table IV.2-3.

Link to Table IV.2-3

IV.2.D Uncertainty Analysis

There are numerous sources of uncertainty in this cost analysis. They are discussed throughout the text as assumptions and inputs from various data sources (e.g., CDC reports). Because these are discussed in detail in the text, a detailed discussion of the sources of uncertainty is not duplicated in this section. The sources of uncertainty are summarized in Table IV.2.20. The table lists the nature of the uncertainty, the likely impact of the uncertainty on costs (leading to an over- or underestimate), and the location in the text where the issue was first discussed. In most cases, it is unknown whether the impact leads to an overestimate or underestimate of costs.

Table IV.2-20 Sources of Uncertainty in the Cost Estimates

Source of Uncertainty	Expected Impact	Location in Chapter
Prevalence and service use statistics from CDC — extrapolated from surveys	Unknown	IV.2.A.1.2
Use of services by high-use patients — based on five studies	Unknown	IV.2.A.1.11
Concurrent Effects Caused by Asthma — not quantitatively considered in cost analysis	Underestimate Costs	IV.2.A.2
Remission rate — may differ at this time.	Unknown	IV.2.A.5
Specific services provided to patients during diagnosis, office visits, emergency room use, and hospitalization — estimated from general statements in NHLBI and recommendations of 1991 panel	Unknown	IV.2.B.1.2.2
Assumed lifespan of 75 years — based on Exposure Factors Handbook and an assumption of minimal asthma mortality	Unknown	IV.2.B.2.3
Estimated age of diagnosis of four years	Unknown	IV.2.A.1.2
Infrequent diagnosis of asthma in children younger than one year of age — may impact estimated age of diagnosis	Underestimate	IV.2.B.2.1
Diagnostic tests that may be carried out but are not included in cost estimates	Underestimate	IV.2.B.2.2
Distribution of current asthma severity level in the population — based on 1991 panel recommendations	Underestimate	IV.2.B.2.3
Assumption that average and high-use patients' drug costs are represented by the profile of drug use recommended by NHLBI and the specific drugs selected for cost estimation	Unknown	IV.2.B.2.4

Table IV.2-20 Sources of Uncertainty in the Cost Estimates		
Source of Uncertainty	**Expected Impact**	**Location in Chapter**
Assumption that a specific percentage of patients are referred to a specialist and that they will see the specialist only once	Underestimate	IV.2.B.2.5
Assumption that costs associated with a visit to a specialist will be the same as an office visit, as specified	Underestimate	IV.2.B.2.5
Assumptions that a level 5 office visits is most relevant for diagnosis and follow-up care	Overestimate	IV.2.B.2.6
Assumption that the Medicare reimbursement system accurately represents average costs	Unknown	IV.2.B.5.2
Assumption that the severity of asthma over the lifespan doesn't change, except among 30% who become symptom-free.	Unknown	IV.2.B.
Assumptions regarding the proportion of high-use patients who have severe versus moderate asthma — used to estimate drug therapy costs and visits to specialists	Unknown	IV.2.B.5.3.2 — drug therapy IV.2.B.2.5 — referral to specialist

Of the sources listed above, some may have a larger impact than others *if* they deviate substantially from the actual experience of the national population of asthmatics. These generally include those assumptions or parameters that impact the costs across the board for most services of patients. They include the assumption that Medicare costs are relevant, the profile of services described for patients (including diagnostic tests), and the rate of office visits, emergency room visits, and hospitalizations per asthmatic.

The uncertainties described above have either an unknown impact, or, in most cases, tend to underestimate costs (or have an unknown impact). Consequently, this cost estimate should be considered a lower-bound estimate of costs for the average patient.

APPENDIX IV.2-A. CHEMICALS ASSOCIATED WITH ASTHMA

The toxic chemicals listed in this appendix are a sample of the potential environmental hazards associated with this diseases (the chemicals with asterisks are subject to reporting requirements under the Toxics Release Inventory, Section 313 of the Emergency Planning and Community Right-to-Know Act). Although the tables contain many chemicals associated with the disease, the list is incomplete for two reasons:

1. It does not include toxicological data from sources other than HSDB through 1996. The toxicological literature currently available is vast, and a thorough review was beyond the scope of this analysis.

2. The human health effects of many environmental hazards are unknown, especially at concentrations found in the environment.

For these reasons, Table IV.2.A-1 should not be used as a definitive source of information on the links between chemical hazards and asthma. Rather, further research should be done by analysts using this handbook to identify the dose-response relationships between the chemical hazards of concern and the diseases.

Table IV.2.A-1: Chemicals Associated with Asthma in the Hazardous Substances Data Bank (HSDB) Human Toxicity Excerpts (metal compounds are assumed to have characteristics of parent element)

CAS Number	HSDB Entry Revision	Chemical name
811-97-2	2/1/96	1,1,1,2-TETRAFLUOROETHANE
1717-00-6	2/1/96	1,1-DICHLORO-1-FLUOROETHANE*
124-73-2	6/27/96	1,2-DIBROMOTETRAFLUOROETHANE*
76-14-2	6/7/96	1,2-DICHLORO-1,1,2,2-TETRAFLUOROETHANE*
1649-08-7	2/1/96	1,2-DICHLORO-1,1-DIFLUOROETHANE*
624-72-6	2/1/96	1,2-DIFLUOROETHANE
106-50-3	6/24/96	1,4-BENZENEDIAMINE
16245-77-5	1/31/96	1,4-BENZENEDIAMINE SULFATE
762-49-2	2/1/96	1-BROMO-2-FLUOROETHANE
75-68-3	1/26/96	1-CHLORO-1,1-DIFLUOROETHANE*
762-50-5	2/1/96	1-CHLORO-2-FLUOROETHANE
306-83-2	6/7/96	2,2-DICHLORO-1,1,1-TRIFLUOROETHANE*
137-09-7	1/28/96	2,4-DIAMINOPHENOL DIHYDROCHLORIDE
584-84-9	6/11/96	2,4-TOLUENE DIISOCYANATE*
823-40-5	1/27/96	2,6-DIAMINOTOLUENE*
95-55-6	1/27/96	2-AMINOPHENOL

Table IV.2.A-1: Chemicals Associated with Asthma in the Hazardous Substances Data Bank (HSDB) Human Toxicity Excerpts (metal compounds are assumed to have characteristics of parent element)		
CAS Number	**HSDB Entry Revision**	**Chemical name**
151-67-7	5/17/96	2-BROMO-2-CHLORO-1,1,1-TRIFLUOROETHANE
2837-89-0	6/7/96	2-CHLORO-1,1,1,2-TETRAFLUOROETHANE*
496-72-0	1/31/96	3,4-DIAMINOTOLUENE
591-27-5	1/24/96	3-AMINOPHENOL
9000-01-5	1/23/96	ACACIA
37517-30-9	2/1/96	ACEBUTOLOL
315-30-0	6/6/96	ALLOPURINOL
10043-67-1	6/21/96	ALUM, POTASSIUM
7429-90-5	6/21/96	ALUMINUM*
7784-25-0	6/21/96	ALUMINUM AMMONIUM SULFATE
7727-15-3	6/21/96	ALUMINUM BROMIDE
1344-01-0	5/14/96	ALUMINUM CALCIUM SODIUM SILICATE
7446-70-0	3/21/96	ALUMINUM CHLORIDE
7784-18-1	6/21/96	ALUMINUM FLUORIDE
21645-51-2	6/6/96	ALUMINUM HYDROXIDE
13473-90-0	6/21/96	ALUMINUM NITRATE
1344-28-1	6/21/96	ALUMINUM OXIDE*
20859-73-8	3/21/96	ALUMINUM PHOSPHIDE*
15096-52-3	6/24/96	ALUMINUM SODIUM FLUORIDE
10102-71-3	6/21/96	ALUMINUM SODIUM SULFATE
10043-01-3	6/21/96	ALUMINUM SULFATE
1951-25-3	5/14/96	AMIODARONE
16919-58-7	5/10/96	AMMONIUM CHLOROPLATINATE
26787-78-0	7/11/96	AMOXICILLIN
69-53-4	7/11/96	AMPICILLIN
77-02-1	1/26/96	APROBARBITAL
68844-77-9	2/1/96	ASTEMIZOLE
1302-78-9	7/11/96	BENTONITE
65-85-0	3/21/96	BENZOIC ACID
353-59-3	4/18/96	BROMOCHLORODIFLUOROMETHANE*
75-63-8	6/11/96	BROMOTRIFLUOROMETHANE*
125-40-6	6/6/96	BUTABARBITAL
2611-82-7	5/14/96	C..I ACID RED 18
4697-36-3	7/11/96	CARBENICILLIN
25953-19-9	7/11/96	CEFAZOLIN
15686-71-2	7/11/96	CEPHALEXIN
76-15-3	7/22/96	CHLOROPENTAFLUOROETHANE
63938-10-3	8/14/95	CHLOROTETRAFLUOROETHANE*
7738-94-5	6/18/96	CHROMIC ACID
10101-53-8	6/18/96	CHROMIC SULFATE
1308-31-2	6/3/96	CHROMITE
25402-06-6	5/14/96	CINERIN I
121-20-0	5/14/96	CINERIN II

Table IV.2.A-1: Chemicals Associated with Asthma in the Hazardous Substances Data Bank (HSDB) Human Toxicity Excerpts (metal compounds are assumed to have characteristics of parent element)		
CAS Number	**HSDB Entry Revision**	**Chemical name**
15663-27-1	5/13/96	CIS-DIAMINEDICHLOROPLATINUM
61-72-3	7/11/96	CLOXACILLIN
7440-48-4	6/21/96	COBALT*
13426-91-0	5/3/96	CUPRIETHYLENEDIAMINE
973-21-7	1/21/96	DESSIN
334-88-3	6/24/96	DIAZOMETHANE*
90454-18-5	6/7/96	DICHLORO-1,1,2-TRIFLUOROETHANE*
75-71-8	5/9/96	DICHLORODIFLUOROMETHANE*
34077-87-7	6/7/96	DICHLOROTRIFLUOROETHANE*
3116-76-5	7/11/96	DICLOXACILLIN
2425-06-1	4/23/96	DIFOLATAN
75847-73-3	5/14/96	ENALAPRIL
51-79-6	5/11/96	ETHYL CARBAMATE
107-15-3	5/14/96	ETHYLENEDIAMINE
69409-94-5	5/14/96	FLUVALINATE*
50-00-0	7/11/96	FORMALDEHYDE*
111-30-8	7/11/96	GLUTARALDEHYDE
5051-62-7	2/1/96	GUANABENZ
354-23-4	6/7/96	HCFC-123a *
812-04-4	6/7/96	HCFC-123b*
354-25-6	6/7/96	HCFC-124a*
9005-49-6	5/11/96	HEPARIN
757-58-4	1/19/96	HEXAETHYLTETRAPHOSPHATE
822-06-0	5/17/96	HEXAMETHYLENE DIISOCYANATE*
53-86-1	1/26/96	INDOMETHACIN
4098-71-9	6/3/96	ISOPHORONE DIISOCYANATE*
16853-85-3	5/10/96	LITHIUM ALUMINUM HYDRIDE
108-31-6	6/3/96	MALEIC ANHYDRIDE*
1344-43-0	7/11/96	MANGANOUS OXIDE
61-68-7	1/26/96	MEFENAMIC ACID
100-97-0	1/19/96	METHENAMINE
61-32-5	7/11/96	METHICILLIN
101-68-8	6/24/96	METHYLENEBIS(4-PHENYLISOCYANATE)*
142-47-2	5/10/96	MONOSODIUM GLUTAMATE
57-27-2	7/11/96	MORPHINE
147-52-4	7/11/96	NAFCILLIN
9006-04-6	2/1/96	NATURAL RUBBER
7440-02-0	6/21/96	NICKEL*
373-02-4	6/21/96	NICKEL ACETATE*
15699-18-0	6/21/96	NICKEL AMMONIUM SULFATE*
3333-67-3	6/21/96	NICKEL CARBONATE*
7718-54-9	6/21/96	NICKEL CHLORIDE*
557-19-7	6/21/96	NICKEL CYANIDE*

Table IV.2.A-1: Chemicals Associated with Asthma in the Hazardous Substances Data Bank (HSDB) Human Toxicity Excerpts (metal compounds are assumed to have characteristics of parent element)		
CAS Number	**HSDB Entry Revision**	**Chemical name**
15843-02-4	6/21/96	NICKEL FORMATE*
12054-48-7	6/21/96	NICKEL HYDROXIDE*
13138-45-9	6/21/96	NICKEL NITRATE*
7786-81-4	6/21/96	NICKEL SULFATE*
10102-44-0	7/11/96	NITROGEN DIOXIDE*
95-54-5	6/6/96	O-PHENYLENEDIAMINE
20816-12-0	6/6/96	OSMIUM TETROXIDE*
79-57-2	1/26/96	OXYTETRACYCLINE
101-54-2	1/23/96	P-AMINODIPHENYLAMINE
51-78-5	1/23/96	P-AMINOPHENOL HYDROCHLORIDE
61-33-6	7/11/96	PENICILLIN G
87-08-1	7/11/96	PENICILLIN V
132-98-9	7/11/96	PENICILLIN VK
354-33-6	2/1/96	PENTAFLUOROETHANE
53910-25-1	2/1/96	PENTOSTATIN
132-93-4	7/11/96	PHENETHICILLIN POTASSIUM
50-33-9	1/26/96	PHENYLBUTAZONE
85-44-9	6/24/96	PHTHALIC ANHYDRIDE*
110-85-0	1/21/96	PIPERAZINE
142-64-3	6/6/96	PIPERAZINE HYDROCHLORIDE
51-03-6	6/6/96	PIPERONYL BUTOXIDE*
10025-65-7	5/14/96	PLATINOUS CHLORIDE
7440-06-4	6/6/96	PLATINUM
13454-96-1	6/6/96	PLATINUM TETRACHLORIDE
50-24-8	1/26/96	PREDNISOLONE
121-21-1	5/14/96	PYRETHRIN I
121-29-9	5/14/96	PYRETHRIN II
8003-34-7	6/24/96	PYRETHRUM
50-54-4	5/14/96	QUINIDINE SULFATE
130-95-0	6/6/96	QUININE
36791-04-5	2/1/96	RIBAVIRIN
9009-86-3	1/27/96	RICIN
1302-42-7	6/21/96	SODIUM ALUMINATE
13770-96-2	5/10/96	SODIUM ALUMINUM HYDRIDE
7785-88-8	5/10/96	SODIUM ALUMINUM PHOSPHATE
7631-90-5	7/11/96	SODIUM BISULFITE
7681-57-4	7/11/96	SODIUM METABISULFITE
1344-06-5	5/10/96	SODIUM PHOSPHOALUMINATE
9000-36-6	1/21/96	STERCULIA GUM
17784-12-2	1/26/96	SULFACYTINE
7704-34-9	1/28/96	SULFUR
7446-09-5	6/11/96	SULFUR DIOXIDE
115-44-6	1/26/96	TALBUTAL

Table IV.2.A-1: Chemicals Associated with Asthma in the Hazardous Substances Data Bank (HSDB) Human Toxicity Excerpts (metal compounds are assumed to have characteristics of parent element)		
CAS Number	**HSDB Entry Revision**	**Chemical name**
117-08-8	1/26/96	TETRACHLOROPHTHALIC ANHYDRIDE
26839-75-8	2/1/96	TIMOLOL
26471-62-5	5/14/96	TOLUENE DIISOCYANATE*
95-80-7	7/22/96	TOLUENE-2,4-DIAMINE
25376-45-8	1/31/96	TOLUENE-AR,AR'-DIAMINE
9000-65-1	1/23/96	TRAGACANTH GUM
14913-33-8	5/13/96	TRANS-DIAMMINEDICHLOROPLATINUM
75-69-4	6/11/96	TRICHLOROFLUOROMETHANE*
84-96-8		TRIMEPRAZINE
12035-72-2	6/21/96	TRINICKEL DISULFIDE
1314-62-1	6/11/96	VANADIUM PENTOXIDE
[1]Compounds of the metals are assumed to fall under the category of compounds listed in TRI.		

APPENDIX IV.2-B. DRUG THERAPIES RECOMMENDED BY NHLBI

Tables IV.2.B-1, IV.2.B-2, IV.2.B-3, and IV.2.B-4 in this appendix list the drug therapies recommended by NHLBI for adults and children. The tables were copied directly from the NHLBI guidelines website:

http://www.nhlbi.nih.gov/index.htm

Link to guidelines

A number of alternative therapies are listed for most situations (e.g., long-term control, quick relief). Data were not available on the distribution of drugs used among asthma patients. To facilitate calculation of costs, a single drug for each type of therapy was selected for most situations, based on those that were most commonly referenced in the literature. The exception to this is the long term control medications. While inhaled corticosteroids are often prescribed for older patients, most children are initially prescribed cromolyn or nedocromil, so costs of the two different groups of medications were considered for the two different age groups. The drug therapy used to calculate costs is shown in italics in the tables that follow. In practice, physicians may choose any of the alternative drug therapies, depending on the specific characteristics of the medication and the patient.

The dosages specified in these tables were used to calculate the annual drug usages and costs. When a range of doses is presented in the tables (e.g., for methylprednisolone) the midpoint of the range was used to estimate the average dose. The alternative drug therapies are provided in this appendix so that the reader can evaluate different alternatives if they wish.

Table IV.2-B-1: Usual Dosages For Long-term-control Medications*				
Medication	**Dosage Form**	**Adult Dose**	**Child Dose**	**Comments**
Inhaled Corticosteroids (see Tables IV.2.B-2 and IV.2.B-3)				
Systemic Corticosteroids (Applies to all three systemic corticosteroids)				
Methylprednisolone Prednisolone Prednisone	*2, 4, 8, 16, 32 mg tablets* 5mg tablets, 5mg/5 cc, 15mg/5 cc 1, 2.5, 5, 10, 20, 25 mg tablets; 5 mg/cc, 5mg/5 cc	• *7.5–60 mg daily in a single dose or qid as needed for control* • Short-course "burst": 40–60 mg per day as single or 2 divided doses for 3–10 days	• *0.25–2 mg/kg daily in single dose or qid as needed for control* • Short course "burst": 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	• For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). If daily doses are required, one study suggests improved efficacy and no increase in adrenal suppression when administered at 3:00 p.m. (Beam et al. 1992). • Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. • The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer treatment. There is no evidence that tapering the dose following improvement prevents relapse.

Table IV.2-B-1: Usual Dosages For Long-term-control Medications*				
Medication	**Dosage Form**	**Adult Dose**	**Child Dose**	**Comments**
Cromolyn and Nedocromyl				
Cromolyn	*MDI 1 mg/puff* *Nebulizer solution* *20 mg/ampule*	*2–4 puffs tid-qid* *1 ampule tid-qid*	*1–2 puffs tid-qid* *1 ampule tid-qid*	• *One dose prior to exercise or allergen exposure provides effective prophylaxis for 1–2 hours.*
Nedocromil	MDI 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid	• See cromolyn above.
Long-Acting beta$_2$ Agonists				
Salmeterol	Inhaled MDI 21 mcg/puff, 60 or 120 puffs DPI 50 mcg/ blister	2 puffs q 12 hours 1 blister q 12 hours	1–2 puffs q 12 hours 1 blister q 12 hours	• May use one dose nightly for symptoms. • Should not be used for symptom relief or for exacerbations.
Sustained-Release Albuterol	Tablet 4 mg tablet	4 mg q 12 hours	0.3–0.6 mg/kg/day, not to exceed 8 mg/day	
Methylxanthines				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: • <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day • ≥1 year of age: 16 mg/kg/day	• Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). • Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important. • See factors on page 87 that can affect levels.

Table IV.2-B-1: Usual Dosages For Long-term-control Medications*				
Medication	**Dosage Form**	**Adult Dose**	**Child Dose**	**Comments**
Leukotriene Modifiers				
Zafirlukast	20 mg tablet	40 mg daily (1 tablet bid)		• For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.
Zileuton	300 mg tablet 600 mg tablet	2,400 mg daily (two 300 mg tablets or one 600 mg tablet, qid)		• For zileuton, monitor hepatic enzymes (ALT).
* q indicates “every”, bid indicates “twice a day,” tid indicates “three times a day,” qid indicates “four times a day.”				

Table IV.2.B-2: Estimated Comparative Daily Dosages For Inhaled Corticosteroids			
Drug	**Low Dose**	**Medium Dose**	**High Dose**
Adults			
Beclomethasone dipropionate *42 mcg/puff* *84 mcg/puff*	*168-504 mcg* *(4-12 puffs — 42 mcg)* *(2-6 puffs — 84 mcg)*	*504-840 mcg* *(12-20 puffs — 42 mcg)* *(6-10 puffs — 84 mcg)*	*>840 mcg* *(>20 puffs — 42 mcg)* *(>10 puffs — 84 mcg)*
Budesonide DPI: 200 mcg/dose	200-400 mcg (1-2 inhalations)	400-600 mcg (2-3 inhalations)	>600 mcg (>3 inhalations)
Flunisolide 250 mcg/puff	500-1,000 mcg (2-4 puffs)	1,000-2,000 mcg (4-8 puffs)	>2,000 mcg (>8 puffs)
Fluticasone MDI: 44, 110, 220 mcg/puff DPI: 50, 100, 250 mcg/dose	88-264 mcg (2-6 puffs — 44 mcg) OR (2 puffs — 110 mcg) (2-6 inhalations — 50 mcg)	264-660 mcg (2-6 puffs — 110 mcg) (3-6 inhalations — 100 mcg)	>660 mcg (>6 puffs — 110 mcg) OR (>3 puffs — 220 mcg) (>6 inhalations — 100 mcg) OR (>2 inhalations — 250 mcg)
Triamcinolone acetonide 100 mcg/puff	400-1,000 mcg (4-10 puffs)	1,000-2,000 mcg (10-20 puffs)	>2,000 mcg (>20 puffs)
Children			
Beclomethasone dipropionate *42 mcg/puff* *84 mcg/puff*	*84-336 mcg* *(2-8 puffs — 42 mcg)* *(1-4 puffs — 84 mcg)*	*336-672 mcg* *(8-16 puffs — 42 mcg)* *(4-8 puffs — 84 mcg)*	*>672 mcg* *(>16 puffs — 42 mcg)* *(>8 puffs — 84 mcg)*
Budesonide DPI: 200 mcg/dose	100-200 mcg	200-400 mcg (1-2 inhalations — 200 mcg)	>400 mcg (>2 inhalations — 200 mcg)
Flunisolide 250 mcg/puff	500-750 mcg (2-3 puffs)	1,000-1,250 mcg (4-5 puffs)	>1,250 mcg (>5 puffs)
Fluticasone MDI: 44, 110, 220 mcg/puff DPI: 50, 100, 250 mcg/dose	88-176 mcg (2-4 puffs — 44 mcg) (2-4 inhalations — 50 mcg)	176-440 mcg (4-10 puffs — 44 mcg) OR (2-4 puffs — 110 mcg) (2-4 inhalations — 100 mcg)	>440 mcg (>4 puffs — 110 mcg) OR (>2 puffs — 220 mcg) (>4 inhalations — 100 mcg) OR (>2 inhalations — 250 mcg)
Triamcinolone acetonide 100 mcg/puff	400-800 mcg (4-8 puffs)	800-1,200 mcg (8-12 puffs)	>1,200 mcg (>12 puffs)

Table IV.2.B-3: Usual Dosages for Quick-relief Medications*				
Medication	**Dosage Form**	**Adult Dose**	**Child Dose**	**Comments**
Short-Acting Inhaled Beta$_2$ -Agonists				
	MDI			
Albuterol Albuterol HFA Bitolterol Pirbuterol Terbutaline	*90 mcg/puff, 200 puffs* 90 mcg/puff, 200 puffs 370 mcg/puff, 300 puffs 200 mcg/puff, 400 puffs 200 mcg/puff, 300 puffs	•2 puffs 5 minutes prior to exercise •2 puffs tid-qid prn	• 1-2 puffs 5 minutes prior to exercise • 2 puffs tid-qid prn	•An increasing use or lack of expected effect indicates diminished control of asthma. •Not generally recommended for long-term treatment. Regular use on a daily basis indicates the need for additional long-term-control therapy. •Differences in potency exist so that all products are essentially equipotent on a per puff basis. •May double usual dose for mild exacerbations. •Nonselective agents (i.e., epinephrine, isoproterenol, etaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
	DPI			
Albuterol Rotahaler	200 mcg/capsule	1-2 capsules 4-6 hours as needed and prior to exercise	1 capsule 4-6 hours as needed and prior to exercise	
Albuterol	Nebulizer solution 5 mg/mL (0.5%)	1.25-5 mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 2-3 cc of saline q 4-6 hours	May mix with cromolyn or ipratropium nebulizer solutions. May double dose for mild exacerbations.
Bitolterol	2 mg/mL (0.2%)	0.5-3.5mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	Not established	May not mix with other nebulizer solutions.
Anticholinergics				
	MDI			
Ipratropium	18 mcg/puff, 200 puffs Nebulizer solution .25 mg/mL (0.025%)	2-3 puffs q 6 hours 0.25 mg q 6 hours	1-2 puffs q 6 hours 0.25-0.5 mg q 6 hours	Evidence is lacking for anticholinergics producing added benefit to beta$_2$ -agonists in long-term asthma therapy.

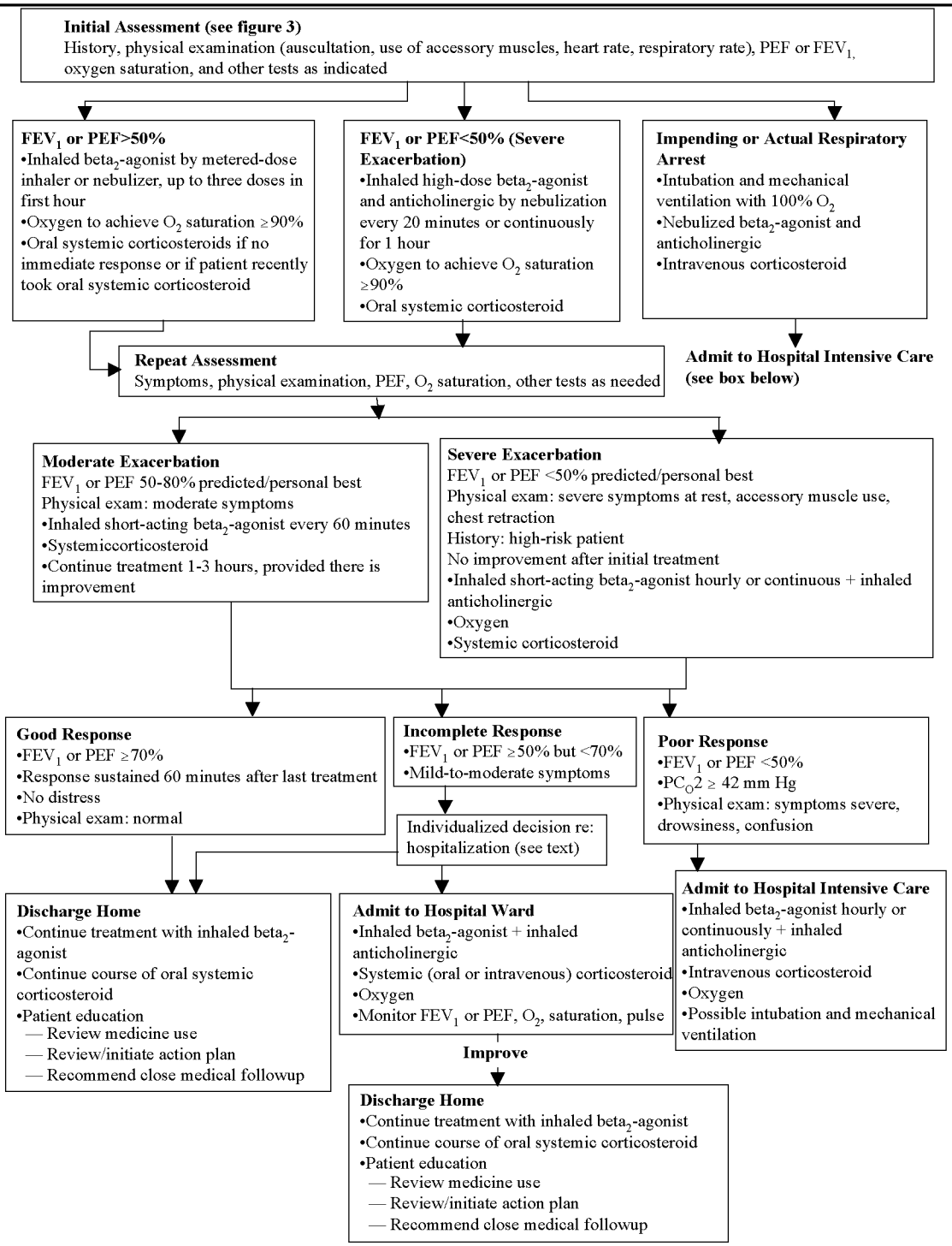
Table IV.2.B-3: Usual Dosages for Quick-relief Medications*				
Medication	**Dosage Form**	**Adult Dose**	**Child Dose**	**Comments**
Systemic Corticosteroids (Applies to all three systemic corticosteroids)				
Methylpred-nisolone Prednis-olone Prednisone	2, 4, 8, 16, 32 mg tablets 5 mg tabs, 5 mg/5 cc, 15 mg/5 cc 1, 2.5, 5, 10, 20, 25 mg tabs; 5 mg/cc, 5 mg/5 cc	•Short course "burst": 40-60 mg/day as single or 2 divided doses for 3-10 days	•Short course "burst": 1-2 mg/kg/day, maximum 60 mg/day, for 3-10 days	•Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. •The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer treatment. There is no evidence that tapering the dose following improvement prevents relapse.
* "tid qid prn" indicates three to four times per day, according to circumstances; "q" indicates "every."				

Table IV.2.B-4: Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital			
	Dosages		
Medication	**Adult Dose**	**Child Dose**	**Comments**
Inhaled Short-Acting Inhaled Beta$_2$ -Agonists			
Albuterol Nebulizer solution (5 mg/mL)	2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed, or 10-15 mg/hour continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization	Only selective beta$_2$-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 4 mL at gas flow of 6-8 l/min.
MDI (90 mcg/puff)	4-8 puffs every 20 minutes up to 4 hours, then every 1-4 hours as needed	4-8 puffs every 20 minutes for 3 doses, then every 1-4 hours inhalation maneuver. Use spacer/holding chamber.	As effective as nebulized therapy if patient is able to coordinate
Bitolterol Nebulizer solution (2 mg/mL)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 mcg/puff)	See albuterol dose	See albuterol dose	Has not been studied in severe asthma exacerbations.
MDI (200 mcg/puff)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations.
Systemic (Injected) Beta$_2$ -Agonists			
Epinephrine 1:1000 (1 mg/mL)	0.3-0.5 mg every 20 minutes for 3 doses sq	0.01 mg/kg up to 0.3-0.5 mg every 20 minutes for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.25 mg every 20 minutes for 3 doses sq	0.01 mg/kg every 20 minutes for 3 doses then every 2-6 hours as needed sq	No proven advantage of systemic therapy over aerosol.
Anticholinergics			
Ipratropium bromide Nebulizer solution (.25 mg/mL)	0.5 mg every 30 minutes for 3 doses then every 2-4 hours as needed	.25 mg every 20 minutes for 3 doses, then every 2 to 4 hours	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to beta$_2$-agonist therapy.
MDI (18 mcg/puff)	4-8 puffs as needed	4-8 puffs as needed	Dose delivered from MDI is low and has not been studied in asthma exacerbations.
Corticosteroids			

Table IV.2.B-4: Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital			
	Dosages		
Medication	**Adult Dose**	**Child Dose**	**Comments**
Prednisone Methylprednisolone Prednisolone	120-180 mg/day in 3 or 4 divided doses for 48 hours, then 60-80 mg/day until PEF reaches 70% of predicted or personal best	1 mg/kg every 6 hours for 48 hours then 1-2 mg/kg/day (maximum = 60 mg/day) in 2 divided doses until PEF 70% of predicted or personal best	For outpatient "burst" use 40-60 mg in single or 2 divided doses for adults (children: 1-2 mg/kg/day, maximum 60 mg/day) for 3-10 days

Note:
- No advantage has been found for higher dose corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired. The usual regimen is to continue the frequent multiple daily dosing until the patient achieves an FEV 1 or PEF of 50 percent of predicted or personal best and then lower the dose to twice daily. This usually occurs within 48 hours. Therapy following a hospitalization or emergency department visit may last from 3 to 10 days. If patients are then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic corticosteroid dose. If the follow-up systemic corticosteroid therapy is to be given once daily, one study indicates that it may be more clinically effective to give the dose in the afternoon at 3:00 p.m., with no increase in adrenal suppression (Beam et al., 1992).

Figure IV.2.B-1: Management of Asthma Exacerbations: Home Treatment



Note:
Patients at high risk of asthma-related death (see table IV.2.B-4) should receive immediate attention clinical attention after initial treatment.
Additional therapy may be required.

Table IV.2.B-5: Hospital Discharge Checklist for Patients with Asthma Exacerbations			
Intervention	**Dose/Timing**	**Education/Advice**	**M.D./R.N. Initials**
Inhaled medication (MDI + spacer/holding chamber) $Beta_2$-agonist Corticosteroids	Select agent, dose, and frequency (e.g., albuterol) 2-6 puffs q 3-4 hr prn Medium dose	Teach purpose Teach technique Emphasize need for spacer/holding chamber Check patient technique	
Oral medications	Select agent, dose, and frequency (e.g., prednisone 20 mg bid for 3-10 days)	Teach purpose Teach side effects	
Peak flow meter	Measure a.m. and p.m. PEF and record best of three tries each time.	Teach purpose Teach technique Distribute peak flow diary	
Follow-up visit	Make appointment for follow-up care with primary clinician or asthma specialist	Advise patient (or caregiver) of date, time, and location of appointment within 7 days of hospital discharge	
Action plan	Before or at discharge	Instruct patient (or caregiver) on simple plan for actions to be taken when symptoms, signs, and PEF values suggest recurrent airflow obstruction	
q indicates “every,” prn indicates “according to circumstances.”			

CHAPTER IV.3 COST OF ACUTE RESPIRATORY DISEASES: HYPERSENSITIVITY PNEUMONITIS, HUMIDIFIER FEVER, AND LEGIONNAIRES' DISEASE

Clicking on the sections below will take you to the relevant text.

CHAPTER IV.3 COST OF ACUTE RESPIRATORY DISEASES: HYPERSENSITIVITY PNEUMONITIS, HUMIDIFIER FEVER, AND LEGIONNAIRES' DISEASE

IV.3.A Background

Indoor air contamination in non-industrial buildings has received increased attention in recent years due to improved understanding of the potential impact of indoor air quality on the health of residents and workers. Air pollutants that are known to cause irritation, allergic responses, and infection are numerous, and vary widely in their potency and in the responses they elicit. Groups of illnesses that result from exposure to contaminants in indoor air have been categorized as "sick or tight building syndrome," or with other designations that encompass a variety of diseases and symptoms. Some groups of illnesses have highly specific target organs. For example, hypersensitivity pneumonitis, which includes over 30 specific diseases, is characterized by specific pathology in the lung.

This chapter addresses illnesses with a rapid onset that are associated with indoor air pollutants. At this time, three diseases of this type have been evaluated for direct medical costs:

- Legionnaires' disease (Legionelliosis),
- hypersensitivity pneumonitis, and
- humidifier fever.

Humidifier fever is included because it is considered by some to be a type of hypersensitivity pneumonitis, even though the most obvious symptoms are not respiratory.[1]

Humidifier fever, hypersensitivity pneumonitis, and Legionelliosis are all illnesses that have been associated with exposure to allergenic or pathogenic materials in indoor air. The first two are similar in both cause and resolution. A variety of allergens can trigger these illnesses, which are mediated by the immune system, and elimination of exposure can eliminate the illness. Legionelliosis results from exposure to the bacteria of the genus Legionella. Antibiotics are effective in eliminating the illness.

Hypersensitivity pneumonitis and humidifier fever share the characteristic that removal of the patient from the contaminated environment, or removal

[1]Patients with this disease typically have reduced lung function, although this symptom is often not evaluated.

of the contaminant from the patient's environment, is the primary and only fully effective method of treatment. Symptomatic treatments exist (e.g., fever-reducing medications for humidifier fever), but do not provide long-term solutions.

Cost estimates for the three diseases were developed to address specific requirements of the Indoor Environments Division, which was evaluating impacts of various indoor air pollutants[2]. The Agency wanted cost estimates for these diseases developed on a quick-response basis, in the absence of other complicating factors or diseases. Consequently, the methods used to estimate costs were relatively simple and direct. The usual format of chapters in the Handbook, with considerable detail on medical definition, causality, susceptibility, prognosis, etc., was not considered appropriate under the circumstances.

This chapter contains a discussion of incremental direct medical costs incurred by individuals in whom these diseases occur in response to poor indoor air quality. The symptoms associated with these diseases could also result from other causes, but the cost may be different, depending on the circumstances (indicating differences in underlying pathology)[3]. The costs are for a single occurrence of the disease, which can last from one day to a few months, depending on the disease.

Regulation of ambient air pollutants may result in a reduced number of individuals with air-related symptoms. Programs to reduce indoor air pollutants are also crucial in reducing adverse health effects. The benefits of such activities can be estimated in part by evaluating the direct medical costs avoided as a result. Some elements of total benefit, such as the avoided indirect medical costs, willingness to pay to avoid pain and suffering, the value of lost time of unpaid caregivers, the value of lost productivity of patients, etc., are not included here. These costs may be substantial. The direct medical costs presented in this chapter may be useful in providing a lower-bound measure of total benefit. The reader is referred to Chapter I.1 for a discussion of direct cost estimation methods and cost elements that are relevant to all benefits estimates.

[2]This work was done in conjunction with the work on Chapter V.1, Costs of Symptoms, and shares a common methodology.

[3]For example, hypersensitivity pneumonitis associated with agricultural activities may occur with other, more serious pathological conditions.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1 and IV.1
Link to inflation factors

IV.3.B Cost Estimation

IV.3.B.1 Sources

Medical costs were estimated for this chapter by:

1) describing the anticipated diagnosis and treatment services using national guidelines and the medical literature, and

2) assigning costs to those services, based on current (1999) Medicare reimbursement values.

The primary sources consulted to identify medical services were clinical practice guidelines (AHCPR, 1999; CDC, 1999), medical texts (e.g., Bennett and Plum, 1996), and the Medicare reimbursement *Federal Register* notices regarding costs (numerous; discussed Chapter IV.2). EPA also reviewed numerous journal article abstracts, but used these primarily as supporting information (to confirm other sources). The abstracts are cited when used as the only source. EPA obtained most information on medical services from the National Guidelines Clearinghouse (www.guidelines.gov) developed by clinicians and researchers, which provides clinical practice guidelines for specific diseases.

Link to Chapter IV.2

EPA estimated costs of medical services using current (1999) Medicare reimbursements. The rationale for using this source of cost information is that it is a national system for medical services reimbursement that approximates the average cost of medical services in the United States. For a more detailed discussion of the use of Medicare information, see Section B in Chapter IV.2, Medical Costs of Asthma. Supporting information for medical services came from the medical and economics literature.

Link to Chapter IV.2, Section B.

EPA estimated medication costs for common, over-the-counter medications (i.e., those available at both drug and other types of stores such as groceries and discount stores) using the lowest cost for a generic

product, based on prices obtained from a relatively low-cost national pharmacy chain store on October 27, 1999. EPA preferred prices taken directly from consumer goods over those taken from an industry source (e.g., the Red Book) because these are over-the-counter medications and their consumer prices were readily available directly from the marketplace.

Since the medications considered are very common (e.g., aspirin) and there is a high demand for these products, market pressures have made their prices fairly uniform. Most patients are not expected to pay substantially higher prices than those used in this analysis. For prescription medications, the Health Care Financing Authority (HCFA) prices were used.

IV.3.B.2 Humidifier Fever

Humidifier fever, which may be a type of hypersensitivity pneumonitis, is a hypersensitivity disease that occurs in response to exposure to a variety of airborne organisms and materials, often organic (EPA, 1999; Mamolen, et al., 1993). Responses will vary considerably from individual to individual because it is an immune system-mediated disease. The disease will affect some but not all individuals who are exposed. Humidifier fever has a delayed onset of a few hours from the time of exposure and usually is self-limiting. Fever, myalgia, and other symptoms last up to 24 hours. Humidifier fever may also cause transient changes in lung function and white blood cell count, although these changes are not the focus of clinical evaluation for a single event of a short-term fever. Numerous studies confirm the short-term nature of the illness and the lack of long-term effects (Teake et al., 1999; Baur et al., 1988; McSharry et al., 1987; Edwards, 1980; Philipp, 1983; Belin, et al., 1979; Anderson et al., 1989; Mamelon et al, 1993; Cockcroft et al., 1981).

Due to the short-term and mild nature of its effects, individuals with humidifier fever would not be expected to see a physician when allergic response first occurs. According to EPA's Indoor Environments Division webpage, "It [humidifier fever] normally subsides within 24 hours without residual effects, and a physician is rarely consulted" (EPA, 1999). The likely course would be to take one of the following over-the-counter medications for a maximum of one day: aspirin, ibuprofen, or acetaminophen. These medications lower fever and lessen pain (e.g., those associated with myalgia), and are the most commonly used fever-reducing medications.

If the illness recurs repeatedly, an individual might visit a physician. The length of the office visit would depend on the patient and physician, and no estimate is made here of the level of visit that would occur. This report presents all five levels of both new and established patient visit costs. The analyst can choose the level determined to be most appropriate.

If a cluster of individuals experienced this illness at the same time (as reported in the literature), a local or state health department would likely investigate the cause. The costs of this type of effort are not estimated in this analysis, but could be substantial as a public sector expense.

Table IV.3-1 provides cost estimates for medications. A 12-hour average duration of illness was assumed because it is one half, or the midpoint, of the total potential duration of 24 hours. Table IV.3-1 also lists costs for the five potential levels of office visits. Using the values in this table, the costs could range from $0.03 (three cents) for a patient who takes two doses of aspirin only and does not visit a physician, to $139.02 for a patient who has an extended new patient visit to a physician's office (level 5) and takes acetaminophen for fever and pain. *It is not possible to accurately estimate the average cost,* but the literature suggests that most patients would not see a physician. This assumption would indicate a cost of less than one dollar for most patients. Patients can incur other costs if they visit a physician who in turn performs some tests. This alternative appears very unlikely for a 24-hour fever.

Table IV.3-1. Cost components for humidifier fever

Goods or Service	Medicare Code	Cost (1999$)
aspirin: 2 doses	not applicable	0.03
acetaminophen: 2 doses	not applicable	0.09
ibuprofen: 2 doses	not applicable	0.08
office visit: new patient level 1	99201	34.73
level 2	99202	53.53
level 3	99203	76.06
level 4	99204	111.14
level 5	99205	138.93
office visit: established patient level 1	99211	16.32
level 2	99212	30.22
level 3	99213	41.68
level 4	99214	63.56
level 5	99215	97.94

If the episodes of humidifier fever are frequent, and humidifier fever is not diagnosed on the first visit, further investigation by a physician might include blood tests for white cell counts, tests of delayed hypersensitivity allergic response, and respiratory function tests. The costs of these tests

are not listed above because they are not anticipated. These costs are described in the next section of this chapter on hypersensitivity pneumonitis and in Chapter IV.2, submitted on October 22, 1999. Additional office visits may also occur in response to these symptoms.

Link to Chapter IV.2

Humidifier lung appears to be a more advanced form of this disease, wherein the response is also seen prominently in the respiratory system (Bauer et al., 1988).

IV.3.B.3 Hypersensitivity Pneumonitis

This group of similar illnesses encompasses a very large number of different diseases (Pitcher, 1990), with 30 or more specific diseases defined (Ando and Suga, 1997). This type of pneumonitis is characterized by diffuse, predominantly mononuclear inflammation of the lung parenchyma, particularly the terminal bronchioles and alveoli. Hypersensitivity pneumonitis may progress to fibrosis under extreme conditions. This illness is suspected when repeated bouts of influenza-like pneumonitis, or active interstitial lung disease occur. No single clinical feature or laboratory test is diagnostic of the disease. In addition to symptoms and physical findings, X-rays, pulmonary function tests, and immunological tests are used to diagnose the disease. Numerous immunological tests may be considered because a large group of potential antigens can cause the disease. IgG immunoglobulins occur as serum precipitins in the presence of the causative antigens (CDC, 1996; Pitcher, 1990).

Hypersensitivity pneumonitis is treated through removal of either 1) the allergen(s) from the patient's environment, or 2) the patient from the contaminated environment (all sources consulted). Treatment may also involve the use of steroids, such as prednisone (at 40 mg/day in doses of 10 mg for 10 days) to reduce lung inflammation (Pitcher, 1990). Steroid use is not a long-term solution and is not recommended for the majority of patients. Only 10 percent of patients are assumed to receive this medication because routine use of steroids is discouraged (Pitcher, 1990). Hypersensitivity pneumonitis is not a bacterial disease, and therefore requires no antibiotics (unless an infection secondary to hypersensitivity pneumonitis occurs).

Table IV.3-2 lists the direct medical costs of diagnosis and treatment. The patient is assumed to have an initial office visit of average duration (level 3), during which a chest X-ray, lung function test, and allergen test for 20 allergens are administered. The patient is assumed to be established,

because the nature of IgG allergic responses would likely lead most people to have seen a physician in the past. Costs are available for new patients visits and for all level of office visits in Table IV.3-1 above.

Link to Table IV.3-1

Although the diagnosis procedures are fairly well-defined, the average period of illness prior to disease diagnosis is not described and will vary, depending on the patient and physician. When not diagnosed and treated, this disease can cause fever, chills, malaise, dry cough, dyspnea, tiredness, weight loss, and other effects. If diagnosis is delayed, these effects can lead to lost work time and the use of over-the-counter medications.

Table IV.3-2. Cost components for hypersensitivity pneumonitis

Goods and Services	Medicare Code	Cost (1999$)
office visit: established patient , level 3	99213	41.68
chest X-ray in physician's office	71020	34.74
allergen tests, delayed type: 20 allergens	95028	8.68 x 20 = 173.60
lung function test	94010	30.56
prednisone (HCFA price) x 10% of patients	not applicable	1.80 x 0.1 = 0.18 *
Total		**280.76**

* The cost of this medication is very low and is assumed to be provided to only 10 percent of patients (as discussed in the text). The listed cost represents the cost for the full course of treatment.

Patients may be hospitalized if the disease becomes severe. Although no statistics were located on its probability, hospitalization is unlikely, based on qualitative information provided in the sources reviewed for this analysis. Hypersensitivity pneumonitis, aggregated with other types of interstitial lung diseases as a diagnostically related group (DRG) category (93), is often not treated as a specific disease in hospitalization information. The National Hospital Discharge Database does not make distinctions among different categories within DRG 93. Additional information may be obtainable on hospitalization probabilities, but extensive searching and consulting was not performed due to the quick-turnaround nature of this task

If the Agency plans to include hospitalization costs, then the Medicare hospitalization cost for interstitial lung disease without complications (DRG 93) can be used. This category maps to the International Classification of Diseases Code (ICD-9) for hypersensitivity pneumonitis (495.9). The Medicare reimbursement values for adult hospitalizations are $3450.58 for urban areas and $3262.43 for rural areas.

IV.3.B.4 Legionnaires' Disease (Legionelliosis)

Legionnaires' disease is a respiratory disease caused by the pathogen Legionella. Patients with this disease may have numerous symptoms, with fever and pneumonia predominating. The pneumonia is not clinically distinguishable from the most common type of pneumonia (pneumococcal), and some cases of Legionnaires' disease are indistinguishable from other causes of pneumonia. One to five percent of all pneumonias are estimated to be due to Legionnaires disease (Edelstein, 1996); many cases of Legionnaires' disease may not be diagnosed as such.
Although a variety of clinical test results may be abnormal, the definitive diagnosis is made through a positive test for the pathogen Legionella (Edelstein, 1996; CDC, 1994; CDC, 1997).

As with hypersensitivity pneumonitis described in this chapter, the period prior to diagnosis may vary widely, depending on the physician(s) consulted and patient characteristics. When not diagnosed and treated, the disease may cause numerous symptoms and lead to lost work time and the use of over-the-counter medications. The costs associated with delayed diagnosis are not considered in this analysis.

Diagnostic tools specifically used for Legionnaires' disease include chest X-ray and sputum culture for Legionella. Serological testing is primarily useful for epidemiologists rather than for clinicians, and is not considered in this analysis. The first choice for therapy is erythromycin, which may be administered orally, or, when the patient is hospitalized with a serious case, intravenously. Oral dosage is 500 mg, four times per day for 14 to 21 days (the average of 18 days was used) (Edelstein, 1996)[4]. Most patients respond within one to two days of specific antimicrobial therapy. Fever may persist for a week, and weeks to months are required to resolve pulmonary infiltrates. Patients with respiratory failure due to Legionnaires' disease have a relatively poor prognosis and a much slower recovery (CDC, 1994). Other antibiotics and therapy regimens may be used to treat this disease and are likely to incur different costs than those reported in this chapter.

Table IV.3-3 summarizes the direct medical costs of goods and services and hospitalization for Legionnaires' disease. For patients who do not require hospitalization, costs for a chest X-ray, sputum culture, and erythromycin are listed with an office visit (level 3, established patient) in Table IV.3-3 below.

[4] Doxycycline, which is somewhat less expensive, was cited as the drug of choice in one paper (Klein and Cunha, 1998). The authors note, however, that erythromycin is the most commonly used. Erythromycin is therefore used in this analysis.

Table IV.3-3 also lists hospitalization costs for the more seriously affected patients. An office diagnosis may be made prior to hospitalization. Given the relatively low cost of office visit diagnoses and treatment compared with hospitalization, the addition of the office visit costs will have a minimal impact on the overall cost estimate.

Hospitalization costs should not always be added to the other costs because they are relevant to a different patient subset. To obtain hospitalization costs from Medicare reimbursement data, the ICD-9 code for Legionella (482.4) was mapped to DRG codes 80 and 81 for hospitalization of adults and children, respectively. Hospitalization costs vary considerably between adults and children.

No data were located on the percentage of patients with Legionnaire's disease who are hospitalized. Analysts may use the costs in Table IV.3-3 with a proportionate allocation of patients to hospital and non-hospital treatment, based on their best judgement. The likelihood of hospitalization varies with many factors, including health status of the patient (i.e., other respiratory diseases), age, and promptness of diagnosis and treatment.

Table IV.3-3. Cost components for Legionelliosis

Goods and Services	**Medicare Code**	**Cost (1999$)**
office visit: established patient level 3	99213	41.68
chest X-ray, physician's office	71020	34.74
sputum culture for Legionella (least expensive culture option)	87278	16.58
erythromycin (HCFA price)	not applicable	25.82
Total outpatient care		**118.82**
Hospitalization	**DRG Code**	**Cost (1999$)**
hospitalization: urban, adult	80	4,093.17
hospitalization urban, child 0 - 17 years	81	6,756.17
hospitalization rural, adult	80	3,869.99
hospitalization: rural, child 0 - 17 years	81	6,387.78

CHAPTER V.1 SYMPTOMS

Symptoms are "subjective evidence of a disease or a patient's condition" (Dorland's Medical Dictionary, 1982), and are often the first indication of an adverse response to environmental pollutants. They may be relatively mild, such as a slight headache or runny nose, or be much more severe in nature. Symptoms are of interest because in some cases they are the only information sources available that describe the adverse response effect to pollutant exposure. This situation is commonly encountered in the study of indoor air pollutants, which may elicit a number of symptoms in the absence of a definitive disease diagnosis. Symptoms that have been linked to indoor air pollutants are grouped and discussed in Chapter V.2.

Evaluation of symptoms can be complex because they are not diseases per se. Symptoms are typically evaluated with other clinical information by a medical professional to determine an underlying cause. This evaluation usually results in the diagnosis of a specific illness.[1] For example, a sore throat may be associated with a streptococcal infection, a cold, or a variety of other causes. A runny nose may be due to a cold, allergies, or some other cause. When symptoms arise due to a low level physiological response to a pollutant, however, the patient and the physician may not determine cause and effect, or may not have the means to eliminate the source. Consequently, some symptoms occur over long periods of time.

Symptoms usually incur relatively low medical costs and are often treated with over-the-counter (OTC) medications, but exceptions exist. An aggressive medical investigation of a patient's symptoms and underlying causes may involve computed tomography (CT) scans, magnetic resonance imagery (MRIs), and other expensive medical tests. It is difficult to determine the probability of intensive diagnostic analysis, which introduces uncertainty into the cost analysis of symptoms. An additional source of uncertainty is the differing responses of patients to their symptoms. Some may seek medical attention quickly; others may tolerate headaches, tiredness, sore throat, and symptoms for a long time without seeking medical attention, or may use only OTC medications.

As our understanding of symptoms and illnesses associated with environmental pollutants improves, fewer symptoms may be considered in isolation — they will be linked to diseases or syndromes that can then be treated effectively. At this point in time (2000), however, it is useful to have estimates of some potential costs which may be incurred by people experiencing symptoms in the absence of obvious disease. This section of the *COI Handbook* provides that type of information.

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[1]Illness and disease are used in this handbook to designate any adverse health condition.

CHAPTER V.2. SYMPTOM GROUPS

Clicking on the sections below will take you to the relevant text.

CHAPTER V.2. SYMPTOM GROUPS

V.2.A. Background

Many environmental irritants and allergens, whether chemical or biological, can cause systemic toxicity and irritation of mucous membranes, leading to pain and related symptoms. The Indoor Environments Division has been evaluating impacts of various indoor air pollutants. This analysis examines the direct medical costs of addressing symptom groups, such as eye irritation, throat irritation and pain, coughing, headaches, and other non-life-threatening medical conditions, to address the division's specific requirements.

This chapter contains a discussion of the methods used to estimate the annual direct medical costs of treating specific symptoms in the absence of serious disease. It does not include information on cost elements such as indirect medical costs, pain and suffering, lost time, etc.[1] The reader is referred to Chapter I.1 for a discussion of the general methods and cost elements relevant to all benefits estimates, and for a discussion of the limitations of estimating medical costs.

The costs presented in this chapter were current in the year the chapter was written. They can be updated using inflation factors accessible by clicking on the sidebar at left.

Link to Chapters I.1
Link to inflation factors

V.2.A.1. Symptoms Evaluated

The symptoms evaluated in this chapter are:

- dry, itching or irritated eyes;
- headaches;
- sore or dry throat;
- unusual tiredness;
- fatigue or drowsiness;
- stuffy or runny nose or sinus congestion; and
- dry or itchy skin.

The costs of diagnosis and treatment are moderate because these symptoms are hypothesized in this analysis to result from irritation and allergies. They

[11] Some of these cost elements, especially pain and suffering, may comprise a very large portion of the benefits of avoiding symptoms. Because these cost elements are difficult to assess, it was not feasible to estimate them for this chapter.

may also indicate, but are not considered in this chapter to be symptoms of, more serious diseases. In addition to treating the symptoms listed above, this analysis includes the cost of evaluating allergic responses that may also trigger these symptoms. The allergic diagnosis and treatment costs may be applicable to many of the symptom groups for some patients.

This chapter contains a discussion of the annual incremental direct medical costs incurred by individuals experiencing symptoms assumed to be related to poor indoor air quality. The symptoms could also result from other causes but may incur different costs, depending on the circumstances (indicating differences in underlying pathology). The methods used to estimate costs are relatively simple and direct because the symptoms are evaluated under the specified condition that they occur in the absence of other complicating factors and are not a result of serious diseases. Consequently, this chapter does not follow the usual format of chapters in the Handbook. Many details on medical definition, causality, susceptibility, prognosis, etc., are omitted because they are not appropriate to this chapter.

Patients may experience the symptoms for weeks, months, or years. The costs, presented as annual costs, can be pro-rated for the duration of time appropriate to the analysis being performed. An exception is made for the costs of allergy treatment, included here as supplementary information. This information includes those costs associated with the usual five-year course of allergy treatment. This analysis also provides sufficient information for the reader to calculate allergy treatment costs for periods other than five years.

The costs provided in this chapter may be used in a variety of applications; but the data have limitations. Regulation of air pollutants may result in a reduced number of individuals with air-related symptoms. Programs to reduce indoor air pollutants, such as environmental tobacco smoke (ETS), are also crucial in reducing adverse health effects. The benefits of such activities can be estimated, in part, by evaluating the direct medical costs avoided. As noted above, a full measure of cost would also include direct non-medical costs and indirect costs. The direct medical costs presented in this chapter may be useful in providing a lower-bound measure of willingness-to-pay.

V.2.A.2 Nature of Symptoms

As discussed in Chapter V.1 , evaluation of symptoms can be complex because they are not diseases per se. Symptoms are evaluated with other clinical information by a medical professional to determine an underlying cause that usually results in the diagnosis of a specific illness.[2] For

[2]Illness and disease are used in this handbook to designate any adverse health condition.

example, a sore throat may be associated with a streptococcal infection, a cold, or a variety of other causes. Unusual tiredness may be linked to chronic fatigue syndrome (CFS), anemia, pregnancy, stress, and multiple other causes. A runny nose may be due to a cold, allergies, or some other cause. It is not always possible to link the symptoms and clinical data to a specific disease, and may be very difficult especially in the case of indoor pollutant-induced symptoms. Many physicians are not familiar with the potential effects of such pollutants and consequently may not consider them as a source of the patient's symptoms.

The difficulties in estimating costs for symptoms are twofold:

1. symptoms related to irritation and allergic responses vary widely in their severity, from a barely noticeable annoyance to a life-threatening systematic response; and

2. the medical literature and system of payments for care is based on diagnosis of a disease or the cause of the medical visit.

Cost data are derived from a description of the medical services most likely to be provided to a patient seen for a specific symptom or array of symptoms. Determining which services are likely to be provided then yields reasonable cost estimates. In the specific case of indoor air pollution, symptoms can be associated with a variety of indoor air quality problems. Consequently, most cases involve no specific, readily identifiable disease. *It is an open question as to whether physicians could discern from the patient's medical history and a physical examination that the symptoms are the result of indoor air quality problems.* If they do not diagnose the actual cause of the symptoms, and the symptoms persist, the physician may do a wide variety of tests to try to determine the cause. These tests can be very expensive.

Allergies pose a particular problem, and illustrate the dilemma posed by symptom cost analysis. Allergies are a common cause of most of the symptoms listed above. Allergy screening and follow-up allergy management are relatively expensive when compared with the cost of treating only the symptoms. In addition, medications to treat allergies may cause other diseases, which in turn require treatment. The medications may also cause activity restrictions and limit school and job performance.

Various components of the immune system mediate many types of allergies. Due to the complexity of diagnosing and treating allergies, patients are commonly referred to an allergist when allergies are suspected by a primary care physician. This chapter provides data on one type of allergy testing and treatment, IgE-mediated, which is the most common type of allergy and often causes the symptoms listed above. Its applicability will depend on the agents responsible for causing the allergy.

Symptoms do not necessarily indicate relevance; other types of allergic responses may cause the same symptoms as those listed. Determining which allergic responses apply requires a clinical understanding of symptom induction, likely immune system response (e.g., IgE, IgG), and responses to various medical tests. The IgE-mediated allergic response is used as an example in this discussion of allergy testing and treatment costs. Medical diagnosis and treatment of other types of allergic responses may have higher or lower costs than those reported in this chapter.

Numerous other difficulties are associated with evaluating the medical costs of diagnosing and treating symptoms. Evaluating some symptom groups can result in extensive testing. Unusual tiredness, fatigue, or drowsiness may result from a large number of diseases and disorders, including (but not limited to) anemia, sleep disorders, apnea, leukemia, and chronic fatigue syndrome. Screening for all these diseases would be very costly and time consuming. Headaches may also be evaluated through sophisticated methods, including magnetic resonance imaging (MRI), computed tomography (CT) scans, spinal taps, evaluations by neurological specialists or ophthalmologists, and many other procedures.

Although extensive testing and referrals to a specialist may be used in some cases, the percentage of patients who will undergo this level of evaluation is unclear for most symptom groups. Data were located on CT scan use for patients with headaches in a study of 58 medical practices. The study found that CT scans were ordered for only 3 percent of patients, mainly for those believed by physicians to have a tumor. Additional neurological signs and symptoms beyond the presence of a headache would indicate this procedure. The percentage of patients with only a headache who would receive a CT scan is unclear, but is likely to be considerably less than 3 percent. This example illustrates the difficulty, even in the presence of studies, in assessing the probability of medical services for symptoms that go beyond a basic examination.

One of the more difficult symptom groups to evaluate is fatigue and drowsiness. These symptoms are similar to those reported for chronic fatigue syndrome, and it was felt that the diagnosis might have some common elements. EPA consulted a project manager of a large study of chronic fatigue syndrome to gain some insight into what tests might likely be conducted on patients who visit a physician due to fatigue. Her observations of numerous physicians' methods indicated that careful history taking and physical examination were of paramount use and the most common diagnostic tools. In addition, physicians usually do a simple blood screen (complete blood count and in some cases thyroid screening) to rule out anemia, hypothyroidism and other obvious and common causes

(systemic infections, etc). Even though chronic fatigue syndrome is a diagnosis of exclusion, extensive diagnostic testing was not done routinely (Carrol Emmons, Abt Associates, 1999).[3]

If patients are screened to rule out most other possible disorders, then medical costs will be high and treatment may be time consuming. There are many options for the evaluation of each group of symptoms listed above, including x-rays, laboratory tests, biopsies, and other costly diagnostic tools. Even the treatment of symptoms that may be considered minor, such as runny nose, may be costly. Treatment of runny nose (rhinitis) is considered costly by some practitioners, and rhinitis and its treatment can complicate other illnesses (Guarderas, 1996).

Due to the potential variability in diagnosis and treatment practices and costs, it is not possible to precisely describe the "likely" approaches taken by clinicians. To clearly define the basis of cost, however, it is necessary to either establish the way in which symptoms will be approached by the "average" physician, or make explicit assumptions regarding medical services. The cost estimation method used in this analysis, as stated above, is based on a best cost-conservative estimate of how the average physician will diagnose and treat the patient.

V.2.B. Methods of Cost Estimation

Medical costs were estimated for this chapter by:

1) describing the anticipated diagnosis and treatment services using national guidelines and the medical literature;

2) assigning costs to those services, based on current (1999) Medicare reimbursement values; and

3) estimating the costs over a period of one year for all symptom groups and over five years for allergy treatment.

V.2.B.1 Sources

The primary sources consulted for this chapter were clinical practice guidelines (AHCPR, 1999; CDC, 1999), medical texts (e.g., Bennett and Plum, 1996), and the Medicare reimbursement Federal Register notices

[3] Published articles from the Abt study will not be available for some time. The study focuses on chronic fatigue syndrome, not air-related fatigue, but the diagnosis of chronic fatigue syndrome has clear implications for this analysis.

regarding costs (numerous; discussed in Chapter IV.2 on asthma). This chapter relies extensively on the National Guidelines Clearinghouse (www.guidelines.gov) developed by clinicians and researchers, which provides clinical practice guidelines. EPA also reviewed numerous journal article abstracts, but used these primarily as supporting information (to confirm other sources). The abstracts are cited when used as the only source.

Link to Chapter IV.2
Link to www.guidelines.gov

EPA used current Medicare reimbursement guidelines (1999) to obtain cost estimates for medical services. Supporting information came from the medical and economics literature. As a national system for medical services reimbursement, Medicare approximates the average cost of medical services in the United States. EPA therefore considered Medicare to be a reliable source for the cost estimates. For a more detailed discussion of the use of Medicare information, see Section B in Chapter IV.2, Medical Costs of Asthma.

Link to Chapter IV.2, Section B.

EPA determined medication costs using consumer prices for the common, over-the-counter (OTC) medications used to treat the symptoms. These costs are discussed in detail below.

V.2.B.2. Approaches Considered

There are at least two ways to approach the cost estimation of these symptom groups. The first is based on an assumption that a physician would not readily determine that the patient's symptoms were related to indoor air quality problems. Using this approach would involve estimating the likelihood that physicians would carry out numerous diagnostic tests, estimating the costs of each test and/or referral to a specialist, evaluating treatment options with their probability and cost, and summing these across all patients. This approach requires data on:

1) the specific services that may be provided,

2) the probability of any service being provided to the cross-section of patients within the symptom group, and

3) national average costs for the treatment or service.

Demographic characteristics would also be important because there are differences in treatment of children, adults, and elderly adults.

The second approach, and the one used in this analysis, is based on the much simpler assumption that the physician would diagnose the cause of the problem during the first visit, based on a careful review of the patient's history and symptoms. Additional cost data are provided to supplement the rapid diagnosis approach and can be used at the analyst's discretion.

This rapid diagnosis assumption has three advantages:

1) From a medical/scientific perspective, it is reasonable to assume that many physicians are aware of sick building syndrome or other potential effects of indoor air pollution. Sufficient information is provided in the medical literature to alert them to the problem.

2) This approach provides cost-conservative values and avoids overestimation of costs. The assumptions made using this approach are that symptoms result from relatively simple causes and that they will require relatively simple treatments. (These assumptions also pose a disadvantage, as noted below). It is extremely likely that the cost estimates provided in this report will NOT overestimate costs. This approach is more likely to underestimate costs because some physicians will do additional testing or refer the patient to a specialist.

3) This approach is a rapid and cost-effective response required for this analysis, and provides a quick and low-cost evaluation.

The major drawback of this approach is that it is likely to underestimate costs. It is not likely that all physicians will diagnose the symptoms listed above as a syndrome related to air quality problems on the first visit. In fact, there is considerable variation in how medicine is practiced and how aware physicians are of new types of diagnoses.

V.2.B.3 Additional Diagnostic Costs

To address the contingency that additional office visits may be made and that tests unrelated to the actual cause of the symptoms may be performed, additional information is provided for each symptom group regarding various medical actions that may be taken. These services and evaluations would not be included in a quick diagnosis of the source and resolution of the problem (i.e., removing the environmental cause of the symptom), but may be carried out for some patients. The analyst can use this information to construct a more complex and costly diagnostic scenario.

"Assumptions" regarding diagnosis and treatment are listed for each symptom group and area based on the simplest likely approach to diagnosis. To address additional diagnostic costs, they include a list of services that are *not* considered in this analysis (e.g., no referral to an

allergist). These elements can also be considered as additional costs, based on the application of these data.

A separate listing is provided of some other symptom causes that may be considered during diagnosis, tests that may be done, and referrals that could be made with costs for some of the more complex procedures. This supplementary information is provided under the heading "other costs," and may be used to estimate the costs of services, evaluations, and/or diagnostic tests that are not considered very likely to but which may be incurred. Use of these values can also provide a range of cost estimates.

Obtaining information on all potential screening tests for symptoms would necessitate consultation with a number of physicians (e.g., physician panels), which is beyond the scope of this work. The information provided here (as noted above) is based on a brief review of clinical practice guidelines, medical texts, and journal articles.

V.2.B.4 Symptom Treatment Description

To obtain a diagnosis and treatment description for each symptom group, clinical practice guidelines, medical abstracts, and clinical texts were reviewed. These sources all focus on linking symptoms to specific diseases or underlying causes (as discussed in Section V.2.A, above). When they proceeded to address the problem of poor indoor air quality, all the sources reiterated the most obvious medical approach to symptoms resulting from indoor air quality problems: *altering the air quality in the environment of the patient*. This change is accomplished through either moving the patient's indoor location, or by improving the air quality where that patient is exposed.[4] Most practice guidelines specify this approach as the *only* effective method of eliminating symptoms that result from poor indoor air quality.

Changing the worker's environment is legally enforceable for most jobs under the Americans With Disabilities Act (according to Occupational Medicine specialists). In practice this is not always a solution. Changing a home environment, while possible, may also be difficult.

When the assumption is being made that members of the exposed population cannot improve their air quality, the treatment of the symptoms becomes "symptomatic." This means that physicians will provide patients with recommendations about how they can minimize the discomfort associated with their symptoms. In some cases, the patients may not see a physician and may determine on their own that they should use symptomatic treatment. To address this option, costs are presented

[4] If the cause of the symptoms is through some other media (e.g., drinking water), then the environmental trigger would need to be removed as well.

below, in sufficient detail so that calculations can be made of total medical costs both with and without physician's office visits. For purposes of totaling the costs, it is assumed that persistent symptoms would result in an office visit.

The exposures resulting in these symptoms are unlike "dangerous" occupational exposures, which can lead to permanent major physical damage (e.g., liver or kidney disease, cancer, birth defects). The symptoms caused by air quality problems would not routinely be expected to result in medical problems requiring surgery, other in-hospital treatments, or ongoing in-office treatments. For most symptom groups, diagnosis is likely to consist of one visit and one or a few diagnostic tests. Treatment may consist of obtaining OTC medication, such as analgesics (e.g., aspirin, ibuprofen, acetaminophen), sore throat lozenges, body lotion, eye drops, etc.

Although standard practices are discussed in this chapter, there are substantial differences in how medicine is practiced. Even when diagnoses are identical, physicians differ in their acceptance of, and adherence to, clinical guidelines. The physician may also want to see the patient for follow-up periodically, or the patient may want further consultation after the initial visit. Individual cost elements, such as the cost of office visits, are described below so that different assumptions can be made regarding the number of office visits. Relatively simple assumptions are made to calculate total costs in this analysis, but it is very straightforward to alter these assumptions if necessary.

V.2.B.5. Cost Estimate Assumptions

Cost estimation usually relies on either:

1) obtaining cost data from the literature for a specific disease; or

2) describing a treatment profile, consisting of treatments and services that would commonly be followed for a particular disease, and obtaining probabilities of use and expenditure values for each treatment component.

This analysis follows the latter approach because recent publications did not contain information on the costs of treating the symptom groups.

The descriptions of diagnosis and treatment services contain many options. These options, discussed below, were selected to provide the most representative approach, based on the information reviewed. They were also selected to provide a reasonable low-cost estimate, assuming that the consumer would make wise choices when options are available (e.g., choose generic low-cost aspirin, rather than expensive name brand

options). Consequently, the assumptions that were made contribute to the overall cost-conservative approach taken in this analysis.

V.2.B.5.1 Office Visits

EPA used the Medicare reimbursement system was used as a source of cost information for medical treatments and tests. This system designates each reimbursable event with a Current Procedural Terminology CPT code, which is listed with the cost data below.[5] A basic diagnostic process is assumed, with history-taking and physical examination. Only those tests are included that are recommended in clinical practice guidelines (AHCPR, 1999; CDC, 1999) or commonly referred to in the medical literature. As indicated in the discussion above, it was assumed that a patient would have one diagnostic visit in a physician's office.

Costs for office visits differ based on their length. Visits are designated as levels 1 through 5, with 5 being the longest and most expensive. All office visits in this analysis were assumed to be at level 3, because it is the midpoint in both duration and cost. Office visit costs also differ, depending on whether the visit is for a new patient or an established patient (i.e., one who was seen previously by the same physician). It was assumed that half the patients had a personal physician and had been seen before by whomever they visited, and the other half were new patient visits. The costs are allocated between new and established patients with 50 percent in each group. A second visit during the same year was assumed to take place for 50 percent of patients; all patients were assumed to be established for the second visit. Using the above assumptions, the full cost for office visits is approximately $80.00 per year. This value, broken out into specific visits and the probability of receiving services, is shown in tables of each symptom's costs in later sections of this chapter.

Including this level of detail makes it possible to analyze different assumptions regarding the length and cost of the visit. In addition, Appendix V.2.B provides costs for the full spectrum of office visits (levels 1 through 5) for new and established patients.

Link to Appendix V.2.B

V.2.B.5.2 Medications

All medications considered in this analysis are common, OTC medications available at both drug and other types of stores (e.g., groceries, discount stores). EPA estimated medication costs using the lowest cost for a

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[5]Additional information on the Medicare reimbursement system, and specific sources within the system that were used for costs of office visits and diagnostic tests, are listed in Section B of the Chapter IV.2 (asthma).

Link to IV.2.B

generic product, based on prices obtained from a relatively low-cost national pharmacy chain store on October 27, 1999. EPA preferred prices taken directly from consumer goods over those taken from an industry source (e.g., the Red Book) because these are OTC medications and their consumer prices were readily available directly from the marketplace.

The medications considered are very common (e.g., aspirin) and there a high demand for these products, market pressures have therefore made their prices fairly uniform. Most patients are not expected to pay substantially higher prices than those used in this analysis. When more than one medication could commonly be used for a particular purpose (e.g., analgesics), EPA calculated the average of the costs for the different types of medications. If one option was much more expensive than others, consumers were assumed to make an informed choice to use the less expensive option.

Medications were assumed to be taken daily. Most package regimens indicate they are taken more than once per day and were assumed to be taken throughout the day, not to exceed the recommended dose. When the medication is to be taken more than once per day (e.g., every 4 hours) the daily dose was calculated for only waking hours. It was assumed that symptoms will not be sufficiently bad that someone would get up at night to take the medication. Sore throat medication is assumed not to be taken at mealtime (which occurs 3 times per day), thus reducing the daily dose frequency. Medications were assumed to be taken at the average recommended dose levels for adults. Lacking an average level, it was assumed that the lowest recommended dose was taken. For example, if one to two tablets are recommended, it was assumed that one would be taken. Eye drops and nose drops can be applied to one or two eyes or nostrils. It was assumed that both eyes or both nostrils would be affected and require medication.

It is not known what percentage of patients with these types of symptoms actually use the recommended daily dose. Assuming a full set of doses per day may be appropriate for some people, but may overestimate or underestimate doses and costs for others. Some patients use more than the recommended dose. For the medications considered in this analysis, such practices would not usually result in overt symptoms associated with an overdose. Consequently, patients could continue to exceed the recommended dose. Some patients are likely not to use any medication for symptoms, due to personal beliefs, or interactions of the symptom medications with other medications or conditions. Costs for medical treatments without medication can be calculated from the other cost components listed in the tables that follow. Due to the popularity of "natural" medicines and the common nature of the symptoms, it is very likely that some people may treat their symptoms using this approach.

"Natural" medications are often more expensive than those evaluated in this analysis.

Appendix V.2.A contains information on the cost calculations for medications.

Link to Appendix V.2.A

V.2.B.6. Cost Estimates for Symptom Groups

This section contains information on the cost of medical services and products used to address the symptoms. These costs are summarized in a table for each symptom group. Diagnostic tests and medications are listed along with assumptions regarding the medical services. The assumptions listed with each symptom group table itemize treatment options that were NOT used in this analysis because they are considered unlikely, based on the literature reviewed. The sources of additional costs that may be incurred but are unlikely are listed under "other costs" at the end of each symptom group discussion. The dollar values of these services are listed in Appendix V.2.B for office visits and services, and in Appendix V.2.C for services related to allergy diagnosis and treatment.[6] This information can be used as the basis for additional evaluations if the cost of more complex diagnosis and treatment is desired. The basic cost information presented in the tables below can be modified using the data in the appendices, and through making different assumptions regarding the length of services and other parameters, depending on the nature of the cost analysis being carried out.

Link to Appendix V.2.B
Link to Appendix V.2.C

The costs of each good or service are listed in the table with their probability of use. The weighted cost is the unit cost times the probability of service. The cost estimates below are for a one-year period, and rely on specific assumptions about the number of office visits and medications taken (e.g., one office visit is assumed for all patients and 50 percent of patients, are assumed to have a follow up visit within a year).

In all cases, the referral to a specialist is possible and is not considered in this analysis. Lacking reliable information in the literature on these and other cost factors (e.g., testing), assumptions were made that are relatively cost-conservative. When using these numbers in specific analyses, the actual duration of the symptoms (if known) can be used to pro-rate the costs appropriately. Likewise, specific information on the severity of

[6] Note that office visit costs do not vary by the level or type of practitioner specialization. Consequently, a single cost for any single level of office visit is provided.

symptoms, physician practice patterns, and patient behavior can be used with the cost information below, to tailor an economic analysis to appropriately fit the exposure and response scenarios of interest.

The costs of treating allergies that may be responsible for symptoms are described in Appendix V.2.C. Whether or not these costs are added to symptom group costs when symptoms are likely to occur in response to allergens will depend on the specific pollutant eliciting the symptom. The proportion of patients electing to undergo allergy therapy will vary based on many factors. No estimate of the proportion of patients who undergo allergy treatment as a result of the symptoms discussed is made in this chapter.

Link to Appendix V.2.C

V.2.B.6.1 Dry, Itching or Irritated Eyes

Diagnostic tests: none

Medications: eye drops

Assumptions: a full evaluation for "dry eye" will not be done, referral to an opthamologist or allergist will not take place, and an allergic work up will not be done.

Annual Estimated Direct Medical Costs for the Average Patient			
Cost Category (CPT code for medical services)	**Cost**	**Probability of Use (%)**	**Weighted Cost**
office visit: new patient, level 3 (CPT code: 99203)	$76.06	50	$38.03
office visit: established patient, level 3	$41.68	50	$20.84
second office visit: established patient, level 3	$41.68	50	$20.84
medication: eye drops	$ 17.76	100	$ 17.76
Total cost			**$ 97.27**

Other costs: additional office visits to an opthamologist or allergist. Office visit costs are listed in Appendix V.2.B, and the costs of allergy diagnosis and treatment are listed in Appendix V.2.C.

Link to Appendix V.2.B
Link to Appendix V.2.C

V.2.B.6.2. Headaches

Diagnostic tests: none

Medications: analgesics. The average of the costs for aspirin, acetaminophen, and ibuprofen was calculated.

Assumptions: CT scans, MRIs, and other sophisticated tests to evaluate anatomical or physiologically-based brain disorders will not be done and the patient will not be referred to a neurologist.[7]

Annual Estimated Direct Medical Costs for the Average Patient			
Cost Category (CPT code for medical services)	**Cost**	**Probability of Use (%)**	**Weighted Cost**
office visit: new patient, level 3 (CPT code: 99203)	$76.06	50	$38.03
office visit: established patient, level 3	$41.68	50	$20.84
second office visit: established patient, level 3	$41.68	50	$20.84
medication: analgesics	$42.27	100	$42.27
Total cost			**$121.98**

Other costs: additional office visits to an neurologist or allergist. Office visit costs and costs associated with CT scans and MRIs are also listed in Appendix V.2.B, and the costs of allergy diagnosis and treatment are listed in Appendix V.2.C.

Link to Appendix V.2.B
Link to Appendix V.2.C

[7] One study of clinical practices found that approximately 3 percent of patients complaining of headaches were given CT scans. These were primarily patients who were thought to have tumors (Becker et al., 1993).

V.2.B.6.3. Sore or dry throat

Diagnostic tests: strep throat (for streptococcal pharyngitis)

Medications: throat lozenges

Assumptions: these patients would be screened for the most common cause of sore throat that requires medical treatment (strep throat), but would not be evaluated for gastric reflux, cardiac disorders, or other relatively uncommon causes of sore throat; referral to an ear, nose, and throat specialist will not occur.

Annual Estimated Direct Medical Costs for the Average Patient			
Cost Category (CPT code for medical services)	**Cost**	**Probability of Use (%)**	**Weighted Cost**
office visit: new patient, level 3 (CPT code: 99203)	$76.06	50	$38.03
office visit: established patient, level 3	$41.68	50	$20.84
second office visit: established patient, level 3	$41.68	50	$20.84
Diagnostic tests: streptococcal throat culture	$13.05	100	$13.05
medication: throat lozenges	$201.76	100	$201.76
Total cost			**$294.32**

Other costs: additional office visits to an ear, nose, and throat specialist or allergist. Office visit costs are listed in Appendix V.2.B, and the costs of allergy diagnosis and treatment are listed in Appendix V.2.C.

Link to Appendix V.2.B
Link to Appendix V.2.C

V.2.B.6.4. Unusual tiredness, fatigue, or drowsiness

Diagnostic tests: complete blood count (CBC), thyroid screen

Medications: CDC specifies that there are no known treatments for chronic fatigue syndrome (the most analogous medical condition), although there is not complete medical consensus on this. Some physicians recommend nutritional changes. These changes are not anticipated to incur additional direct medical costs.

Assumptions: these patients would be screened for very common causes of fatigue, such as anemia and thyroid deficiencies, but they would not be intensively evaluated for apnea, sleep disorders, or other disease-related or structural causes of fatigue.

Annual Estimated Direct Medical Costs for the Average Patient			
Cost Category (CPT code for medical services)	**Cost**	**Probability of Use (%)**	**Weighted Cost**
office visit: new patient, level 3 (CPT code: 99203)	$76.06	50	$38.03
office visit: established patient, level 3	$41.68	50	$20.84
second office visit: established patient, level 3	$41.68	50	$20.84
diagnostic tests: CBC, thyroid screen (T3, T4, TSH)	$62.40	100	$62.40
medication: none	not applicable	not applicable	not applicable
Total cost			**$141.91**

Other costs: additional office visits to an allergist. Office visit costs and the costs of allergy diagnosis and treatment are listed in Appendix V.2.C.

Link to Appendix V.2.C

V.2.B.6.5. Stuffy or runny nose (rhinitis) or sinus congestion

These symptoms are evaluated as rhinitis, defined as an imflammation of the mucous membranes in the nose (Dorland's, 1994). Diagnosis is subjective; a runny nose may not be considered rhinitis, and sinus congestion may not be considered sinusitis under all circumstances. If a runny nose or sinus congestion continue for a long time or recur many times, they are more likely to be considered rhinitis or sinusitis, leading to the medical tests listed below.

Diagnostic tests: nasal cytology. The Medicare reimbursement system does not list costs for nasal cytology, which is likely for rhinitis (based on the literature). It is recommended that the cost of throat culture be used, due to their similarity.

Medications: nose drops. Oral antihistamines and other medications could be used, but they act systemically, causing side effects. It was assumed that patients would select the medication with the most specific action and minimal side effects, so nose drops were chosen for the analysis.

Assumptions: these patients would be screened for common causes of rhinitis (via nasal cytology tests), but would not be extensively evaluated for sinusitis (e.g., via x-rays), or allergies. They would not be referred to an allergist.

Annual Estimated Direct Medical Costs for the Average Patient			
Cost Category (CPT code for medical services)	**Cost**	**Probability of Use (%)**	**Weighted Cost**
office visit: new patient, level 3 (CPT code: 99203)	$76.06	50	$38.03
office visit: established patient, level 3	$41.68	50	$20.84
second office visit: established patient, level 3	$41.68	50	$20.84
Diagnostic tests: streptococcal throat culture	$13.05	100	$13.05
medication: nose drops	$42.66	100	$42.66
Total cost			**$137.22**

Other costs: additional office visits to an ear, nose, and throat specialist or to an allergist. Office visit costs and the costs of nasopharyngoscopy and rhinometry, and x-rays to examine the sinuses, are included in Appendix V.2.B. The costs of allergy diagnosis and treatment are listed in Appendix V.2.C.

Link to Appendix V.2.B
Link to Appendix V.2.C

Additional information on rhinitis (runny nose) was collected that may be relevant. Rhinitis is associated with sleep loss, secondary daytime fatigue, learning impairment, acute and chronic sinusitis, nasal polyps, otitis media with and without effusion, hearing impairment, abnormal cranofacial development in children, apnea, and asthma aggravations. There is also an increased likelihood of developing asthma. Sedating antihistamines used to treat rhinitis may cause dangerous situations due to sleepiness (Settipane, 1999).

A survey of 2,600 adults with seasonal and allergic rhinitis determined the following medication patterns: 18 percent used prescription drugs, 17 percent used prescription and OTC drugs, 46 percent used OTC only, and 18 percent used no medications. Severely-affected patients need environmental control and immunotherapy (Slavin, 1999).

V.2.B.6.6. Dry or itchy skin

Diagnostic tests: none

Medications: skin lotion

Assumptions: the patient would not be evaluated for allergies or for rare skin disorders.

Annual Estimated Direct Medical Costs for the Average Patient			
Cost Category (CPT code for medical services)	**Cost**	**Probability of Use (%)**	**Weighted Cost**
office visit: new patient, level 3 (CPT code: 99203)	$76.06	50	$38.03
office visit: established patient, level 3	$41.68	50	$20.84
second office visit: established patient, level 3	$41.68	50	$20.84
medication: dry skin lotion	$ 6.66	100	$ 6.66
Total cost			**$86.17**

Other costs: additional office visits to a dermatologist or an allergist. Office visit costs are listed in Appendix V.2.B, and the costs of allergy diagnosis and treatment are listed in Appendix V.2.C.

Link to Appendix V.2.B
Link to Appendix V.2.C

APPENDIX V.2.A. MEDICATION COST CALCULATIONS

This appendix presents the calculation of medication costs for each symptom group. EPA estimated annual doses using the recommended daily doses on each package, multiplied by 365. Assumptions regarding dose are discussed in Section V.2.B.5.2. The cost calculations are carried out by dividing the annual dose by the number of doses per package, yielding the number of packages per year. That number is multiplied by the cost per package to obtain the annual cost.

Analgesics:

ingredient	cost per pkg/ doses per pkg	daily dose	annual dose	annual cost
aspirin	6.49/500	6	2190	$28.43
acetaminophen	8.59/200	4	1460	$62.71
ibuprofen	12.22/500	4	1460	$35.68

The average was calculated based on an assumption that a third of patients would use each of the three options above; the average cost per year is $42.27. Consumer choice in this case is not based solely on price. The more expensive options have characteristics that may make them more advisable for some groups (e.g., children cannot take aspirin and some physicians won't prescribe ibuprofen to them, so acetaminophen may be the only option).

ingredient	cost per pkg/ doses per pkg	daily dose	annual dose	annual cost
Eye Drops:				
tetrahydrozoline	3.59/590	8	2920	$ 17.76
Throat Lozenges:				
dyclonine	1.99/18	5	1825	$201.76
hexylresourcinol	1.99/18	5	1825	$201.76
menthol	1.59/16	10	3650	$362.72

The cost of menthol lozenges was not used in the analysis because it was assumed that consumers would choose the less expensive therapy, and because menthol drops are taken hourly, which would also be a disincentive to using this product.

	ingredient	cost per pkg/ doses per pkg	daily dose	annual dose	annual cost
Nose drops:					
	phenylephrine	4.27/590	16	5840	$ 42.66
Dry skin lotion:					
	numerous	2.19/120	1	365	$ 6.66

The use of dry skin lotion was very difficult to assess because people may apply it to some or all of their body. This could easily generate an order of magnitude difference in dose and cost estimates. There is no standard "dose." For purposes of this analysis, it was assumed that the areas of skin normally not covered with clothes among indoor workers (hands and face) would be treated. It was also assumed that no expensive prescription medications were used. It was not possible to precisely determine the quantity of lotion used; EPA estimated that people would use 1/8 ounce per day, and would use it once per day. This assumption may underestimate costs for some people.

APPENDIX V.2.B. SUPPLEMENTAL COST INFORMATION

This appendix provides cost information for services that are designated in the "other" category for each symptom group. These services are unlikely to be carried out, but may be used by some practitioners. In addition, hospitalization costs are provided for some symptoms (this is discussed in more detail below).

Services:

The costs of diagnostic tests and all levels of office visits are listed in Table V.2.B-1 below, with their Medicare code (HCPCS), costs, and potential relevance to symptom groups. Many of the tests are relevant to multiple symptom groups. As the table shows, each type of test has many variations. The MRI and CT scans costs represent the total or "global" reimbursement, including both professional and technical services related to performing and interpreting the test. Two new medical tests for rhinitis are included in Table V.2.B-1, based on a review of the literature. These two tests, listed under "special otorhinolaryngologic services," are used to diagnose and determine both the severity of disease and the cause.

Hospitalization:

Although expected to be rare, hospitalization may occur for some symptoms, when they are diagnosed as serious forms of some diseases: rhinitis and sinusitis. The costs for other potential diseases related to the symptoms groups are not listed; no diseases were identified that require hospitalization and are likely to occur as a result of poor indoor air quality in a non-industrial setting. Although indoor air contaminants are not expected to result in hospitalization, these data can be used to estimate an upper bound on costs that may be incurred under unusual circumstances.

The Medicare costs associated with hospitalizations for sinusitis and rhinitis are listed with the costs of otitis media and URI (upper respiratory system infection) in the Medicare system (the ICD-9 code for these diseases is linked to the DRG in the Medicare system). Hospitalization costs are listed for urban and rural areas in Table V.2.B-2 below (there is no single average value).

Table V.2.B-1: Cost of Services				
HCPCS	**Description**	**Source**	**1999 Medicare**	**Relevance to Symptoms**
Diagnostic Radiology				
70210	X-ray exam, sinuses, less than three views	1	$32.30	headache, sinus
70220	X-ray exam, sinuses, complete, minimum of three views	1	$42.72	headache, sinus
70450	CT scan, head or brain, without contrast material	1	$221.93	headache, sinus
70460	CT scan, head or brain, with contrast material	1	$270.91	headache, sinus
70470	CT scan, head or brain, without and with contrast material	1	$331.34	headache, sinus
70486	CT scan, maxillofacial area, without contrast material	1	$236.17	headache, sinus
70487	CT scan, maxillofacial area, with contrast material	1	$279.59	headache, sinus
70488	CT scan, maxillofacial area, without and with contrast material	1	$339.33	headache, sinus
70551	MRI, brain, without contrast material	1	$497.36	headache, sinus
70552	MRI, brain, with contrast material	1	$597.03	headache, sinus
70553	MRI, brain, without and with contrast material	1	$1,057.57	headache, sinus
Special Otorhinolaryngologic Services				
92511	Nasopharyngoscopy with endoscope (separate procedure)	1	$63.56	nose
92512	Nasal function studies (e.g., rhinomanometry)	1	$41.33	nose
Office Visits				
99201	Office/outpatient visit, new patient, level 1	1	$34.73	all
99202	Office/outpatient visit, new patient, level 2	1	$54.53	all
99203	Office/outpatient visit, new patient, level 3	1	$76.06	all
99204	Office/outpatient visit, new patient, level 4	1	$111.14	all
99205	Office/outpatient visit, new patient, level 5	1	$138.93	all
99211	Office/outpatient visit, established patient, level 1	1	$16.32	all
99212	Office/outpatient visit, established patient, level 2	1	$30.22	all
99213	Office/outpatient visit, established patient, level 3	1	$41.68	all
99214	Office/outpatient visit, established patient, level 4	1	$63.56	all
99215	Office/outpatient visit, established patient, level 5	1	$97.94	all

* Source 1: Medicare Physician Fee Schedule
Source 2: Medicare Clinical Laboratory Fee Schedule
** "all" refers to all symptom groups

Table V.2.B-2: Cost of Inpatient Hospital Care for Sinusitis/Rhinitis					
DRG	DRG Description	ICD-9 Diagnosis Codes	DRG Relative Weight	DRG Payment for Operating and Capital for Large Urban Areas	DRG Payment for Operating and Capital for Other Areas
68	Otitis Media & URI Age > 17 With Complications*	477.0, 477.8, 477.9	0.6699	$2,997.72	$2,834.27
69	Otitis Media & URI Age > 17 Without Complications	477.0, 477.8, 477.9	0.5053	$2,261.16	$2,137.86
70	Otitis Media & URI Age 0-17	477.0, 477.8, 477.9	0.3841	$1,718.80	$1,625.08
* URI refers to upper respiratory infection					

APPENDIX V.2.C. COSTS OF ALLERGY DIAGNOSIS AND TREATMENT

A brief analysis of the likely costs of diagnosing and treating allergies for five years is provided in this appendix. Of the various diagnostic investigations that may take place beyond primary care office visits (described above), allergy screening is most likely because many of the symptoms, as chronic events, would be suspected of arising from allergies. In addition, some symptoms may actually be due to allergic responses (e.g., to molds and mildews). Most symptom groups could be associated with allergies under some conditions. For example, rhinitis is often associated with headache and tiredness when it is due to allergies. In this case, the presenting symptom may be headache or tiredness if the runny nose is mild, while the underlying cause remains an allergic response. The distinction among the clusters of symptoms is to some degree anatomical, rather than functional.

This appendix provides cost data on allergy diagnosis and therapy because allergies may be suspected of causing many of the symptom groups considered in this chapter. Patients who have one or more symptoms that indicate allergy may undergo allergy screening. The patients may or may not ultimately be diagnosed as having allergies. Consequently, costs are provided for both diagnosis and treatment. Patients found to have allergies may not have "treatable" allergies. Only those patients found to be allergic to substances for which desensitization is possible will incur the treatment costs. Whether or not a patient can be treated depends on the nature of the allergy (i.e., the type of immune response elicited). Consequently, a small subset of patients with indoor air-induced symptoms may actually be treated for allergies.

Although numerous types of allergies are mediated by different components of the immune system, this section examines the most common type, IgE-mediated. Other types may result in higher diagnostic expenses and may not necessarily be treatable.

Allergy diagnosis usually involves exposing the patient to trace amounts of suspected allergens through various types of skin tests. This section provides a summary of costs for one approach: using numerous individual allergenic screens via skin testing. Sources reviewed for this work indicated that allergen tests relying on grouped allergens were less reliable and often produced results that are difficult to interpret. It was assumed that percutaneous skin tests would be done, rather than sequential tests, intradermal tests, etc. Table V.2.C-1 lists many of the allergy-related diagnostic tests and treatments that are carried out, along with their Medicare costs.

Table V.2.C-1: Cost of Allergy Services			
HCPCS	**Description**	**Source**	**1999 Medicare Payment**
Immunology			
86003	Allergen specific IgE, quantitative or semiquantitative, each allergen	2	$7.22
86005	Allergen specific IgE, qualitative, multiallergen screen (dipstick, paddle, or disk)	2	$11.02
Allergy Testing			
95004	Percutaneous (scratch, puncture, prick) tests with allergenic extracts, immediate type reaction	1	$3.82
95010	Percutaneous (scratch, puncture, prick) tests, sequential and incremental, with drugs, biologicals or venoms, immediate type reaction	1	$11.46
95015	Intracutaneous (intradermal) tests, sequential and incremental, with drugs, biologicals or venoms, immediate type reaction	1	$12.16
95024	Intracutaneous (intradermal) tests with allergenic extracts, immediate type reaction	1	$5.56
95027	Skin end point titration	1	$5.56
95028	Intracutaneous (intradermal) tests with allergenic extracts, delayed type reaction, including reading	1	$8.68
95044	Patch or application test(s)	1	$7.64
95060	Ophthalmic mucous membrane tests	1	$13.20
95065	Direct nasal mucous membrane test	1	$7.64
Allergen Immunotherapy			
95115	Professional services for allergen immunotherapy not including provision of allergenic extracts; single injection	1	$14.59
95117	Professional services for allergen immunotherapy not including provision of allergenic extracts; two or more injections	1	$18.76
95165	Professional services for the supervision and provision of antigens got allergen immunotherapy; single or multiple antigens	1	$7.29
99205	Office/outpatient visit, new patient, level 5	1	$138.93

* Source 1: Medicare Physician Fee Schedule
Source 2: Medicare Clinical Laboratory Fee Schedule

** "all" refers to all symptom groups

Percutaneous administration, the approach selected for cost evaluation, is the least expensive and generates the most cost-conservative estimate. The other tests are used less frequently, and are used primarily when percutaneous tests do not provide clear results. It was not known how often these or other tests listed (e.g., ophthalmic mucous membrane tests, direct nasal mucous membrane test) are used. Based on a rapid review of

the past two years of medical journals on allergy, they do not appear frequently. Cost data for these less common tests can be used to generate estimates using other assumptions regarding diagnosis and treatment.

In this analysis, the number of office visits, types of diagnostic screening, and treatment methods are estimated based on a review of national guidelines (CPG, 1995, and 1996). These guidelines are not very specific with regard to testing and treatment, because the course of action depends on the patient. EPA assumed that testing would be carried out for 50 allergens. More than 200 indoor air pollutants can be tested as allergens; a review of the literature indicated that 50 allergens would be a reasonable number. In the absence of specific statements regarding the "average" amount of testing, EPA used 50 as an estimate. Due to the number of tests performed, and the fact that the results are obtained through observation during the office visit, EPA assumed that a level 5 office visit would be required. It was assumed that the patient's first visit to the allergist is designated as a "new patient visit."

If an allergic response is diagnosed as the cause of the symptoms, the patients may choose to:

1) take over-the-counter (OTC) medications (or prescriptions) for the relief of symptoms and avoid allergy treatment,

2) remove the allergens from their environment or themselves from the environment and avoid allergy treatment, or

3) undertake therapy for desensitization to the allergen.

Symptomatic relief costs are shown for each symptom group in the body of the chapter above. The costs associated with option 2 are not direct medical costs. Option 3 costs are described here.

Immunotherapy treatment was assumed to be conducted over a five-year period. This duration appeared several times in the literature, although no clear statements were found regarding "average" treatment duration. After five years of treatment, many patients (although not all) can cease treatment and will probably be symptom-free. Allergy shots (immunotherapy) are administered on a regular basis. It was assumed in this analysis that they were administered weekly.

Medicare lists specific reimbursement for allergen immunotherapy, rather than using office visit costs plus specific services costs. The Medicare cost is listed in Table V.2.C-2 below. This cost analysis used the least expensive option. If the costs were assigned to an office visit, as may be the case for some private insurers, one could assume that administration of the immunotherapy injection would require little time in the office and a

level 1 office visit.[8] The costs of levels 1 through 5 office visits are listed in Table V.2.B-1 ($16.32 through $97.94) so that this cost can be estimated, if so desired.

The costs of allergy treatment and diagnosis, based on the assumptions stated above, are summarized in Table V.2.C-2, with a total cost estimate of approximately $4,500 for a five-year period. The majority of costs for allergic patients occurs during the long-term treatment to desensitize them to the allergens. This cost can be added to the costs described for those symptom groups where some percentage of patients are to be assumed to undergo allergy diagnosis and/or treatment. OTC medications were included in the symptom treatment cost estimate above, however, so are not included in Table V.2.C-2. Patients are unlikely to take both immunology and OTC medications.

Patients who are tested but determined not to have allergies (or who have allergies that cannot be treated) will incur only the costs of diagnosis. Based on the costs presented in Table V.2.C-2, these costs would total $690.93.

[8] Given the difficulty and expense of desensitizing someone with allergies, it seems quite unlikely that the patient would take no steps to remove the allergen during the five-year period.

Table V.2.C-2. Costs of Allergy Diagnosis and Treatment for Five Years (undiscounted, 1999$)		
Procedure	**Medicare HSPCS Code**	**Cost Calculation and Result**
Allergy testing for 50 allergens — materials	86003	$7.22 per allergen × 50 allergens = $361.00
Allergy testing for 50 allergens — services	95115	$3.82 per allergen × 50 allergens = $191.00
Office visit level 5 — new patient	99205	$138.93
Immunotherapy for allergen	95115	$14.59 for a single allergen × 5 years of treatment × 52 visits per year = $3,793.40
Total cost		$4,484.33
Average annual cost for five-year period from diagnosis to completion of treatment*		$ 896.87
* The costs in the first year are higher due to diagnosis. This value is the average cost over the average period of treatment of 5 years.		

APPENDIX A: INFLATION AND DISCOUNTING FACTORS

Clicking on the sections below will take you to the relevant text.

APPENDIX A: INFLATION AND DISCOUNTING FACTORS

A.1 Introduction

This appendix provides information on the inflation of medical services and computations that can be used to calculate the present value of future costs. This information can be used to modify the values presented in the various Handbook chapters.

The chapters typically present various cost components that are expressed in the year that the data were obtained (i.e., unadjusted, or "original," dollar value). The final cost estimates are presented inflated to the dollar value in the year the chapter was completed (i.e., adjusted, or "present," dollar value). For example, in the tables leading up to the final cost calculations, data from a 1995 study are listed in the original (1995) dollars. When the various cost components are summed to calculate a total estimated medical cost, the final results are presented in present dollars for the year that the Handbook chapter was prepared, usually 1996 through 1999. The inflation factors data provided in this appendix, which are based on the Consumer Price Index Medical Care Services, can be used to obtain:

1) a current valuation of an interim cost component to a year other than the year of the Handbook presented in one of the early tables in a chapter, or

2) an inflated valuation of the final cost estimate (e.g., prior to 1999).

Methods to do this are described below. Inflation factors for future years will be added to this appendix as they become available.

Each chapter presents the final estimated costs with both zero discounting and with various discount rates, usually, one, three, five, and seven percent. The cost components leading up to the final cost estimate, however, are presented without discounting. Discounting of individual cost components is not usually required, and is therefore not included in the chapter. If those data are required, then the discounting factors and methods described below can be used to carry out discounting of any value presented in the Handbook, projected into the future for up to 20 years. It is assumed that if an analyst wishes to discount further into the future, then he or she can use the formula provided below to perform those calculations.

A.2 Inflation

Medical costs, along with most other costs, increase over time. These increases have been borne out especially in recent decades. The Consumer Price Index (CPI), which is determined by the U.S. Department of Commerce's Bureau of Labor Statistics, provides a U.S. Medical Care Services inflation value for each year, based on a review of the costs of medical services. A variety of services are reviewed by the Department of Commerce to calculate this value. Detailed information on their methods of calculation and sources of information can be obtained at their website URL (click below to link):

http://146.142.4.24/cgi-bin/surveymost?cu

CPI Medical Care Services inflation are provided in Table A.1 below for the years 1980 through 1999. The factor listed for each year can be used to inflate the cost provided in the previous years dollars (see text). Because the inflation rate is based on data from the entire year, the value to be used for the year 2000 will not be available until 2001. The for future years can be obtained directly from the above-listed URL when they become available.

Table A.1 Inflation Factors from the CPI

Year	Annual Factor	Factor to Convert to 1999$
1980	74.80	3.41
1981	82.80	3.08
1982	92.60	2.75
1983	100.70	2.53
1984	106.70	2.39
1985	113.20	2.25
1986	121.90	2.09
1987	130.00	1.96
1988	138.30	1.84
1989	148.90	1.71
1990	162.70	1.57
1991	177.10	1.44
1992	190.50	1.34
1993	202.90	1.26
1994	213.40	1.20
1995	224.20	1.14

Table A.1 Inflation Factors from the CPI		
Year	Annual Factor	Factor to Convert to 1999$
1996	232.40	1.10
1997	239.10	1.07
1998	246.80	1.03
1999	255.10	1.00

Adapted from the U.S. Department of Commerce Bureau of Labor Statistics, 2000. URL: http://146.142.4.24/cgi-bin/surveymost?cu

The information in Table A.1 can be used with a cost provided in dollars for any year from 1980 through 1998 (1999 does not need adjustment during the year 2000). The table is set up so that data from any of these years can easily be carried forward to 1999 dollars. For example, if a medical cost of $200.00 was incurred in 1983, then the multiplier of 2.53 would be applied to yield the following:

$$\$200.00 \times 2.53 = \$506 \text{ in 1999 dollars.}$$

Although costs can be calculated for years prior to the current year (i.e., 1999), this requires an additional calculation. It was assumed that such a calculation would rarely be used, since interim year costs are not generally of use. For example, if a 1987 cost of $200.00 was desired in 1991 dollars, then a new conversion factor would need to be calculated. The conversion factor is determined by dividing the CPI value of the year to which the analyst wishes to inflate (in this case 1991) by the CPI value of the year from which the data are taken. In this example, the CPI value is 177.10 for 1991, and 130.00 for 1987. The new conversion factor is the quotient of these two numbers:

$$\text{CPI value 1991/CPI value 1987} = 177.10/130.00 = 1.36$$

This new conversion factor is multiplied by the 1987 cost of $200.00 to obtain the 1991 cost:

$$1.36 \times \$200.00 = \$272.00 \text{ in \$1991.}$$

There are uncertainties associated with use of these factors. The CPI are based on average increases in costs. Some medical services increase more than others during a given year. Given the uncertainty inherent in the estimated medical costs provided in this Handbook, such uncertainties are not likely to have a substantial impact. Most medical costs of diseases that are presented in the Handbook represent an aggregate of costs arising from

many types of services and materials, and can be inflated with the CPI-generated inflation factors, which also are derived from a spectrum of services and materials.

A.3 Discounting

Discounting is used by economists when costs are to be incurred in the future. It is applied to make future costs comparable to current costs because consumers have a preference for current consumption compared to future consumption. Because health-related costs limit the funds available for consumption, a consumer would prefer to postpone payment of a given cost and the resulting reduction in consumption into the future. The current value of a given dollar amount to a consumer is therefore less if it has to be paid in the future than if it is incurred today.

The present value of costs are calculated by taking into account the amount of time between the present and the point when the costs are incurred, and by making some assumption regarding the degree to which current consumption is more highly valued. This amount is usually expressed as a present value discount rate ranging from one to ten percent, although it is possible to use no (0) discounting or to apply a higher rate. This chapter uses the discount rates most commonly used by EPA of one, three, five, and seven percent. Costs are also presented in undiscounted form.

The basic equation used to carry out discounting is:

$$PV = C\ (1+r)^{-t}$$

where: PV = present discounted value
C = future cost to be incurred
r = discount rate
t = number of years to be discounted

Table A.2 shows the factors that can be used to apply this equation to a specific cost (C), when one uses these discount rates over specific periods of time. The number of years is calculated by subtracting the present year from the future year. For example, to discount a cost to be incurred in 2010 to the year 2000, a discounting factor for year 10 in the table would be used (2010-2000 = 10). These factors were calculated using the portion of the above equation: $(1+r)^{-t}$, to obtain a simple multiplier corresponding to each discount rate and the first 20 years into the future. For example, a cost of $300 discounted for 10 years at five percent would result in the following calculating using the equation above without discounting factors:

$$PV = \$300 \times (1 + 0.05)^{-10} \quad = \$183$$

Using the factors in Table A.2, a simpler equation can be used with the factor of 0.61 for five percent at 10 years:

$$PV = \$300 \times .61 = \$183.$$

It is important to note that the years listed in the table represent the number of years in the future one wishes to discount to (i.e. Year 1 represents one year in the future). The number of years is calculated by subtracting the present year from the future year of interest. For example, to discount a cost to be incurred in 2010 to the year 2000, a discounting factor for year 10 from Table A.2 would be used (2010 – 2000 = 10). The discounting factors can be applied to costs presented in the Handbook to obtain the present discounted value of an individual cost or a stream of costs, as discussed below.

Table A.2 Discounting Factors for 20 Years into the Future
Factors are the multipliers applied to the original cost to obtain a discounted cost (see text).

Year	1%	3%	5%	7%
1	0.99	0.97	0.95	0.93
2	0.98	0.94	0.91	0.87
3	0.97	0.92	0.86	0.82
4	0.96	0.89	0.82	0.76
5	0.95	0.86	0.78	0.71
6	0.94	0.84	0.75	0.67
7	0.93	0.81	0.71	0.62
8	0.92	0.79	0.68	0.58
9	0.91	0.77	0.64	0.54
10	0.91	0.74	0.61	0.51
11	0.90	0.72	0.58	0.48
12	0.89	0.70	0.56	0.44
13	0.88	0.68	0.53	0.41
14	0.87	0.66	0.51	0.39
15	0.86	0.64	0.48	0.36
16	0.85	0.62	0.46	0.34
17	0.84	0.61	0.44	0.32
18	0.84	0.59	0.42	0.30
19	0.83	0.57	0.40	0.28
20	0.82	0.55	0.38	0.26

Often, analysts evaluate a stream of costs incurred on a regular basis over many years. This method requires a more complex calculation. The present discounted value must be calculated independently for each year that new costs are introduced. When medical costs are likely to occur sequentially over time, such as long term care or monitoring for chronic diseases, the present discounted value is calculated for those costs incurred in each year in the future. That is, the appropriate factor is multiplied by the cost for each individual year of service. These costs are then summed to obtain the total present discounted value of the long-term treatment.

For example, a common occurrence is that follow up medical monitoring is required after an initial high cost treatment year. If the follow up costs $500.00 per year for five years into the future, then the total present value of the follow-up care can be calculated by summing the present for each of those five years. Assume that the monitoring costs are discounted at three percent. The factors taken from Table A.2 for a three percent discount rate are multiplied by $500 as follows:

$$\underset{\text{(Year 1)}}{0.97 \times \$500} + \underset{\text{(Year 2)}}{0.94 \times \$500} + \underset{\text{(Year 3)}}{0.92 \times \$500} + \underset{\text{(Year 4)}}{0.89 \times \$500} + \underset{\text{(Year 5)}}{0.86 \times \$500} = \$2{,}289.85.$$

It is usually advisable to set up the factors in a spreadsheet to carry out this type of calculation if costs extend long into the future, or if there are numerous discount rates or cost elements being considered.

When calculating the present value of medical services, it is essential to determine the timing of those services. In many cases, there are various levels of care that gradually decline over time, but in some cases these may increase (e.g., when it is estimated for non-surviving patients that terminal care will be provided at some point in the future). Consequently, there may be different costs incurred at different points in the future, and these must each be discounted appropriately. As noted above, *each chapter presents the final medical cost estimates both of undiscounted and present discounted , that take the specific staging and timing of services into account.* It is therefore not necessary to perform discounting calculations unless interim or partial cost calculations are required, as in the case, for example, of the need for only hospitalization or pharmaceutical costs for asthmatics, but not the full spectrum of costs for all medical services. Due to the relatively unlikely need for such data, the discounted of components of total costs were not provided in the chapters.

Additional data or guidance needed on the genesis and application of inflation or discounting factors can be found in most basic economic text books.

GLOSSARY AND ABBREVIATIONS

This glossary provides brief definitions of some technical terms used in the handbook. Special effort was made to include those that are used repeatedly or that may cause confusion because they have a number of different meanings (e.g., colloquial versus technical). It does not provide definitions of many medical terms used in the Background section of the chapters to describe a disease because it is assumed that if the reader wishes to obtain more detailed information on a disease they will consult a medical text book. Commonly used abbreviations are also included with their full spelling.

antineoplastic: anticarcinogenic.
ATSDR: Agency for Toxic Substances and Disease Reduction.
carcinomas: malignant tumor.
CDC Centers For Disease Control.
cellular proliferation: cell growth.
CFS: chronic fatigue syndrome.
chelation therapy: therapy to remove metals.
chemotherapeutics: chemical therapy, usually.
chromosomal aberrations.
chronic bioassays: studies over long periods of time.
congenital anomalies: birth abnormalities.
COPD: chronic obstructive pulmonary disease.
CPI: consumer price index.
CPT: current procedural terminology.
CT: computerized tomography.
cytogenic abnormalities: cell abnormalities.
DRG: diagnostically related group.
EKG:electrocardiogram.
embryogenesis: development of an embryo.
environmental agents (e.g., DDT and its metabolites).
ER: emergency room.
ETS: environmental tobacco smoke.
FEV: forced expiratory volume.
genotoxicity: toxic to genetic material.
GI: gastrointestinal.
hepatic: liver.
heritable cell lines: genetic information passed from one generation to the next.
histology: cell evaluation.
HMO: Health Maintenance Organization.
HSDB: Hazardous Substances Data Base.
ICD: International Classification of Disease.
immunotherapy: therapy involving the immune system.
indigent population: population with very limited financial resources.
involvement of nodes: lymph node pathology.
IV: intervenous.
latency period: time between exposure and disease onset or detection.
LRI: lower respiratory infection.

metasticize: pathological spread of disease.
MRI: magnetic resonance imagery.
mucosa: mucous membranes.
mutagenicity: causing genetic change.
NAS: National Academy of Sciences.
NCHS: National Center for Health Statistics.
NCI: National Cancer Institute.
NHLBI: National Heart, Lung, and Blood Institute.
NIH: National Institutes of Health.
OTC: over the counter.
palliative care: care for terminally ill patients.
peripheral neuropathy: nerve damage affecting limbs.
placental barrier: barrier preventing transfer of some materials from mother to fetus.
sarcomas: malignant tumor of specific mesinchymal origin.
SNF: skilled nursing facility.
somatic cell lines: genetic information relevant to one individual, not heritable.
TRI: Toxic Release Inventory.
URI: upper respiratory infection.
WTP: willingness-to-pay.
xenoestrogens: estrogens introduced from outside sources.

REFERENCES

(Citations obtained on-line often do not contain page numbers.)

AAFA (Asthma and Allergy Foundation of America). 1999. At website: http://www.aafa.org/whatis.html

Abeloff, M.D., J.D. Armitage, A.S. Lichter, J.E. Niederhuber. 1995. *Clinical Oncology*. New York: Churchill Livingston.

AHCPR (Agency for Health Care Policy and Research). 1999. National Guideline Clearinghouse, website: http://www.guidelines.gov. (This is a compendium of guidelines from numerous government agencies, professional medical societies, and other sources. It theoretically includes all guidelines developed in the U.S. and those with international consensus. The degree to which these are followed is questionable, and there is a considerable literature that discusses the fact that physicians do not follow some guidelines.)

Aligne, Andrew, MD. 1999. Personal communication with Dr. Kathleen Cunningham, September 29, Rochester, New York.

American Medical Association. 1993. *Physicians Current Procedural Terminology CPT '94*. Chicago, IL: American Medical Association.

American Thoracic Society. 1986. *Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease and Asthma*. American Lung Association.

Anderson, K., A.D. Watt, D. Sinclair, et al. 1989. "Climate, intermittent humidification, and humidifier fever." *Brit J of Ind Med*. Vol. 46, pp 671-674.

Ando, M., M. Suga. 1997. "Hypersensitivity pneumonitis," *Curr Opin Pulm Med*. Vol. 3, No. 5, p. 391-395.

Archer, V.E., G.K. Livingston. 1983. "Environmental carcinogenesis and mutagenesis." In: *Environmental and Occupational Medicine*, Rom, W.N., Ed. Little Brown and Company, Boston, Mass.

ATSDR. 1993. *Toxicological Profile for Chromium*. (Draft.) Washington, DC.

ATSDR. 1997. *Draft Toxicological Profile for Lead*. Washington, D.C.: DHHS.

ATSDR. 1998. *Toxicological Profile for Arsenic*. Washington, D.C.: DHHS.

Baker, Mary S., N. Kessler, N. Urban, R. Smucker. 1991. "Estimating the treatment costs of breast and lung cancer." *Medical Care*, Vol. 29, No. 1, January: 40-49.

Baker, Mary S. et al. 1989. "Site specific treatment costs for cancer: an analysis of the medicare continuous history sample file." In: *Cancer Care and Cost. DRGs and Beyond*. Richard M. Scheffler and Neil C. Andrews, Eds. Ann Arbor, MI: Health Administration Press Perspectives.

Baler, G. Robert. 1995. Conversation with Abt Associates. Brockton, MA. January 23.

Balinsky, B.I. 1970. *An Introduction to Embryology*, W.B. Saunders, Co. Philadelphia.

Balter, Michael. 1992. "Studies set to test competing theories about early infection. (childhood leukemia)," *Science*. 256(5064): 1633.

Bartoshesky, L.E. et al. 1985. "Seizures in children with meningomylocele.," *AJDC*. 139: 400-402.

Baur, X., J. Behr, M. Dewair, et al. 1988. "Humidifier lung and humidifier fever," *Lung*. Vol. 166, pp. 113-124.

Bebout, D.E., J. Hodgkin, E. Zorn, A. Yee, E. Sammer. 1983. "Clinical and physiological outcomes of a university-hospital pulmonary rehabilitation program," *Respiratory Care*, Vol. 28, No. 11, November.

Becker, L.A., L.A. Green, D. Beaufait, J. Kirk, J. Froom, and W.L. Freeman. 1993. "Use of CT scans for the investigation of headache: a report from ASPN, Part I," *J. Fam Pract*, Aug, Vol. 37, No. 2, pp 129-134. (Note: ASPN is Clinicians in the Ambulatory Sentinel Practice Network)

BEIR VI (Biological Effects of Ionizing Radiation). 1998. National Academy of Sciences Press, Washington, D.C.

Belin, L., N.A. Ekstrom, and E. Falsen. 1979. "Immunological and clinical responses to humidifier fever antigens," *Monogr. Allergy*. Vol. 14, pp.146-149.

Bennett, J.C., F. Plum. 1996. *Cecil Textbook of Medicine*, 20th Edition. W.B. Saunders Company, Philadelphia.

Blum, R.W. et al. 1992. "Family and peer issues among adolescents with spina bifida and cerebral palsy," *Pediatrics*. 88: 280-285.

Bove, E.L. et al. 1989. "Repair of truncus arteriosus in the neonate and young infant," *Annals of Thoracic Surgery*. 47: 499-506.

Boyle, M., G. Torrence, J. Sinclair, and S. Horwood. 1983. "Economic evaluation of neonatal intensive care of very low birth weight infants," *N.E. Jnl Med*, June 2, 1983. Vol: 308, pp 1330+

Breast Cancer Prevention Collaborative Research Group. 1992. "Breast cancer: environmental factors," *The Lancet*. 340: 904.

Bureau of the Census. 1990. *Statistical Abstract of the United States*. Washington, D.C.: U.S. Government Printing Office.

Burrows, Benjamin. 1987. "The natural history of asthma," *Journal of Allergy and Clinical Immunology*, pp. 373-376.

CDC (Centers for Disease Control). 1994. *Legionnaires' Disease*, at CDC's clinical practice guidelines website: http://www.cdc.gov/ncidod/diseases/hip/pneumonia/1-legion.htm

CDC (Centers for Disease Control). 1996. *Biopsy-confirmed Hypersensitivity Pneumonitis in Automobile Production Workers Exposed to Metalworking Fluids–Michigan, 1994-1995.* At CDC website: http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/0043265.htm

CDC (Centers for Disease Control). 1997. *Legionellosis*, at CDC's clinical practice guidelines website: http://www.cdc.gov/epo/mmwr/other/case_def/legion97.html

CDC (Centers for Disease Control). 1998a. At website: http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00052262.htm

CDC (Centers for Disease Control). 1998b. At website: http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00055803.htm

CDC (Centers for Disease Control). 1998c. *Ambulatory Health Care Visits by Children: Principal Diagnosis and Place of Visit.* At website: http://www.cdc.gov/nchswww/data/

CDC (Centers for Disease Control). 1999. At website: http://www.cdc.gov

CDC (Centers for Disease Control). 1999a. At website: http://www.cdc.gov/epo/mmwr/nchswww/fastats/asthma/htm

CDC (Centers for Disease Control). 1999b. At website: http://www.cdc.gov/nchswww/datawh/statab/unubd/mortabs/ gmwk291.htm and gmwk291a.htm

Chambers, J.E., J. Yarbrough (Eds). 1982. *Effects of Chronic Exposure to Pesticides on Animal Systems.* Raven Press, New York.

Chomitz, V., L. Cheung, and E. Lieberman. 1995. "The role of lifestyle in preventing low birth weight," *The Future of Children*, Vol: 5, No. 1, spring, 1995.

Civin, Curt I. 1989. "Reducing the Cost of the Cure in Childhood Leukemia" (Editorial), *The New England Journal of Medicine*. 321(3): 185.

Clayton, G.D. and F.E. Clayton (Eds). 1982. *Patty's Industrial Hygiene and Toxicology*, 3rd edition, Volumes 2A, 2B, 2C. New York: Wiley.

Cockcroft, A., J. Edwards, C. Bevan, et al. 1981. "An investigation of operating theatre staff exposed to humidifier fever antigens," *Brit J of Ind Med.* Vol. 38, pp.144-151.

Cohen, P. and J.G. Kohn. 1979. "Follow-up study of patients with cerebral palsy," *West Journal of Medicine*. 130: 6-11.

Corman, H. 1994. *The Effects of Low Birth Weight and Other Medical Risk Factors on Resource Utilization in the Preschool Years*. Report to the Center for the Future of Children, June, 1994.

Corman, H. and Chaikind, S. 1993. *The Effect of Low Birth Weigh Ton the Heatlh, Behavior and School Performance of School-aged Children.* Working Paper No. 4409. Cambridge, MA. National Bureau of Economic Research, July, 1993.

Council on Environmental Quality. 1981. *Chemical Hazards to Human Reproduction.* Washington, D.C.: U.S. General Printing Office.

Coventry J.A., M.S. Weston, and P.M. Collins. 1996. "Emergency room encounters of pediatric patients with asthma: cost comparisons with other treatment settings," *J Ambulatory Care Manage*. 19(2): 9-21.

CPG (Clinical Practice Guidelines). 1995. "Practice parameters for allergy diagnostic testing," *Ann Allergy Asthma Immunol*, Dec., Vol. 75 (6 Pt 2) (no author listed) obtained from National Guideline Clearinghouse, 11/1/99, at http://www.guidelines.gov

CPG (Clinical Practice Guidelines). 1996. "Practice parameters for allergen immunotherapy," *J. Allergy Clin Immunol*, Dec., Vol. 98 (6 Pt 1) (no author listed) obtained from National Guideline Clearinghouse, 11/1/99, at http://www.guidelines.gov

Crocker , T.D., and M.D. Agee. 1995. "Parental altruism and child lead exposure, inferences from the demand for chelation therapy," *Jnl of Hum Resources*.

Cunningham, K.C. and W.H. Hallenbeck. 1985. *Pesticides and Human Health*. Springer-Verlag Press, New York.

Doll, Richard and Richard Peto. 1981. *The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today*. New York: Oxford University Press.

Dorland's (*Dorland's Illustrated Medical Dictionary*). 1982. W.B. Saunders, Philadelphia, Pa.

Dorland's (*Dorland's Illustrated Medical Dictionary*). 1994. W.B. Saunders, Philadelphia, Pa.

Dorland's Pocket Medical Dictionary, 23rd Edition. 1994. W.B. Saunders, Philadelphia, Pa.

Doroshow, James H. 1991. "Doxorubicin-induced cardiac toxicity" (Editorial) (Abstract), *The New England Journal of Medicine*. 324(12): 843.

Doull, J., C.D. Klassen, and M.O. Amdur (Eds.). 1980. *Casarett and Doull's Toxicology, The Basic Science of Poisons*, 2nd Ed. New York: Macmillan.

Dunger, David B. 1989. "The frequency and natural history of diabetes insipidus in children with langerhans-cell histiocytosis (histiocytosis X)" (Abstract), *The New England Journal of Medicine*. 321(17): 1157.

Ebert, P.A. et al. 1984. "Surgical treatment of truncus arteriosus in the first 6 months of life," *Annals of Surgery*. 200: 451-456.

Edelstein, P.H. 1996. "Legionellosis." In: *Cecil's Textbook of Medicine*. Bennett and Plum, Eds., Saunders, Philadelphia.

Edwards, J.H. 1980. "Microbial and immunological investigations and remedial action after an outbreak of humidifier fever," *Brit J of Ind Med.* Vol. 37, pp 55-62.

Eggleston, P.A. 1994. "Asthma." In Oski et al Eds, *Principles and Practices in Pediatrics*, Lippincott Co., Philadelphia

Emmons, Carrol, Abt Associates. 1999. Conversation, November.

Feld, R., R. Ginsberg, D. Payne, and F. Shepherd. 1995. "Lung." In *Clinical Oncology*. Abeloff et al, eds., Churchill Livingstone, New York.

Finkler, Steven A. 1982. "The distinction between costs and charges," *Annals of Internal Medicine*, 96:102-109. Philidelphia, PA.

Fischer, A., L. Chestnut, and D. Violette. 1989. "The value of reducing risks of death: a note on new evidence," *Journal of Policy Analysis and Management,* Vol. 8, No. 1., 1989.

Fraser, F.C. 1970. "The genetics of cleft lip and cleft palate," *Am. J. Human Genet.* V 22: 336-352.

Froster-Iskenius, U.G. and P.A. Baird. 1990. "Amelia: incidence and associated defects in a large population," *Teratology*. 41: 23-31.

Gaioni S.J., M. Korenblat-Hanin, E.B. Fisher, and P. Korenblat. 1996. "Treatment outcome in an outpatient asthma center: retrospective questionnaire data," *The American Journal of Managed Care*. 2(8):999-1008.

Garry, V., D. Schreinemachers, M. Harkins, and J. Griffith. 1996. "Pesticide appliers, biocides, and birth defects in rural Minnesota," *Envir. Health Persp.* Vol: 104, No. 4, April.

Gaston, H. 1985. "Does the spina bifida clinic need an ophthalmologist?" *Z. Kinderchir*. 40 (suppl I): 46-50.

Greineder, D.K., K.C. Loane, and P. Parks. 1995. "Reduction in resource utilization by an asthma outreach programj," *Arch Pediatr Adolesc Med.* 149: 415-420.

Guarderas, J.C. 1996. "Rhinitis and sinusitis: office management," *Mayo Clin Proc*, Sep. 7, Vol. 71, No. 9 pp 882-8.

Gunderson, L., J.H. Donohue, and P.A. Burch. 1995. "Lung." In: *Clinical Oncology* Abeloff, M.D. et al., eds. Churchill Livingstone, New York.

Hack, M., N. Klein, and H. Taylor. 1995. "Long-term developmental outcomes of low birth weight infants," *The Future of Children*, Vol:5, No. 1, Spring, 1995.

Hannigan, M.P., G.R. Cass, A.L. Lafleur, W.F. Busby, and W.G. Thilly. 1996. "Seasonal and spatial variation of the bacterial mutagenitic of fine organic aerosol in southern California," *Envir Health. Persp.* Vol:104, No. 4, April.

Hartunian, Nelson, C. Smart, and M. Thompson. 1981. *The Incidence and Economic Costs of Major Health Impairments*. Lexington, MA: Lexington Books.

Hayes, W.H. 1982. *Pesticides Studied in Man*. Baltimore, MD: Williams & Wilkins.

Higgins J.C., W.R. Kiser, S. McClenathan, and N.L. Tynan. 1998. "Influence of an interventional program on resource use and cost in pediatric asthma," *The American Journal of Managed Care*. 4(10):1465-1469.

Hoffmann, G.R. 1991. "Genetic toxicology." In: *Casarett and Doull's Toxicology, The Basic Science of Poisons*, Fourth Edition, Amdur, M.O, Doull, J., Klaassen, C.D. Eds., McGraw-Hill, Inc., New York

Hunter, D.J., et al. 1990. "A prospective study of selenium status and breast cancer risk," *Journal of the American Medical Association.* 264(9): 1128-31.

Hutton, J.L. et al. 1994. "Life expectancy in children with cerebral palsy," *BMJ*. 309: 431-435.

International Agency for Research on Cancer. 1979. *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Some Halogenated Hydrocarbons*, Volume 20. Lyon, France: World Health Organization.

Javadpour, Nasser., Ed. 1984. *Cancer of the Kidney*. New York: Thieme-Stratton, Inc.

Jones PA and R.K. Ross. 1999. "Prevention of bladder cancer," *N Engl J Med.,* May 6, 340(18):1424-6.

Judson, J.P. et al. 1983. "Double-outlet right ventricle; surgical results, 1970-1980," *Journal of Thoracic Cardiovascular Surgery*. 85: 32-40.

Kanitz, S., Franco, Y., Patrone, V., Caltrabellotta, M., Raffo, E., Riggi, C., Timitilli, D., Giambattista, R. 1996. "Association between drinking water disinfection and somatic parameters at birth," *Envir. Health Persp.* Vol: 104, No. 5, May.

Key, M.M., A.F. Henschel, J. Butler, R.N. Ligo, I.R. Tabershaw, and L. Ede (Eds). 1977. *Occupational Diseases: A Guide to Their Recognition*. Washington, DC: U.S. General Printing Office.

Kimmel, C.A. 1993. "Approaches to evaluating reproductive hazards and risks," *Environ Health Persp.* Vol 101: Supplement 2, pp 137-143.

Kirklin, J.W. 1991. "The surgical repair for complete transposition," *Cardiol. Young.* 1: 13-25.

Klein, Eric A., et al., Eds. 1993. *Renal Cell Carcinoma: Immunotherapy and Cellular Biology*. New York: Marcel Dekker, Inc.

Klein, N.C. and B.A. Cunha. 1998. "Treatment of legionnaires' disease," *Semin Respir Infect.* June, Vol. 13, No.2, pp.140-146

Konishi, Noboru et al. 1994. "Renal carcinogenesis." In: Waalkes, Michael P., and Jerrold M. Ward, Eds. 1994. *Carcinogenesis*. New York: Raven Press.

Krupnick, Alan J., M. Cropper, et al. 1989. *Valuing Chronic Morbidity Damages: Medical Costs and Labor Market Effects*. Draft Final Report on EPA Cooperative Agreement CR-814559-01-0. Washington, D.C.: Resources for the Future. June 26.

Lewit, E., L. Baker, H. Corman, and P. ShioNo. 1995. "The direct cost of low birth weight," *The Future of Children,* Vol: 5, No. 1, Spring, 1995.

Lipscomb, J. 1986. *Human Capital, Willingness-to-Pay and Cost-Effectiveness Analyses of Screening for Birth Defects in North Carolina*. Durham, NC: Duke University.

MMWR. 1999. URL: http://www.cdc.gov

Mamelon, M., D.M. Lewis, M.A. Blanchet, et al. 1993. Investigation of an outbreak of "humidifier fever" in a print shop. *Am J of Ind Med.* Vol. 23, pp. 483-490.

Mason, K.J. 1991. "Congenital orthopedic anomalies and their impact on the family," *Nursing Clin. North Am*. 26: 1-19.

Mayer, R.J. 1998. "Gastro intestinal tract cancer." In Fauci, A.S. et al., eds. *Harrison's Principles of Internal Medicine*, 14th ed, part 6, section 1, chapter 92. NY: McGraw-Hill Companies, Inc., Health Professional's Division, 2784 pp. ISBN 0-07-020291-5.

Mayo, P.H., J. Richman, and H.W. Harris. 1990. "Results of a program to reduce admissions for adult asthma," *Annals of Internal Medicine*. 112(11): 864-871.

McCredie, Margaret. 1994. "Bladder and kidney cancers." In: *Cancer Surveys: Trends in Cancer Incidence and Mortality. Volume 19/20.* Plainview, NY: Cold Spring Harbor Laboratory Press.

McLone, D.G. 1983. "Results of treatment of children born with a myelomeningocele," *Clinical Neurosurgery*. 30: 407-412.

McSharry, C., K. Anderson, and G. Boyd. 1987. "Serological and clinical investigation of humidifier fever," *Clin Allergy*. Vol. 17, pp 15-22.

McVicker, R.W. et al. 1994. "Prevalence and associated features of epilepsy in adults with Down syndrome," *British Journal of Psychiatry*. 164: 528-532.

Mendez, A.A. et al. 1988. "Treatment of patellofemoral instability in Down's syndrome," *Clinical Orthopedics*. 234: 148-158.

Modan, Baruch et al. 1989. "Increased risk of breast cancer after low-dose radiation," *The Lancet*. March 25, pp. 629-30.

Montie, James E. et al., Eds. 1990. *Clinical Management of Renal Cell Cancer*. Chicago: Year Book Medical Publishers.

Mor, Vincent. 1993. Brown University Center for Gerontology and Health Care Research. Conversation with Abt Associates. September 21.

Mor, Vincent, Edward Guadagnoli, and Christian Brostrup-Jensen. 1990. *Medical Care Costs Incurred by Newly Diagnosed Cancer Patients.* Brown University Center for Gerontology and Health Care Research. Draft Report, Supported in Part by National Cancer Institute Grant #CA 44100.

Morris, C.D. and V.D. Menashe. 1991. "25-year mortality after surgical repair of congenital heart defect in childhood: a population-based cohort study," *Journal of the American Medical Association*. 266: 3447-3452.

Morton, William E. 1992. "Freon and hypertension" (Letter to the Editor; includes reply), *JAMA, The Journal of the American Medical Association*. 268(12): 1540+.

Mulhern, Raymond K. 1992. "Deterioration of intellect among children surviving leukemia: IQ test changes modify estimates of treatment toxicity" (Brief Report), *Journal of Consulting and Clinical Psychology*. 60(3): 477.

Munger, R., P. Isacson, S. Hu, T. Burns, J. Hanson, C. Lynch, K. Cherryholmes, P. Van Dorpe, and W. Hausler. 1997. "Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies," *Envir. Health Persp.* Vol 105, No. 3.

Murray, Robert F., Jr. 1991. "Skin color and blood pressure: genetics or environment?" *JAMA, The Journal of the American Medical Association*. 265(5): 639+.

Nathan, R. and J. Santilli. 1999. Research Abstract. *Allergy and Asthma Proceedings*, Vol. 20, No. 3. May - June.

National Academy of Sciences (NAS). 1983. *Identifying and Estimating the Genetic Impact of Chemical Mutagens,* National Academy Press, Washington, D.C.

National Academy of Sciences (NAS). 1994. *Pesticides in the Diets of Infants and Children.* Washington, D.C.: NAS.

National Cancer Institute. Referenced in multiple years. URL: http://www.nci.nih.gov/

National Cancer Institute (NCI). 1994. *SEER Cancer Statistics Review, 1973-1991.* Edited by L.A.G. Ries et al. NIH Pub. No. 94-2789. Bethesda, MD.

National Cancer Institute (NCI). 1995. Chemical Carcinogenesis Research Information System (CCRIS). Accessed via TOXNET.

National Cancer Institute (NCI). 1998. Surveillance, Epidemiology and End Results (SEER) reports and tables provided on line at: http://www-seer.ims.mci.nih.gov. The data used in these reports vary in their dates of origin, but the data used in the chapter are generally current through 1994.

National Center for Health Statistics. 1987. "1985 summary: national ambulatory medical care survey," from *Vital and Health Statistics*, Number 128, January 23. U.S. Department of Health and Human Services.

National Center for Health Statistics. 1989. *Current Estimates from the National Health Interview Survey, 1988.* Series 10, No. 173. Centers for Disease Control, U.S. Department of Health and Human Services.

National Center for Health Statistics. 1990a. *Current Estimates from the National Health Interview Survey, 1989.* Series 10, No. 176. Centers for Disease Control, U.S. Department of Health and Human Services.

National Center for Health Statistics. 1990b. "1988 Summary: National Hospital Discharge Survey," Advance Data Number 185 from *Vital and Health Statistics.* Centers for Disease Control, U.S. Department of Health and Human Services, June 19.

National Center for Health Statistics. 1990c. "1987 life tables," *Vital Statistics of the United States. Volume II.* Public Health Service.

National Center for Health Statistics. 1991. Telephone communication with James Deloizier, July 31, regarding data in the National Ambulatory Care Survey.

National Center for Health Statistics. *Vital Statistics in the United States.* Referenced in multiple years. URL: http://www.cdc.gov/nchs

National Center for Health Statistics (NCHS). 1998. *Vital Statistics in the United States*, 1995, Preprint of Volume II, Mortality, Part A Section 6 Life Tables. Hyattsville, MD.

National Foundation for Brain Research. *The Cost of Disorders of the Brain.* Washington, DC: Author, 1992.

National Heart, Lung, and Blood Institute. 1987. *The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Section 34. Some Risk Factors Related to the Annual Incidence of Cardiovascular Disease and Death Using Pooled Repeated Biennial Measurements Framingham Heart Study, 30-Year Followup*. Kannel, W.B., Wolf, P.A., and Garrison, R.J., Eds. NIH Publ. No. 87-2703. February.

National Heart, Lung, and Blood Institute (NHLBI). 1991. *Guidelines for the Diagnosis and Management of Asthma.* Draft, January.

National Heart, Lung, and Blood Institute (NHLBI). 1993. *The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure*. NIH Publication No. 93-1088. January.

National Heart, Lung, and Blood Institute (NHLBI). 1993. Spokesperson, Conversation with Abt Associates. December 3.

National Heart Lung and Blood Institute (NHLBI). 1997. *Guidelines for the Diagnosis and Management of Asthma*, obtained at website:http://www.nhlbi.nih.gov/nhlbi/lung/asthma /prof/asthgldln.htm

Nelson, Harold. 1991. "The natural history of asthma," *Annals of Allergy*, Volume 66, March.

NIH Consensus Conference. 1991. "Treatment of early-stage breast cancer," *Journal of the American Medical Association.* 265(3): 391-5.

Oldham, H.N. et al. 1972. "Pulmonary artery banding in infants with complex congenital heart defects," *Annals of Thoracic Surgery*. 13:342.

Oski, F.A., et al. (Eds.) 1994. *Principles and Practice of Pediatrics*. 2nd Edition. J.B. Lippincott. Philadelphia.

Oster, G. et al. 1984. *The Economic Cost of Smoking and Benefits of Quitting*. D.C. Heath and Company.

OTA (Office of Technology Assessment, U.S. Congress). 1988. *Healthy Children: Investing in the Future*. OTA-A-345. Washington, D.C. USGPO, February, pp 212+

Pal, T.M., Monchy, J.R., Groothoff, J.W., et al. 1999. "Follow up investigation of workers in synthetic fibre plants with humidifier disease and work related asthma," *Occup. Environ. Med.* Vol. 56, pp. 403-410.

Paneth, N. 1995. "The problem of low birth weight," *The Future of Children*, Vol: 5, No. 1, Spring, 1995, p 19+.

Peto, Julian. 1990. "Radon and the risks of cancer" (Abstract), *Nature*. 345(6274): 389.

Philipp, R. 1983. "Humidifier fever: Clinical recognition and environmental control," *New Zealand Med J.* June 8, pp. 426-427.

Pinsky, W.W. and E. Arciniegas. 1990. "Tetralogy of Fallot," *Pediatr. Clin. N. Amer.* 37: 179-192.

Pitcher, W.D. 1990. "Hypersensitivity pneumonitis," *Am J Med Sci.* Vol. 300, No. 4, pp 251-266.

Pomerance, J.J. L.J. Pomerance, and J.A. Gottleib. 1993. "Costs of caring for infants weighting 500 - 749 g at birth," *Ped Rsch*, Vol: 4, pp 231A+

Pueschel, S.M. and J.E. Rynders. 1982. *Down Syndrome: Advances in Biomedicine and the Behavioral Sciences.* Cambridge, Massachusetts: Ware Press.

Raven, P.H. and G.B. Johnson. 1986. *Biology.* Times Mirror/Mosby College Publ., St. Louis, Mo.

Red Book Annual Pharmacists Reference. 1991. Oradell, NJ: Medical Economics Co.

Red Book Annual Pharmacists Reference. 1998. Oradell, NJ: Medical Economics Co.

Rice, D.P., T.A. Hodgson, and A.N. Kopstein. "The Economics costs of illness: a replication and update," *Health Care Financing and Review.* 1985;7(1).

Riley, Jerry. 1993. Division of Beneficiary Studies, Health Care Financing Administration. Conversation with Abt Associates. October 6.

Riley, G., A. Potsky, J. Lubitz, and L. Kessler. 1995. "Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis," *Medical Care,* Vol. 33. No. 8.

Robbins, S., R. Contran, R., and V. Kumar. 1989. *Robbins Pathological Basis of Disease*, 4th Edition, W.B. Saunders Col, Philadelphia, PA.

Rodgers, Gary, M.D. 1995. Conversation with Abt Associates. Boston University Medical Center, Boston, MA. January 25.

Roscoe, Cathy. 1995. Conversation with Abt Associates. New England Medical Center, Boston, MA. August 8.

Samuelsson, L. and O. Eklof. 1988. "Scoliosis in myelomeningocene," *Acta Orthop Scand.* 59(2): 122-127.

Semine, A.A. et al. 1978. "Cervical-spine instability in children with Down syndrome (Trisomy 21)," *Journal of Bone and Joint Surgery.* 60-A: 649-652.

Settipane, R.A. 1999. "Complication of allergic rhinitis," *Allergy and Asthma Proceedings*, Vol. 20, No. 4.

Shen, W.K. et al. 1990. "Sudden death after repair of double-outlet right ventricle," *Circulation*. 81: 128-136.

Shiono, P. and R. Behrman. 1995. "Low birth weight: analysis and recommendations," *The Future of Children,* Vol: 5, No. 1, Spring, 1995.

Slavin, R.G. 1999. "The future of allergy practice: a different perspective from another academician," *Allergy and Asthma Proceedings*, Vol 20., No. 4.

Sober, Arthur, M.D. 1994. Conversation with Abt Associates. Massachusetts General Hospital, Boston, MA. November 29, 1994.

Stellman, J.M. 1983. "The occupational and environment and reproductive health." In: *Environmental and Occupational Health*, W. Rom, Ed. Little Brown and Co., Boston, Mass.

Strauss, Michael, D. Conrad, J. LoGerfo, L. Hudson, and M. Bergner. 1986. "Cost and outcome of care for patients with chronic obstructive lung disease," *Medical Care*, Vol. 24, No. 10, October.

Thomas, A.P. et al. 1987. "The health care of physically handicapped young adults," *Z. Kinderchir*. 42 (suppl I): 57-59.

Tice, R.R., H.F. Stack, and M.D. Waters. 1996. "Human exposures to mutagens - an analysis using the genetic activity profile database," *Envir Health Persp.* Vol: 104, Suppl. 3, May.

Touati, G.D. et al. 1990. "Primary repair of tetralogy of Fallot in infancy," *Journal of Thoracic Cardiovascular Surgery*. 99: 396-403.

Turner, A. 1986. "Upper limb functioning of children with myelomeningocele," *Developmental Medicine and Child Neurology*. 28: 790-798.

U.S. Bureau of the Census, *Statistical Abstract of the United States: 1995* (115th edition.) Washington, DC, 1995.

U.S. Department of Commerce. 1994. *Statistical Abstract of the United States 1994. 114th Edition*. Bureau of the Census. ISBN 0-16-045174-4. Table 747.

U.S. Department of Health and Human Services, PHS, CDC, NIOSH. 1983. *Registry of Toxic Effects of Chemical Substances*. Washington, DC: U.S. General Printing Office.

U.S. Department of Health and Human Services (USDHHS). 1988a. *Child Health Supplement of the 1988 National Health Interview Survey*. Washington, D.C.

U.S. Department of Health and Human Services (USDHHS). 1988b. *1987 National Medical Expenditure Survey*. Washington, D.C.

U.S. Department of Labor. 1989. *Handbook of Labor Statistics*. Bureau of Labor Statistics, August.

U.S. Department of Labor. Bureau of Labor Statistics. 1994. *CPI Detailed Report Data for October 1994*. ISSN 0161-7311. November.

U.S. Department of Labor. 1995. *CPI Detailed Report. Data for January 1995*. ISSN 0161-7311. Bureau of Labor Statistics. February. Table 3.

U.S. Department of Labor. Bureau of Labor Statistics. 1996a. *CPI Detailed Report Data for November 1995*. ISSN 0161-7331. December.

U.S. Department of Labor. Bureau of Labor Statistics. 1996b. *Consumer Price Index*. Washington, DC. (http://www.bls.gov)

U.S. Department of Labor. 1997. *CPI Detailed Report*. Bureau of Labor Statistics. World Wide Web site: http://stats.bls.gov/cgi-bin/surveymost

U.S. Environmental Protection Agency. 1983a. *Tox One-liners* are brief summaries of the results of animal studies that were submitted by the pesticide manufacturers to U.S. EPA for purposes of registration and tolerance setting. Data collected in 1983 as cited in Cunningham and Hallenbeck, 1985.

U.S. Environmental Protection Agency. 1983b. *Surveillance Indices* are summaries of data on pesticide composition, use, food residue tolerances, ecologic effects, and health effects. Data collected in 1983, as cited in Cunningham and Hallenbeck, 1985.

U.S. Environmental Protection Agency. 1985. *Costs and Benefits of Reducing Lead in Gasoline; Final Regulatory Impact Analysis*. Washington, D.C.: Office of Policy Analysis, February.

U.S. Environmental Protection Agency. 1986. *Guidelines for Carcinogen Risk Assessment*, FR Vol 51, No. 185. September 24. 1986, pp. 33992+, Washington D.C.

U.S. Environmental Protection Agency. 1987. *Methodology for Valuing Health Risks of Ambient Lead Exposure*. Research Triangle Park, NC: Office of Air Quality Planning and Standards, December.

U.S. Environmental Protection Agency. 1991. *Guidelines for Developmental Toxicity and Risk Assessment*. Federal Register Vol 56, No. 234, December 5, 1991. Pp 63798+

U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. 1992a. *The Medical Costs of Five Illnesses Related to Exposure to Pollutants*. June. Prepared by Abt Associates.

U.S. Environmental Protection Agency. 1992b. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*, Office of Air and Radiation, Washington, D.C.

U.S. Environmental Protection Agency. 1995a. *Toxic Chemical Release Inventory Reporting Form R and Instructions. Revised 1994 Version*. EPA 745-K-95-051. March.

U.S. Environmental Protection Agency. 1995b. *Toxics Release Inventory Reporting Modifications Beginning With 1995 Reporting Year*. EPA 745-R-95-009. February.

U.S. Environmental Protection Agency. 1996a. *Air Quality Criteria for Ozone and Related Photochemical Oxidants*, Office of Research and Development, Washington,D.C.

U.S. Environmental Protection Agency. 1996b. *Proposed Guidelines for Carcinogen Risk Assessment*. EPA/600/P-92-003C. Office of Research and Development, Washington, D.C.

U.S. Environmental Protection Agency. 1997. *Exposure Factors Handbook*. Office of Research and Development, Washington, D.C.

U.S. Environmental Protection Agency 1999. *Indoor Air Pollution - An Introduction for Health Professionals*. At website: http://www.epa.gov/iaq/pubs/hpguide.html

Vettorazzi, G. 1979. *International Regulatory Aspects for Pesticide Chemicals, Volume 1, Toxicity Profiles*. Boca Raton, FL: CRC.

Viscusi, K. 1992. *Fatal Tradeoffs: Public & Private Responsibilities for Risk*, Oxford University Press, New York.

Waitzman, Norman J., R. Scheffler and P. Romano. 1996. *The Costs of Birth Defects: Estimates of the Value of Prevention*. Lanham, MD: University Press of America, Inc.

Walsh, E.P. et al. 1988. "Late results in patients with tetralogy of Fallot repaired during infancy," *Circulation*. 77: 1062-1067.

Watkins, M., L. Edmonds, A. McClearn, L. Mullint, J. Mulinare, and M. Khoury. 1996. "The surveillance of birth defects: the usefulness of the revised US standard birth certificate," *Amer J. Pub Health*. Vol: 86, No. 5, pp 731-734.

Wazer, David, M.D. 1994. Conversation with Abt Associates. New England Medical Center, Boston, MA. December 7.

Webster, W.S. and A.A. Valois. 1987. "Reproductive toxicology of manganese in rodents, including exposure during the postnatal period," Neurotoxicology Series, Vol: 8, p 437. In: *Yearbook of Toxicology I.* Sunshine, Ed. CRC Press Boca Raton, Fla.

Weiss K.B., P.J. Gergen, and T.A. Hodgson. 1992. "An economic evaluation of asthma in the United States," *The New England Journal of Medicine*. 326(13):862-866.

Westley C.R., R.N. Spiecher, L. Starr, et al. 1997. "Cost effectiveness of an allergy consultation in the management of asthma," *Allergy and Asthma Proc*. 18(1):15-18.

Williams, G., Weisburger, J. 1993. "Chemical carcinogenesis." In Amdur, M., Doull, J., Klassen, C., eds., *Casarett and Doull's Toxicology, The Basic Science of Poisons*, Fourth Ed. New York: McGraw-Hill, Inc.

Wollack, J.B. et al. 1991. "Static encephalopathies." In: Rudolph, A.M. et al., eds., *Rudolph's Pediatrics*. Norwalk, Connecticut: Appleton Lange: 1721-1724.