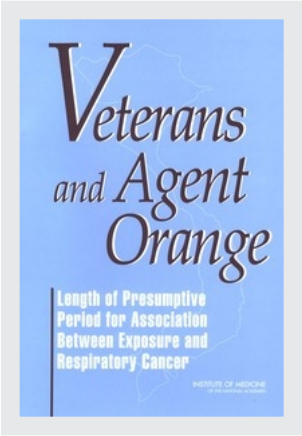

Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer

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Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides

Veterans and Agent Orange

Length of Presumptive Period for Association Between Exposure and Respiratory Cancer

Committee to Review the Health Effects in
Vietnam Veterans of Exposure to Herbicides

Board on Health Promotion and Disease Prevention

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recom-

mendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **David J. Tollerud, MD, MPH,** of the Institute of Public Health Research at the University of Louisville. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the institution.

Preface

In 1991, because of continuing uncertainty about the long-term health effects on Vietnam veterans who where exposed to herbicides during their service in Vietnam (mixtures of 2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T], picloram, and cacodylic acid), Congress passed Public Law 102-4, the Agent Orange Act of 1991. That legislation directed the secretary of veterans affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of those herbicides, including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The secretary was also to ask NAS to conduct updates at least every 2 years for 10 years from the date of the first report to review newly available literature and draw conclusions from the overall evidence.

In response to the request, the Institute of Medicine (IOM) of NAS convened a committee, whose conclusions IOM published in 1994 in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (hereafter referred to as *VAO*). The work of later committees resulted in the publication of biennial updates (*Update 1996*, *Update 1998*, *Update 2000*, and *Update 2002*) and of focused reports reviewing the scientific evidence regarding type 2 (non-insulin-dependent) diabetes (*Type 2 Diabetes*) and acute myelogenous leukemia in children (*Acute Myelogenous Leukemia*).

VAO concluded that there is "limited/suggestive" evidence of an association between exposure to at least one of the chemicals of interest (2,4-D, 2,4,5-T and its contaminant TCDD, picloram, and cacodylic acid) and respiratory cancer.

That conclusion was reaffirmed in *Update 1996*, *Update 1998*, *Update 2000*, and *Update 2002*.

The Department of Veterans Affairs (VA), on the basis of the findings of *VAO* and its own review of the available literature, published a notice in the *Federal Register* on February 3, 1994, stating that there is "a positive association between exposure to herbicides used in the Republic of Vietnam and the subsequent development of respiratory cancers." The VA further found that "the weight of the available evidence indicates that chemically-induced respiratory cancers manifest within a definitive period following exposure, after which there is little effect from the exposure," and proposed, as part of its rule, that respiratory cancer will be presumed service connected only if it is manifest within 30 years after exposure.

In the Veterans Education and Benefits Expansion Act of 2001, Public Law 107-103, Congress removed the 30-year presumptive period for respiratory cancer and mandated that the secretary of veterans affairs ask NAS to conduct a study. That study was to review "available scientific literature on the effects of exposure to an herbicide agent containing dioxin on the development of respiratory cancers in humans." And to review "whether it is possible to identify a period of time after exposure to herbicides after which a presumption of service-connection" of respiratory cancer would not be warranted.

To complete this task, the IOM called upon the *Update 2002* committee to extend its service and address this issue. This committee consists of members who are leading experts in their fields, have no conflicts of interest with regard to the matter under study, and have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or TCDD exposure. Biographical sketches of committee members and staff appear in the appendix.

The committee worked on several fronts in conducting this updated review, always with the goal of seeking the most accurate information and advice from the widest possible range of knowledgeable sources. Consistent with procedures of the NAS, the committee met in closed sessions and working group meetings in which members could freely examine, characterize, and weigh the strengths and limitations of the evidence.

The committee is grateful to Michelle Catlin who skillfully served as the study director for this project. The committee would also like to acknowledge the excellent work of IOM staff members Jennifer Cohen, Joe Esparza, and Elizabeth Albrigo. Thanks are also extended to Jim Banihashemi, who handled the finances for the project; Norman Grossblatt, who provided excellent editorial skills; and William McLeod, who conducted database searches.

Irva Hertz-Picciotto, *Chair*

Contents

Executive Summary

From 1962 to 1971, US military forces sprayed herbicides over Vietnam to strip the thick jungle canopy that helped conceal opposition forces, to destroy crops that enemy forces might depend on, and to clear tall grasses and bushes from the perimeters of US base camps and outlying fire-support bases. Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the majority of the herbicides sprayed. Agent Orange was a 50:50 mixture of 2,4-D and 2,4,5-T. At the time of the spraying, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, one form of dioxin) was an unintended contaminant from the production of 2,4,5-T and was present in Agent Orange and some other formulations sprayed in Vietnam.

In 1991, because of continuing uncertainty about the long-term health effects on Vietnam veterans of the herbicides sprayed, Congress passed Public Law 102-4, the Agent Orange Act of 1991. That legislation directed the secretary of veterans affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of those herbicides, including TCDD. The secretary was also to ask that NAS conduct updates at least every 2 years for 10 years from the date of the first report to review newly available literature and draw conclusions from the overall evidence.

In response to the request, the Institute of Medicine (IOM) of NAS convened a committee, whose conclusions IOM published in 1994 in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (hereafter referred to as *VAO*). The work of later committees resulted in the publication of biennial

updates (*Update 1996*, *Update 1998*, *Update 2000*, and *Update 2002*) and of focused reports reviewing the scientific evidence regarding type 2 (non-insulin-dependent) diabetes (*Type 2 Diabetes*) and acute myelogenous leukemia in children (*Acute Myelogenous Leukemia*).

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The Department of Veterans Affairs (VA), on the basis of the findings of *VAO* and its own review of the available literature, published a notice in the *Federal Register* on February 3, 1994, stating that there is "a positive association between exposure to herbicides used in the Republic of Vietnam and the subsequent development of respiratory cancers." The VA further found that "the weight of the available evidence indicates that chemically-induced respiratory cancers manifest within a definitive period following exposure, after which there is little effect from the exposure," and proposed, as part of its rule, that respiratory cancer will be presumed service connected only if it is manifest within 30 years after exposure.

In the Veterans Education and Benefits Expansion Act of 2001, Public Law 107-103, Congress removed the 30-year presumptive period for respiratory cancer and mandated that the secretary of veterans affairs ask NAS to conduct a study. That study was to review "available scientific literature on the effects of exposure to an herbicide agent containing dioxin on the development of respiratory cancers in humans." And to review "whether it is possible to identify a period of time after exposure to herbicides after which a presumption of service-connection" of respiratory cancer would not be warranted.

The question of the latent period between exposure to the chemicals of interest and the time frame for manifestation of increased respiratory cancer risk was addressed in *Update 1996* and *Update 1998*. *Update 1996* reviewed published results on the timing of exposure in relation to several cancers, including respiratory cancer. For respiratory cancer, the reports of some potentially informative studies did not include latency results, and no latent period could be estimated. On the basis of several subsequent studies that did address that issue, *Update 1998* concluded that "the evidence suggests that if respiratory cancer does result from exposure to the herbicides used in Vietnam, the greatest relative risk for lung cancer may be in the first decade after exposure, but until further follow-up has been carried out for some of the cohorts, it will not be possible to put an upper limit on the length of time these herbicides could exert their effect."

CHARGE TO THE COMMITTEE

In response to the request from the VA, IOM extended the service of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to

Herbicides that was responsible for *Update 2002* to address the question of presumptive period and respiratory cancer. The charge to the committee was to undertake a review and evaluation of the evidence regarding the period between cessation of exposure to herbicides used in Vietnam and their contaminants (2,4-D, 2,4,5-T and its contaminant TCDD, cacodylic acid, and picloram) and the occurrence of respiratory cancer.

COMMITTEE'S APPROACH TO THE CHARGE

The committee concluded in *Update 2002* that there is "limited/suggestive" evidence of an association between at least one of the chemicals of interest and respiratory cancer (of lung and bronchus, larynx, and trachea). For the present report, the committee did not reevaluate that conclusion. Rather, its literature review focused on articles that provide information on the time course of exposure and the development of respiratory cancer. In addition to the data on the chemicals of interest, the committee briefly reviewed what is known about the latent period of respiratory cancer after exposure to some other physical and chemical agents. Although it is difficult to extrapolate timeframes from animal bioassays to human cancers, the committee reviewed data from experimental animal and in vitro studies that could provide insight into the mechanisms by which the chemicals might lead to cancer and the toxicokinetics (absorption, distribution, metabolism and elimination) of the chemicals. On the basis of the available epidemiologic and toxicologic data, the committee considered TCDD to be the main chemical of concern for respiratory cancer and therefore focused on the toxicokinetic and mechanistic data related to TCDD.

When discussing how long the effects of exposure in Vietnam might last, the committee found it important to differentiate between the actual latent period (time from disease induction to disease detection), the latent period typically measured in epidemiologic studies (time from beginning of exposure to disease detection), and what can be referred to as the presumptive period (time from cessation of exposure to disease detection). It is important to note that the latent period measured is typically a range representing the latencies of all individuals. Given the congressional mandate to review "whether it is possible to identify a period of time after which a presumption of service-connection" of respiratory cancer would not be warranted, the presumptive period is the primary concern of this committee.

EPIDEMIOLOGIC EVIDENCE

If there is a causal association between TCDD exposure and respiratory cancer, the literature suggests that the risk can be increased beginning as early as 6 years after exposure, but it is less clear on how long the effect lasts. In a study of industrial workers exposed to TCDD conducted by the National Institute for Occupational Safety and Health (NIOSH), risks were most increased 20 years or

more after exposure began, even for those with only 1–4 years of exposure (that is, 16–19 years after exposure ended). In a study conducted by the International Agency for Research on Cancer, the standardized mortality ratio (SMR) in workers exposed to TCDD or higher chlorinated dioxins dropped to 1.0 10–19 years after first exposure and rose to 1.2 20 years or more after first exposure (95% confidence interval [95% CI], 1.0–1.4), but no analyses are presented by years since last exposure. Studies have been conducted on a cohort exposed environmentally to TCDD after an accident at a chemical plant in Seveso, Italy. The 15-year follow-up of the Seveso cohort did not provide any data on lung cancer[1] latency, but the most recent follow-up showed a modest increase in the risk estimate 15-20 years after exposure. A study of Australian Vietnam veterans showed increased lung cancer mortality in the first decade after the start of their military service, but that finding is based on a small number of deaths. The most recent study of the Ranch Hands (Air Force personnel responsible for aerial spraying of Agent Orange) showed an SMR of 1.3 for 20 years or more of latency.

The committee also found evidence in the NIOSH study that the time between exposure and the detection of respiratory cancer depends on the magnitude of exposure. If latency depends on the level of exposure, the pattern of time between exposure and detection would not necessarily be expected to be the same in all studies, nor would the pattern of risk over time since exposure be expected to be the same for Vietnam veterans as it was for those exposed in manufacturing plants or through accidental environmental releases of the same chemicals.

In summary, a number of studies have examined latency by stratifying on time since first exposure. In those analyses, some studies suggest increased risk of respiratory cancer within 10 years of exposure, others indicated increased risk 15–20 years after exposure began, and still others report risks that remained elevated 20 or more years beyond initial exposure. No analyses examined the risks in relation to the presumptive period, so there is no empirical evidence regarding how long this would be for TCDD. In many of the studies, however, there is no indication that risks return to background levels during the entire length of the follow-up.

[1]The committee's conclusions are for respiratory cancer (of the lung, bronchus, larynx, and trachea). Some epidemiology studies look at respiratory cancer together; others separate those cancers into subtypes (for example, lung cancer, tracheal cancer). When discussing the epidemiology studies, the committee refers to the designation used by the study author.

OTHER EVIDENCE

Toxicokinetic Data

TCDD readily crosses cell membranes and accumulates in lipid-rich organs. Estimates of the half-life of TCDD in humans have been consistent in confirming that TCDD is highly persistent in the body, with a half-life averaging about 7.5 years. That long half-life must be taken into consideration in evaluating cessation of exposure and the presumptive period. Mobilization of TCDD stored in lipid-rich organs can result in continued exposure of target organs after external exposure has ended. Although exposure to herbicides in Vietnam was time-limited, potential elevated exposure of target organs could occur until serum TCDD in a Vietnam veteran reached the background value. Therefore, the persistence of an elevated body burden of TCDD could increase the duration of exposure of target organs, during which induction of disease may occur at any time, thereby lengthening the presumptive period (i.e., the interval between external exposure cessation and disease detection) from the cessation of external TCDD exposure in Vietnam to the detection of respiratory cancer.

Mechanistic Data

To mechanistically model and evaluate the carcinogenic properties of a chemical, the multistage-carcinogenesis approach is often used: a chemical might initiate, promote, or alter the progression of a neoplasm. Latent periods and presumptive periods for different chemicals will depend on differences in the mechanisms by which the chemicals act, that is, on whether they are initiators or promoters. Furthermore, carcinogenic chemicals that are relatively persistent in the body may initiate or promote the carcinogenic process over a long period. Therefore, latencies may be short or long from the time of initial exposure because effects on the carcinogenic process may occur at any time during the period when the body burden is increased and at multiple stages of the carcinogenic process. All available experimental evidence indicates that TCDD acts as a promoter by multiple pathways in the regulation of cell proliferation and differentiation. Given the tumor-promoting potential of TCDD and its persistence, latency might be altered by TCDD's acting as a promoter whenever the body burden of TCDD is increased.

Data on Other Respiratory Carcinogens

Although no epidemiologic studies have evaluated the presumptive period for TCDD and respiratory cancer, a substantial body of literature explores issues of timing of exposure and respiratory cancer for other respiratory carcinogens, including gamma rays, radon daughters, smoking, arsenic, and asbestos. Most of

the data on those agents indicate that the risk of respiratory cancer remains increased for many decades after exposure has ended. For example, lung cancer risk posed by exposure to arsenic or radon remained increased in Chinese tin miners for more than 50 years after exposure ended. Time courses cannot be directly extrapolated from other chemicals to TCDD, but the available data indicate that in many instances respiratory cancer can be associated with a chemical exposure that occurred many decades earlier.

UNCERTAINTY

To assess the presumptive period between cessation of exposure and a given health outcome in a particular group, such as Vietnam veterans, it must be established that the exposure in question is associated with the outcome, and then how long the risk of the health outcome remains increased after cessation of exposure must be evaluated. The overall uncertainty in the estimate of the presumptive period includes uncertainty in the association and uncertainty in the time course. *Update 2002* concluded that evidence remains "limited/suggestive" that there is an association between exposure to at least one of the chemicals of interest and respiratory cancer. As is evident from the categorization of the evidence as "limited/suggestive", uncertainty remains with regard to the association between the exposures of interest and respiratory cancer.

For the chemicals of interest and respiratory cancer, uncertainty in the strength of the evidence of an association and in whether the association is causal is a consequence of the absence of data on smoking, occupational exposures, and other confounding factors in published studies. However, some confidence in the lack of confounding by smoking and other exposures comes from evidence that smoking is not a confounder in large-scale occupational studies with internal comparisons; although smoking patterns differ between white-collar and blue-collar workers, there are not large variations in smoking rates within industrial cohorts. The presence of animal data that support the plausibility of an association between TCDD and respiratory cancer—with studies indicating that TCDD can act as a promoter of respiratory cancer—also increases the committee's confidence in its conclusion of "limited/suggestive" evidence of an association between the exposure and respiratory cancer.

With respect to determining the time course of exposure and disease detection, errors in the assignment or timing of exposure could increase uncertainty in the estimates. Other aspects of epidemiologic studies that might affect the presumptive period include whether a study evaluates cancer incidence or cancer mortality, whether competing mortality is affecting the results of a study, and whether a substantial subgroup in the population is genetically susceptible or has acquired a susceptibility to respiratory cancer. There is also the possibility that coexposure to effect modifiers alters the presumptive period. Although other exposures, such as smoking and other chemicals, could potentially modify the

effects of TCDD on respiratory cancer, there is no evidence of such a modification in the epidemiologic studies reviewed.

The greatest uncertainty with respect to the presumptive period for TCDD and respiratory cancer, however, comes from the lack of data on the time between cessation of exposure and manifestation of respiratory cancer in the epidemiologic literature. Such data are needed to provide an accurate estimate of the presumptive period.

COMMITTEE'S CONCLUSIONS ON PRESUMPTIVE PERIOD

There are few data on the latent period and no data on the presumptive period for TCDD and respiratory cancer. The available data on latency suggest that an increased risk of respiratory cancer occurs within 10 years of exposure. In many of the studies, the risk of respiratory cancer is still increased at the end of the follow-up period, or until at least 20 or 25 years after exposure began.

The main question for the committee is whether it is possible to put an upper limit on the length of time that TCDD can exert its effect and, if so, what that limit would be—that is, the presumptive period. Because there are no epidemiologic data on the length of time after exposure to TCDD ceases during which an increase in respiratory cancer is associated with that exposure, the committee cannot determine a period beyond which occurrence of respiratory cancer could no longer be presumed to be related to exposure to TCDD (that is, no upper limits on the latency or presumptive period could be determined). However, given the long latent period seen in epidemiologic studies (risks remaining increased up to 25 years after exposure), the persistence of TCDD in the body, and the fact that the risk of respiratory cancer posed by some other agents remains increased for many decades after exposure has ended (50 years or more following cessation of exposure), the committee concludes that the effects of TCDD on respiratory cancer could last many decades.

1

Introduction

From 1962 to 1971, US military forces sprayed herbicides over Vietnam to strip the thick jungle canopy that helped to conceal opposition forces, to destroy crops that enemy forces might depend on, and to clear tall grasses and bushes from the perimeters of US base camps and outlying fire-support bases. Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the bulk of the herbicides sprayed. The herbicide mixtures used were named according to the colors of identification bands painted on the storage drums; one of the main chemical mixtures sprayed was Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-T). At the time of the spraying, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, one form of dioxin) was an unintended contaminant formed in the production of 2,4,5-T and was present in Agent Orange and some other formulations sprayed in Vietnam.

In 1991, because of continuing uncertainty about the long-term health effects on Vietnam veterans of the herbicides sprayed, Congress passed Public Law (PL) 102-4, the Agent Orange Act of 1991. That legislation directed the secretary of veterans affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of those herbicides, including TCDD. The secretary was also to ask NAS to conduct an update at least every 2 years for 10 years from the date of the first report to review newly available literature and draw conclusions from the overall evidence.

In response to the request, the Institute of Medicine (IOM) convened a committee, whose conclusions were published in 1994 in *Veterans and Agent*

Orange: Health Effects of Herbicides Used in Vietnam (hereafter referred to as *VAO*). The work of later committees resulted in the publication of biennial updates (*Update 1996*, *Update 1998*, *Update 2000*, and *Update 2002*) and focused reports reviewing the scientific evidence regarding type 2 (non-insulin-dependent) diabetes (*Type 2 Diabetes*) and acute myelogenous leukemia in children (*Acute Myelogenous Leukemia*).

VAO (IOM, 1994) concluded that there is "limited/suggestive" evidence of an association between exposure to at least one of the chemicals of interest (2,4-D, 2,4,5-T and its contaminant TCDD, picloram, and cacodylic acid) and respiratory cancer (of lung and bronchus, larynx, and trachea). That conclusion was reaffirmed in *Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), and *Update 2002* (IOM, 2003).

The Department of Veterans Affairs (VA), on the basis of the findings of *VAO* and its own review of the literature, published a notice in the *Federal Register* in February 1994, stating that there is "a positive association between exposure to herbicides used in the Republic of Vietnam and the subsequent development of respiratory cancers" (Federal Register, 1994). The VA further found that "the weight of the available evidence indicates that chemically-induced respiratory cancers manifest within a definitive period following exposure, after which there is little effect from the exposure" (Federal Register, 1994). That Federal Register notice discusses data on chemically-induced respiratory cancers in Ontario steel-plant workers (Finkelstein et al., 1991), people exposed as a result of a trichlorophenol-process accident in West Virginia (Zack and Suskind, 1980), and workers exposed to TCDD after a 1953 accident in a factory in Germany (Zober et al., 1990). The VA therefore proposed, as part of its rule, that respiratory cancer "be presumed service connected only if it is manifest within 30 years after exposure" (Federal Register, 1994).

The Veterans Education and Benefits Expansion Act of 2001, PL 107-103, removed the 30-year presumptive period for respiratory cancer and mandated that the secretary of veterans affairs ask the National Academy of Sciences (NAS) to review "available scientific literature on the effects of exposure to an herbicide agent containing dioxin on the development of respiratory cancers in humans." And to review "whether it is possible to identify a period of time after exposure to herbicides after which a presumption of service-connection" for the disease would not be warranted.

CHARGE TO THE COMMITTEE

In response to the VA request, IOM extended the service of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides that was responsible for *Update 2002* to address the question of presumptive period and respiratory cancer. The charge to the committee was to review and evaluate the evidence regarding the period between cessation of exposure to the

chemicals used in Vietnam (2,4-D, 2,4,5-T and its contaminant TCDD, cacodylic acid, and picloram) and the occurrence of respiratory cancer.

COMMITTEE'S APPROACH TO THE CHARGE

To meet its charge, the committee conducted literature searches to identify relevant research. As discussed earlier, the committee had concluded in *Update 2002* that there is "limited/suggestive" evidence of an association between at least one of the chemicals of interest and respiratory cancer. For the current report, the committee did not reevaluate that conclusion; rather, it focused on articles that provide information on the time course of exposure and development of disease. In addition to the data on the chemicals of interest, the committee briefly reviewed what is known regarding the latent period of respiratory cancer after exposure to other physical and chemical agents. And, although it is not possible to extrapolate directly from animal bioassays to human cancers with respect to the timing of carcinogenesis, the committee reviewed data from experimental animal and in vitro studies that could provide insight into the mechanisms by which the chemicals might lead to cancer.

PREVIOUS CONCLUSION REGARDING RESPIRATORY CANCER

Update 2002 (IOM, 2003) concluded that evidence remained "limited/suggestive" regarding an association between exposure to at least one of the chemicals of interest (2,4-D, 2,4,5-T and its contaminant TCDD, picloram, or cacodylic acid) and respiratory cancer (of the lung and bronchus, larynx, and trachea). A health outcome is classified as being "limited/suggestive" if the evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent. Uncertainty is introduced by the absence of data on smoking, occupational exposures, and other confounding factors in available studies. Animal studies support the plausibility of the association and a role of TCDD as a promoter.

EVALUATIONS OF LATENCY BY PREVIOUS COMMITTEES

The question of the latent period between exposure to the chemicals of interest and respiratory cancer was first addressed by the IOM committee in *Update 1996*. That report reviewed results on the timing of exposure in relation to respiratory cancer and prostate cancer. For respiratory cancer (as well as prostate cancer), the reports of some potentially informative studies did not include latency, and no latent period could be estimated.

Update 1998 reviewed the literature relevant to latency that was published

after *Update 1996*. With respect to respiratory cancer, it discussed evidence from the National Institute for Occupational Safety and Health study of chemical workers (Fingerhut et al., 1991), studies of environmental exposures after an industrial accident in Seveso, Italy (Bertazzi et al., 1989a,b; 1997), a study of Finnish herbicide appliers (Asp et al., 1994), occupational studies on a cohort compiled by the International Agency for Research on Cancer (Kogevinas et al., 1997) and a study on a subset of the cohort (Becher et al., 1996), studies of Vietnam veterans who were involved in the aerial spraying of the herbicides (the Ranch Hands) (Michalek et al., 1998), and studies of Australian Vietnam veterans (Crane et al., 1997). The *Update 1998* committee's conclusion was that "the evidence suggests that if respiratory cancer does result from exposure to the herbicides used in Vietnam, the greatest relative risk for lung cancer may be in the first decade after exposure, but until further follow-up has been carried out for some of the cohorts, it will not be possible to put an upper limit on the length of time these herbicides could exert their effect" (IOM, 1999).

When *Update 2000* was being prepared, the new data on latency were not sufficient to warrant a reexamination of the latent period. In light of the request for the present report, the *Update 2002* committee did not review latency.

ORGANIZATION OF THIS REPORT

The remainder of this report is organized into three chapters. Chapter 2 discusses the committee's use of the terms *latency* and *presumptive period* and the factors that can affect those periods, and briefly discusses chemicals that are known to be associated with respiratory cancer and confounders and cofactors that are especially pertinent to respiratory cancer. Epidemiology studies of the chemicals of interest that provide information on latency are discussed in Chapter 3. Chapter 4 presents the committee's overall conclusions on the period between exposure to the chemicals of interest and the development of respiratory cancer. It also describes how those conclusions are related to the period during which a respiratory cancer could be presumed to have been caused by exposures incurred during service in Vietnam.

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2

Evaluation of Latent and Presumptive Periods

As discussed in Chapter 1, the committee is charged with evaluating the presumptive period between exposure to the herbicides used in Vietnam and their contaminants on the one hand, and risk of respiratory cancer on the other, and with determining whether it is possible to identify a time after cessation of exposure to those compounds beyond which a presumption of service connection for respiratory cancer could not be warranted. Many issues must be taken into consideration in evaluating the period over which a disease can be presumed to be associated with a given exposure. This chapter discusses those issues. It begins by defining concepts of latent period and presumptive period and then discusses factors that can affect the latent period. A discussion of issues to consider in evaluating latent period and presumptive period in epidemiology studies and of statistical methods to use in their analysis follows. Finally, the chapter discusses the time course of respiratory cancer after exposure to chemicals known to be associated with it, and how coexposure to the chemicals might affect the presumptive period for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and respiratory cancer.

LATENT PERIOD VS PRESUMPTIVE PERIOD

When quantifying the relationship between a chemical exposure and a disease, epidemiologists are interested in the rate of disease among exposed people (that is, people exposed to concentrations of the chemical greater than background exposure) compared with the rate expected if people had not been exposed (that is, people exposed only to a background concentration). They are interested in either the relative rate or the excess rate of disease as the measure of

comparison. Because cancer can take a long time to develop (years or even decades), an analysis of the effects of an exposure must take into account the latent period, a complex concept that can be defined as the time between an exposure and the occurrence of disease related to it. Depending on the circumstances, determining the length of the latent period can be simple or complex. The discussion below begins with a simple example of a latent period and progresses to complex examples.

The latent period is simplest in the scenario illustrated in Figure 2-1a: an exposure occurs at a single time, and a disease has a relatively quick onset, as in a sudden outbreak of acute illness in a fixed population with common exposure to contaminated food, water, or air. For instance, if mayonnaise at the church picnic was contaminated with salmonellae and many picnickers became acutely ill with diarrhea and vomiting 1–3 days later, the latent period would be 1–3 days and would correspond to the incubation period (the time during which the microorganisms multiplied). As is evident from the range of days, the latent period can vary even in such simple cases. Factors that affect the length of latency—such as age, health status, and genetic susceptibility—are discussed later. Because of the variation of the latent period within an exposed population—which results in different "latencies" that depend on the various factors involved—epidemiologists usually express latency as a range of intervals between exposure and disease onset.

The latent period is more difficult to identify when an exposure occurs over an extended period, not at just one time. An example is cigarette-smoking. Exposure to smoke usually does not occur at a single time, but over many years. Therefore, it is difficult to know exactly when the exposure caused the cancer. Typically, the latent period is measured from the time of first exposure, that is, when a person began smoking. Evidence that early exposure is most important in determining the risk of respiratory cancer makes such a measurement of latency valid. But there is also evidence that duration of smoking contributes to overall risk, with increasing duration causing greater elevation in risk.

To evaluate the period over which a disease can be presumed to be associated with a given exposure, time since start of exposure and time since cessation of exposure need to be determined. For exposures of short duration, times since start and cessation of exposure are often easy to define; this situation holds for environmental exposures in industrial accidents, particularly if an exposure involves chemicals that do not remain in the environment or are quickly eliminated from the body. If the exposure is protracted, like the exposure of pesticide appliers who repeatedly apply pesticides or of production workers employed for months or years, time since exposure is more difficult to quantify because there may have been many individual incidents of exposure.

It is also important to distinguish between cessation of external exposure and cessation of exposure of the target organs from persistent elevation of TCDD body burden. Some chemicals, including TCDD and many other chlorinated

herbicides, are retained in some body tissues for a long time (even decades), so target organ exposure continues even after external exposure ceases. Even a brief external exposure, such as that which occurred in Seveso, Italy (Bertazzi et al., 1989a,b; 1997), can involve protracted exposure of many organs. This more-complex scenario is illustrated in Figure 2-1b. In that scenario, disease induction, the point at which initiation of the disease occurs (note that the disease might not be apparent or detectable at this point), might even occur after external exposure ceases.

Given the difficulty in establishing the true latent period in studies in which exposure is protracted, several surrogate measures of latency are often estimated. In epidemiologic studies, they can include the time between first exposure and the time of peak relative risks compared with those among the nonexposed, the time between cessation of exposure and the point when disease rates increase above those among the nonexposed, and the time after cessation of exposure when disease rates fall back to those among the nonexposed. It is the third interval that is of interest to this committee. The committee's charge is to assess the length of time after cessation of exposure beyond which respiratory cancer could no longer presumably have been caused by the exposure—the "presumptive period" for respiratory cancer and exposure to TCDD.

The relationship between exposure and chronic diseases can be viewed as a multistage process (see Figure 2-1c) (Checkoway et al., 1990). First, exposure of sufficient duration or intensity begins a disease process. The time between first exposure and the occurrence of the initial steps towards the disease (that is, disease induction) can be called the induction period; this is illustrated in Figure 2-1c as the time from A to B. The induction period can depend on the dose and on other cofactors, such as genetic susceptibility, overall health, and diet. Second, the manifestation of the disease process (when the disease is detected or observed, which could be when symptoms appear, or when subclinical tests indicate positive evidence of early disease) occurs some time after the induction period. The time between induction and disease manifestation (from B to D in Figure 2-1c) is the true, biologic latent period. In practice, however, it is difficult to distinguish the induction period from the latent period. Unless there is a precursor lesion, which serves as a marker, the disease process usually has begun before the disease is manifest. Therefore, in epidemiologic studies, B (disease induction) in Figure 2-1c is not observed and is usually unknowable, and the entire period between first exposure and disease manifestation is often referred to as the latent period. Hence, in the remainder of this report, we will refer to this period, from first exposure to disease manifestation (the time from A to D in Figure 2-1c) as the latent period, and data shown in Chapter 3 have been based on this definition of latency.

The period of concern to the Department of Veterans Affairs, referred to as the presumptive period, is the time from cessation of external exposure to disease manifestation (from C_1 to D in Figure 2-1c); termination of service in Viet-

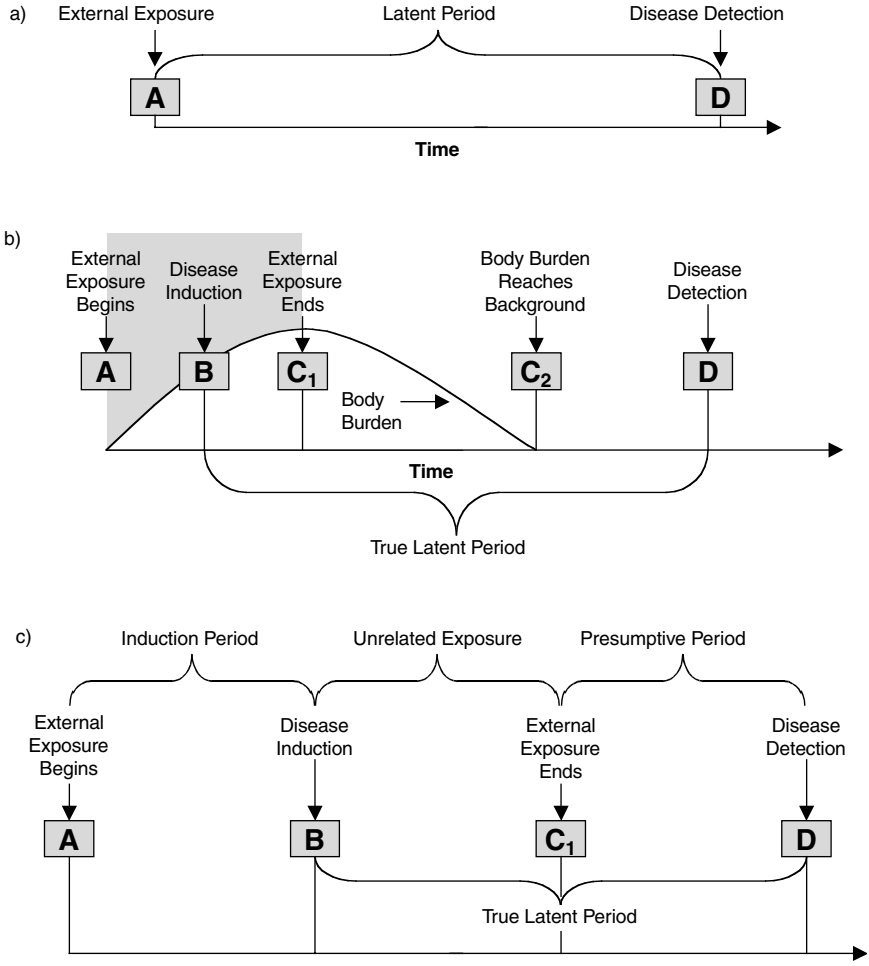

FIGURE 2-1 Schematic time courses for exposure and manifestation of disease. a) Simple model of single, acute exposure to chemical with short half-life in body and no accumulation. b) More complex model of accumulation of chemical in body. c) Model of onset of disease process (modified from Checkoway et al., 1990). Unrelated exposure refers to continued exposure that is not related to the induction of the disease. Although the figure depicts disease induction (B) as occurring prior to the end of external exposure, disease induction can occur at any point (during or after exposure) before disease detection. Note that the latent period depicted in a) through c) is the true latent period, that is, the time from disease induction to disease detection. Typically that period is difficult to determine, therefore, the time between first exposure and the time of elevated relative risk is used as a surrogate measure for the true latent period in epidemiologic studies.

nam is a surrogate for cessation of external exposure. Disease induction by a chemical (B in Figure 2-1c), however, may or may not precede cessation of exposure (C_1 in Figure 2-1c). It is possible that B, the effective exposure, could occur at any point during the external exposure (time A to C_1 in Figure 2-1c) or at any point after the end of the external exposure at which the body burden is still above background concentration (between C_1 and C_2 in Figure 2-1b). If the manifestation of disease is contingent on exposures incurred near the end of the exposure period, the induction period might not end until some time after exposure ends. It should also be noted that the period from B (disease induction) to D (disease manifestation) is influenced by many factors besides the biology of the disease or the aggressiveness of tumor development, such as access to care, quality of screening, health-care use, comorbidity, and tolerance of symptoms. The period from B to D can also depend on the exposure that initiated the disease process; for instance, the characteristics of the exposure can affect progression of a tumor or the speed at which cells proliferate. In the case of TCDD, additional exposure may affect tumor growth and hence latency. Finally, in light of the persistence indicated by the long half-life of TCDD, it is necessary to visualize the various periods with the more complex exposure scenario presented in Figure 2-1b, where point C_1 represents the end of external exposure, but the period from C_1 to C_2 represents the time it takes until exposure declines to that among the general population (who did not receive the high exposure from A to C_1). During the period from C_1 to C_2, the body burden remains high, and exposures of organs may contribute to any stage in the disease process. Thus, point B may actually occur around the time of C_2.

The preceding paragraphs have discussed latency as it may occur in a single individual. Earlier in this chapter, it was pointed out that latency in a population is a range representing the latencies in all the individuals. The range occurs because of variability in the induction period and in the interval from disease induction to diagnosis. When exposure is protracted, the exposures that are relevant to disease in a particular person are generally unknown, and this adds uncertainty to variability. These phenomena apply to the period between cessation of exposure (whether external or from elevated body burdens) and disease detection. To ensure that any veteran who develops respiratory cancer that could be ascribed to exposures incurred during service in Vietnam is taken into account, the presumptive period must be the maximal interval between cessation of exposure and detection of disease ascribable to that exposure.

FACTORS THAT AFFECT TIME COURSE OF DISEASE

Chemical Persistence and Duration of Exposure

Previous *Veterans and Agent Orange* (*VAO*) reports have concluded that there is "limited/suggestive" evidence of an association between respiratory can-

cer and exposure to Agent Orange. Epidemiologic studies suggest that risk is related to dose. In this report, the committee evaluates whether there is evidence of a presumptive period after which risk has decreased to the level among those with background exposure. It is also important to determine how that presumptive period might be related to exposure history and to the dose to which the respiratory system is exposed.

To assess the relationship between body burden and the presumptive period, it is important to know the initial exposure and the initial internal concentration, the course of exposure over time, the duration of exposure, the persistence of the chemical, and, on the basis of those, the cumulative body burden at any time. The routes and rates of uptake, tissue distribution, and transformation of a toxicant, and its elimination from the body determine the amounts of a particular chemical that potentially reach and persist in organs or cells, thereby influencing the toxicity and the frequency of genetic changes or nongenetic carcinogenic events in those organs or cells. The known toxicokinetic behavior of a chemical of interest is central in reconstructing exposure history.

On the basis of the literature reviewed in the *Veterans and Agent Orange* series, the chemical in herbicides sprayed in Vietnam that is of greatest concern with respect to respiratory cancer is TCDD (IOM, 2003). The distribution of TCDD and other chlorodibenzo-*p*-dioxin congeners has been examined extensively in animal models and to a smaller extent in humans throughout the last 2 decades. The toxicokinetic behavior of TCDD has been discussed in greater detail in *VAO* and updates up to the most recent, *Update 2002* (IOM, 2003). As summarized in *Update 2002*, TCDD is distributed to all compartments of the body, although the distribution is not uniform and the proportions accumulated differ from organ to organ. Properties of the chemical, properties of the organs and cells, and the route of exposure affect partitioning, absorption, and accumulation. The concentration of chemical in a given organ or tissue depends on the dose to which one is exposed and on the absorption, lipid content, and metabolism in the organ of concern. In addition, accumulation in one organ can be influenced by processes in other organs.

TCDD is a highly hydrophobic chemical that, like other hydrophobic chemicals, readily crosses cell membranes and accumulates in lipid-rich organs. Lipid content is a major factor in the accumulation of TCDD in different organs and in the body as a whole. Biologic processes, especially metabolism, are less well characterized for humans than for animals. It is clear, however, that chemical stored or sequestered internally will be mobilized to maintain an equilibrium between the blood and lipid-rich organs, constituting a source of the chemical for other organs. Target organ exposure to a chemical may persist long after increased exposure from external sources has ceased. At any given time, the combination of tissue concentrations and blood concentrations represents the body burden. In practice, blood concentrations are used as a surrogate for body burden, particularly for quantifying TCDD, for which blood concentrations are

standardized to lipid concentrations. Blood concentrations over time determine the cumulative exposure of organs, including the lung.

Estimates of the half-life of TCDD in humans have been derived from long-term studies of blood concentrations in Vietnam veterans and other exposed populations. Studies have consistently confirmed that TCDD is highly persistent in the body, with a half-life in humans averaging about 7.5 years. However, as discussed in *Update 2002*, recent data now indicate that elimination of TCDD is biphasic; a faster phase occurs very early, and the curve of this elimination may be much steeper in people who are highly exposed. Variation in half-life has been demonstrated to be associated with a number of variables, including body-mass index (BMI), weight, initial dose, time after exposure, and age (IOM, 2003). Differing half-lives of the biphasic elimination of TCDD might complicate the back-extrapolation from serum measurements to body burden after initial exposure but might not greatly affect the determination of cumulative dose resulting from persistence or continuing exposure. Determination of cumulative dose requires multiple body-burden measurements. The timing of those measurements combined with the nonlinearity in elimination could cause errors in extrapolation to initial peaks (times when exposures were highest) and hence affect the estimate of cumulative dose.

As outlined above, because TCDD and chlorinated herbicides are retained in some body tissues for a long time (such as decades), target organ exposure continues after external exposure ceases. Thus, even an acute external exposure can result in protracted exposure throughout the body. One can think epidemiologically of the effect of exposure in the past as the change in risk today that is ascribable to prolonged exposure of target organs; tissue concentrations may decline slowly, and blood concentrations may be maintained over time by redistribution from one or more storage sites.

Determining at what point a past exposure no longer influences disease induction, or what might be considered the period during which an exposure could be presumed to be associated with a disease requires knowledge of both the beginning and the end of the exposure. In the case of chemicals that are rapidly eliminated from the body, it is reasonable to assume that exposure ends with the termination of contact (for example, the end of a work shift for occupational exposures). In the case of TCDD, as with any chemical that can be stored in the body, a person's exposure can be said to continue as the chemical is released from compartments in the body where it is stored. This continuing elevation in body burden increases the overall duration of exposure of the target organs until the body burden, measured as serum concentration, declines to the background value, that is, until it is indistinguishable from the concentrations in populations that have not had an unusual external exposure.

Although external exposure to herbicides in Vietnam had a finite duration, the presumptive period (i.e., the interval between external exposure cessation and disease detection) for respiratory cancer due to increased TCDD concentra-

tion after service in Vietnam will be extended by virtue of the prolonged elevation in the body burden of TCDD as reflected in the serum concentration. Following that logic, "last exposure" or "end of exposure" would not occur until serum TCDD in Vietnam veterans reaches the background value (C2 in Figure 2-1b). It is also known that loss of weight or body fat, whether intentional or through inanition or cachexia, releases stores of TCDD from adipose tissue. For those reasons, serum concentration at any given time, although correlated with persistent exposure from body burden and external sources combined, does not necessarily reflect the pattern of concentrations through time; consequently, a single measurement cannot reflect overall dose over time, which might be the relevant measurement for risk assessment related to the persistent TCDD.

Mechanism of Carcinogenicity

The multistage carcinogenesis model is often used to evaluate the carcinogenic properties of a chemical by a mechanistic approach (Barrett, 1993; Pitot, 1986). According to that model, a chemical might initiate, promote, or alter the progression of a neoplasm. A chemical that initiates the neoplastic process might do so in a single exposure. Initiation involves a heritable change in the genome of a normal cell whereby it becomes an "initiated" cell. Chemicals that promote the clonal expansion of initiated cells into a histologically visible population are defined as promoters. Promotion might require multiple exposures for a given duration. Often, the first end product of tumor promotion is a benign cellular lesion that is reversible. In progression, initiated cells undergo further changes and expansion into a tissue mass that may progress irreversibly to malignancy. Some chemicals may act specifically in the progression phase of carcinogenesis (Barrett and Wiseman, 1987). For example, an animal can be treated with a chemical that induces initiated cells in the mammary gland; later exposure to another chemical may promote development, clonal expansion, and progression of those cells into a cancer. Multistage models have also been used in experimental animals for the development of pulmonary cancers; such models use *N*-nitrosodimethylamine or urethan as initiators of the tumors (Beebe et al., 1995; Blakley et al., 1992).

Multistage models of carcinogenesis recognize that alterations of multiple independent genes (either by direct or epigenetic actions) are involved in the carcinogenic process (Barrett, 1993). The altered expression of proto-oncogenes can result in positive proliferative signals, and the modulation of tumor-suppressor genes can block the neoplastic growth of cells (Boyd and Barrett, 1991). Chemicals can influence the gene expression of important regulators of clonal expansion and cell proliferation that affect not only induction of neoplasia but also time to full tumor development.

Latent periods for different chemicals depend on differences in the mechanisms by which the chemicals act, that is, on their contribution to the initiation

and promotion phase. They also vary within a population because of individual differences in the biochemical pathways (some of which are induced by such chemicals as TCDD) that regulate the kinetics and metabolism of the chemicals and in the stages of the carcinogenic process at which exposure occurs. Carcinogenic chemicals that are relatively persistent in the body may initiate or promote the carcinogenic process over a long period. In such cases, latency can vary and may be short or long from the time of initial exposure. For example, substantial individual differences in latency might be observed for persistent tumor promoters, such as TCDD, depending on the time of the exposure relative to the time of exposure to the initiating chemicals or events (for example, mutations). For chemicals with relatively short half-lives, such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), initiation or promotion might be expected to occur only during a very short period when the body burden is high. As mentioned earlier, however, the latent period may also be affected by individual differences in biochemical and biologic pathways that affect the carcinogenic process. Such differences generally are based on genetic polymorphisms that affect the function or expression of proto-oncogenes and tumor-suppressor genes or affect biochemical pathways that regulate cellular differentiation and proliferation, including signaling processes that regulate the cell cycle. The relative expression of those pathways is also likely to be tissue-specific. Furthermore, the relative activities of processes that repair mutated DNA and of processes, such as immune surveillance mechanisms, that are responsible for removal of cancerous cells may vary individually and affect not only the ability to develop a tumor but the latent period. Such processes may be considerably less efficient in older people or in people who have compromised health status and potentially can lead to shorter average latent periods.

Metabolism of a chemical may affect the carcinogenic process, as well as the latent period for tumor development. If a chemical requires metabolism to an active intermediate for initiation of a tumorigenic process, tissue-, cell-, and age-specific characteristics of its metabolism may determine the relative amounts of active carcinogen present. That may be more important for chemicals to which there is protracted exposure or that are persistent. In such cases, changes in metabolic processes that occur with changes in health status, coexposure to other chemicals (such as therapeutic drugs or chemicals in cigarette smoke), and aging could affect the amount of the active metabolite produced at any particular time during the exposure period and alter the apparent timing of disease induction or detection. The amounts of carcinogenic metabolites of most chemicals usually depend on dose. At low doses, metabolism by metabolizing enzymes may efficiently limit the accumulation of carcinogenic metabolites; at higher doses, metabolic processes may be overwhelmed and this can result in a greater abundance of active metabolites. Such properties may be responsible for suggestions that dose-response relationships for many carcinogens are nonlinear and have thresh-

olds. If clearance of active compounds is also affected, apparent latency might be altered.

CARCINOGENICITY OF TCDD

Research has been conducted with the herbicides sprayed in Vietnam and with TCDD to investigate the mechanisms by which they might induce respiratory cancer. Most of the experimental data on respiratory cancer are for TCDD, not the herbicides themselves. Therefore, TCDD is the focus of this discussion, however, herbicides are also discussed below.

Development of cancer in experimental animals usually depends on the dose of and duration of exposure to a chemical. Cancers can develop during the exposure period (for example, during the 2 years of dosing in lifetime-exposure studies in rodents) or at some distant time (latency) after a non-lifetime-exposure regimen. To determine whether a chemical is carcinogenic, under some protocols laboratory rodents are exposed to incremental doses of a chemical for a lifetime and monitored for the development of cancer. To assess latency, animals are exposed to a carcinogen for a defined duration and then observed for the rest of their life.

TCDD is a known carcinogen in rats and mice and is considered to be a carcinogen in humans. There is no evidence to indicate that TCDD is genotoxic. All the available evidence indicates that it acts as a promoter through multiple pathways in the regulation of cell proliferation and differentiation.[1] In addition, TCDD is known to alter the relative levels of enzymes that metabolize other chemicals to genotoxic metabolites. Liver tumors have been consistently observed in animals after TCDD treatment, and increases in skin cancer, lung cancer, and thyroid and adrenal cancers have been seen in some studies. Decreases in uterine, pancreatic, pituitary, mammary, and adrenal cancers have also been seen, but most of these decreases occurred only at high doses and were associated with decreases in body-weight gain; the decrease in mammary tumors was seen in only one study (see IOM, 2003 for review).

TCDD has been assessed for tumor-promoting activity in a mouse-lung model. Lung tumors were statistically significantly increased in mice initiated with *N*-nitrosodimethylamine (NDMA) when promoted with low doses of TCDD (Beebe et al., 1995), but not higher doses, which may have caused pulmonary toxicity. The study lasted 52 weeks. It was suggested that the TCDD-elicited induction of cytochrome P4501A1 in the same model system is correlated with and possibly causally involved in the promotion of tumors (Anderson et al.,

[1]The term "initiator" and "promoter" are used in this report to describe the observed behavior of agents in the classical two-stage carcinogenesis model. The committee notes, however, that TCDD can be carcinogenic in rats in the absence of other known exposures (Kociba et al., 1978).

1991). In another study with the NDMA model, it was determined that TCDD might promote tumors by contributing to the down-regulation of the K-ras proto-oncogene and the stimulation of raf-1 (Ramakrishna et al., 2002). Lung lesions were evaluated in rats treated with TCDD for 14, 30, or 60 weeks (Tritscher et al., 2000); a statistically significant increase in alveolar-bronchiolar metaplasia was observed in the rats treated for 60 weeks but not in those treated for 30 weeks and observed for another 30 weeks, and this suggested that the development of lesions in this model system required the longer duration of exposure or perhaps a higher cumulative exposure to TCDD. Despite extensive research in this area, the mechanism underlying TCDD's carcinogenicity remains unknown.

Although TCDD is the main chemical of interest for respiratory cancer, it is important to consider the herbicides used in Vietnam and their possible role in respiratory cancer. Cacodylic acid was present in an herbicide used in Vietnam. Cacodylic acid is dimethylarsinic acid (DMA), which is also a metabolite of inorganic arsenic in humans. As discussed elsewhere (see US EPA, 2004), inorganic arsenic has been associated with lung cancer and other cancers in occupational settings and in studies of individuals exposed to elevated arsenic in drinking water (NRC, 2001), and is classified as "known to be a human carcinogen" by the National Toxicology Program (NTP, 2002). Inorganic arsenic has not been shown to be able to induce tumors in laboratory animals, but exposure of rodents to high concentrations of DMA increased bladder tumors in male Fischer 344 rats (Wei et al., 1999) and pulomary tumors in A/J mice (Hayashi et al., 1998). DMA has also been shown to promote urinary, bladder, kidney, liver, and thyroid tumors in rats and lung tumors in mice (see Kenyon and Hughes, 2001 for review). In a recent study, however, pulmonary neoplasms did not develop in rats exposed to DMA at up to 200 ppm in drinking water for 104 weeks (Wei et al., 2002). Therefore, DMA does not appear to be a potent pulmonary carcinogen in those strains of rats and mice. Furthermore, the mechanism of DMA-induced neoplasia is unknown. Finally, although DMA is formed in humans after exposure to inorganic arsenic, it has not been established and cannot be inferred that the effects seen after that exposure occur after exposure to cacodylic acid.

Epidemiology studies of agricultural workers and chemical-industry workers exposed occupationally to those chemicals have been conducted, but it is difficult in many of those studies to determine which chemical (e.g., 2,4-D, 2,4,5-T or its contaminant TCDD, or other pesticides or chemicals) underlies any effects seen. Those studies are discussed in the Veterans and Agent Orange reports (see IOM, 2003). Any of those studies that are relevant to the presumptive or latent periods and respiratory cancer are discussed in Chapter 3 of this report. There is no strong evidence of tumorigenic potential of 2,4-D, 2,4,5-T, or picloram in laboratory animals or cell-system assays (see IOM, 2001;2003, for reviews). As discussed in *VAO* (IOM, 1994) and reviewed in *Update 2002* (IOM, 2003), three studies have looked at the carcinogenicity of picloram, of which two were negative and one had equivocal results for which a contaminant

(hexachlorobenzene) was thought to mediate the carcinogenicity. The experimental data for the carcinogenicity of 2,4-D and 2,4,5-T have demonstrated a lack of carcinogenic effects (IOM, 2003).

Given the tumor-promoting potential of TCDD and the persistent nature of this chemical, it is possible that, as indicated above, a cancer could be detected either a short or long time after the external exposure to TCDD because promoting effects might occur at any time while the body burden of TCDD is high. It is also possible that enzymes which metabolically activate procarcinogens would be chronically induced by persistent elevation of TCDD concentrations. Exposure to initiating chemicals that are bioactivated could occur at any time while the body burden of TCDD is elevated, contributing to the apparent latency. It is known, for example, that TCDD modulates the metabolism of chemicals in tobacco smoke.

ANALYSIS OF LATENT PERIOD AND PRESUMPTIVE PERIOD

Time-Related Factors

As discussed in *Update 1998* (IOM, 1999), the analysis of latency in epidemiologic studies can be complicated for a variety of reasons. Many of them are related to the correlations among various time-related factors. Specifically, duration of exposure, time since exposure, age at start of exposure, and exposure magnitude may be correlated, so an observed pattern of one of these factors could actually be due to correlation with one or more of the others. To disentangle the confounding of time-related variables, it is commonly necessary to stratify the analysis or model multiple predictors of risk. Realistically, however, most datasets do not have sufficient information to explore those issues; for the most part, they merely serve as a cautionary note in the interpretation of results. In Box 2-1, hypothetical situations help to illustrate how various time-related factors are intertwined. The exposure of interest is referred to as "the agent". The examples in Box 2-1 are fairly typical of what happens in occupational settings. They are presented primarily to show that examining the effects of one time-related factor may be difficult without information about the others. Such relationships, which are presented in Figure 2-1c, can be summarized as:

> Age at end of study = age at start of exposure + duration of exposure + time since end of exposure

As can be seen in Figure 2-1c, the interrelations are also related to the persistence of the chemical in the body and to protracted exposures.

Although it can be difficult to disentangle those interrelated effects, it is not always impossible. Many occupational studies, for instance, have shown that the effects of industrial chemicals on cancer are stronger 10–20 years after initiation

BOX 2-1
Hypothetical Situations That Illustrate How Various Time-Related Factors Are Connected

- Two people are born in 1945. Both are exposed continuously to an agent for 10 years. One person begins exposure at age 20 and continues to age 30; the other begins at age 30 and continues to age 40. In 1995, at age 50, the first person has gone 30 years since first exposure, and the second only 20 years. Thus, *age at first exposure* and *time since first exposure*, for a given duration of exposure and followup, are interrelated; *time since last exposure* differs between the two.
- One person begins exposure to an agent in 1970; a second person begins exposure in 1975. They are the same age at first exposure and exposure continues until 1985. When evaluated in 1995, the first person has both a longer *duration of exposure* (15 years vs 10 years) and a longer *time since first exposure* (25 years vs 20 years); this illustrates the relationship between the two factors for a given age at first exposure. In this scenario, *time since last exposure* is the same for the two persons even though *duration of exposure* is different.
- Two people are born in 1945. One begins exposure at age 20; the other at age 30. Exposure stops for both at age 40. The first person has a lower *age at first exposure*, a longer *duration of exposure*, and a longer *time since first exposure*; all three factors are potentially interrelated.
- Two people are exposed to the same concentration of an agent. The person with the longer *duration of exposure* will, by definition, have a higher cumulative exposure.

of exposure than in the first 10 years, after age and calendar time have been controlled. And several radiation-related cancers—including leukemia, gastrointestinal cancers, and breast cancer—show age at start of exposure to be a strong determinant of risk (NAS, 1990).

In general, the ability to investigate the issue of timing of exposure in a given dataset depends on the quality of the exposure measure, the accuracy of the timing-of-exposure information, the number of people who have the disease in question, and the variation of exposure over time within the study group. Because of the potential for high correlations among time-related factors, changes in the magnitude of exposure over time are especially important in attempts to identify latent periods or presumptive periods because those periods are likely to be dose-dependent (Enterline and Henderson, 1973; Peto, 1985; Thomas, 1987).

Analytic Methods for Addressing Latency

Several analytic methods have been developed over the years for addressing latency issues in assessing exposure-time-response relationships. Most of the epidemiologic studies reviewed in *VAO* and subsequent updates have assumed a

specified latent period and have analyzed exposure-response relationships by using exposure that is lagged by the specified latent period. That method has the advantage of simplicity, but it also has a great potential for model misspecification when the assumed latency structure is wrong. When dealing with protracted exposures, the method is almost certain to misrepresent the effect of latency. As discussed earlier, the increased risk associated with exposure will usually change not only with variation in exposure but also with time since exposure. Hence, it is desirable to use methods that allow for relative-risk estimates to vary with latency, that is, with time since exposure.

Several analytic techniques that have been developed to assess latency are briefly described below. They are presented in chronologic order of development and increasing complexity. They are based on different statistical models, but they all have the general form of allowing the relative-risk estimates to vary with time since exposure. One could therefore think of the latency effect as a weight function of the dose-response relationship. In describing the various methods, we assume that people are subjected to protracted exposure.

Cumulative-Exposure Model

This method, which assumes that risks at various times since exposure have equal weight, estimates a single relative risk for the sum of protracted exposures by assuming that the total cumulative dose is the effective dose. Given the published evidence on latency and lung cancer, which suggests that risk starts at null, rises to a peak, and can then decline to null (Langholz et al., 1999), this method might not properly depict the real exposure-time-response relationship. In some cases, risk does not decline to null; in the case of smoking, for example, former smokers retain a higher risk of lung cancer than people who never smoked.

Stratified Model

This method estimates a separate relative risk for each of several contiguous intervals of time since exposure. For instance, models that lag exposure by 10 years in effect assume no increased risk in the first 10 years. A general pattern in the relative-risk estimates as a function of time since exposure could be gleaned from such analysis, but the disjoint character of the model does not lend itself to a continuous assessment of latency effects. Moreover, the pattern in the relative-risk estimates could be strongly affected by the choice of time-since-exposure intervals. This modeling approach was used in some of the occupational and environmental studies relevant to the charge of the committee, including the National Institute for Occupation Safety and Health (NIOSH) study of chemical production workers (Fingerhut et al., 1991) and the Seveso study (Bertazzi et al., 1989a,b; 1997). When additional covariates (such as confounders and cofactors)

are in the model, adjustments for them are stratum-specific, and this makes the interpretation of the change in relative risk (as a function of latent period) more difficult. Those three studies usually limited their analysis to time since first exposure and did not address the end of exposure.

Piecewise-Constant Model

This method fits a simple piecewise-constant function over "time windows" (Finkelstein, 1991; Langholz et al., 1999). Unlike the stratified model, in which adjustment for all covariates is stratum-specific, this method allows for common overall adjustment of covariates, which leads to a better (more robust) adjustment for confounders. Of course, stratum-specific adjustment for confounders could be easily accommodated in the piecewise-constant model, whenever necessary. This method is useful as a first pass in understanding the general shape of the latency function. However, the discrete nature of the weight function for latency may not give a realistic depiction of a latency curve that is more likely to be continuous. Because the exposures in adjacent time-window intervals are likely to be correlated, the estimated heights of the time-window specific relative-effect estimates can be statistically unstable, particularly when the time windows are narrow. Here, the time-window-specific relative-effect estimates can be interpreted as excess relative risks per unit dose received during the corresponding time window. From those estimates, a total excess relative risk associated with an exposure history is obtained as the sum of all time-window-specific estimates.

Bilinear Model

This model fits a latency-weight function that is constructed by two lines that are attached at an inflection point (usually constrained to be 1) that gives the estimate of the peak in relative effects. It is constructed to give estimates of three important parameters that address the following questions: How long does it take before there is an effect of exposure? At what time is the effect of exposure maximal? How long does the effect last? This method improves on the piecewise-constant model by giving a continuous latency-weight function, which leads to better handling of the correlation between adjacent exposures. Langholz et al. (1999) gives a complete description of the model with variations that accommodate different scenarios, such as whether there is a lag period before effects are first manifested and whether the effect decreases to null after reaching a maximum at the inflection point. It assumes a linear relationship in time, both during the rise and during the fall in the relative risk.

Exponential-Decay Model

This method is a variant of the bilinear model discussed above. The important difference is that it fits a straight-line latency-weight function up to the inflection point but fits an exponential decay curve afterward. The method allows for the fact that the exposure agent of interest (such as TCDD) may be retained in the body and slowly released internally. In such scenarios, the exponential decay curve is affected by the number of years required for the effect to be reduced by one-half, the so-called half-life (Langholz et al., 1999).

Spline-Based Model

This method fits piecewise polynomials within a series of time-window intervals and then smoothly joins the piecewise curves by putting appropriate continuity constraints on the estimation process. The resulting latency curve is called a spline. Hauptmann et al. (2000) discuss the details of the method. It has also been applied to the Colorado Plateau uranium-miner data on radon exposures (Hauptmann et al., 2001).

Mechanistic Models

Unlike the various empirical models discussed above, mechanistically based statistical models assess latency under an assumed theory of carcinogenesis, such as the Armitage-Doll multistage model (Armitage and Doll, 1961) or the Moolgavkar-Knudsen two-stage model (Moolgavkar and Venzon, 1979). If the assumed model of carcinogenesis is correct, mechanistic models provide a powerful means for dealing with exposure-time-response relationships.

Implications of Model Choice

Methods for addressing how long it takes to detect an increase in disease risk after exposure and how long the effects of exposure last are discussed below.

Time After Exposure to Detect Increase in Disease Risk

To determine how long it takes after an exposure (either initial exposure or cessation of exposure) to detect an increase in disease (that is, latency), one must examine the pattern of relative risk over time, looking for the earliest detection of an increase in risk in an exposed population relative to a nonexposed comparison group. For protracted exposure, it is customary to examine relative risk by time since first exposure because the earliest detectable increase in relative risk may be a manifestation of the earliest exposure. In fact, relative risk related to

specific times since first exposure is often the only measure of latency reported in studies of protracted exposure to herbicides.

The critical data items required are the date of first exposure of each subject and the dates of diagnosis of relevant outcomes. With that information, an investigator can determine the contribution of each subject's time-since-first-exposure to the latent period for the study population. If full exposure histories are available, more sophisticated analyses are possible; to account adequately for dose and duration, a full exposure history is needed. With that information, an investigator can determine the contribution from each subject in each exposure category. Several studies provide excellent examples of how a full exposure history, based on employment histories or some combination of external or internal measurements, can be used in a detailed analysis of latency and other time-related factors. One such study is the Colorado Plateau uranium-miner cohort described and analyzed in detail by Langholz et al. (1999). In that study, bilinear and exponential decay models of latency are evaluated, as well as how to fit those models to various types of data.

Duration of Effects of Exposure

Relative risk related to specific intervals of time since last exposure are used to address the question of how long the effect of an exposure lasts. The pattern of relative risk is examined for the latest indication that the relative risk is greater than 1.

The critical data items required for addressing the question are the dates of each start and stop of exposure and the intensity of exposure. Those are needed to classify subjects' time spent in each time-since-first-exposure category. Again, if full exposure histories are available, more sophisticated analyses (for example, time-windows analyses) are possible. However, if the critical issue is time since last exposure, multiple starts and stops present greater complexity in assignment of dose. Data on last exposure before an event are used to determine how long an effect can persist.

Comparison of Methods

In addressing how long it takes after an exposure to detect an increase in disease risk, the earliest indication of an increase in relative risk is difficult to measure and will be refined as more data are collected. Latent period varies among individuals, so risk in a population changes continuously rather than suddenly jumping from "normal" to "above normal". The simpler stratified and piecewise-constant models may not be able to depict that reality. In contrast, the bilinear and spline-based models allow greater flexibility in accounting for the continuity in the latency-weight function and may yield a more realistic picture of the underlying exposure-time-response relationship.

Mechanistic models constitute a more structured way of handling the underlying process and could be informative if the presumed model of carcinogenesis is reasonable. Actual changes in relative risk probably would occur earlier than indicated by the analysis; but because of limitations in study designs, such changes might not be detectable. In other words, the degree to which an increased risk is statistically detectable depends on the size of the particular dataset, on the magnitude of the background risk (which in turn depends on the age distribution of study subjects), and on the magnitude of the increase in risk (which in turn depends on exposure, variation in susceptibility, length of follow-up, and distribution of latent periods among the exposed population). It should be noted that if the latent periods are highly variable among individuals, analysis by time since first exposure may be insensitive because an increase in risk will appear slight and occur gradually. In addition, if the effect of time since first exposure is modified by intensity of exposure or age at exposure, these other factors would have to be accounted for in the analysis. For example, latency might be longer after a small exposure than after a larger one, in which case a study that examined only time since first exposure might encounter greater variability in latency and hence have less ability to assess how long it takes to observe an effect of exposure. Such effect modification would also limit the degree to which results of one study can be generalized to a different population or to another exposure scenario.

If exposure is protracted, time since last exposure must be analyzed in the proper time-dependent fashion to address how long the effect of an exposure lasts (Clayton and Hills, 1993). Adjustment for age is also necessary. To achieve adequate power and precision, a study must use a sufficient number of subjects with a long period since cessation of exposure. If exposure has been protracted, much longer follow-up is needed to determine the presumptive period than the latent period.

Latency and Interpretation of Epidemiologic Literature

Measurement Error

Measurement error in assignment of exposure or timing of exposure could increase observed variation in latent period or presumptive period. If extended elevation of body burden after external exposure ceases was not explicitly taken into account in the analysis, the resulting error would be considered an error in measurement.

Mortality and Incidence Studies for Examining Latency

A chemical with carcinogenic activity may increase the chance of cancer, or it may accelerate development of cancer so that it occurs at an earlier age than it

otherwise would have. The agent may also influence the likelihood that a cancer will result in death, or it may shorten the time between occurrence of the cancer and death caused by it. Which of those processes occurs may depend not only on the agent but also on the site of cancer. For example, lung cancer tends to be fatal in a very high percentage of cases, and death usually comes swiftly. For lung cancer, therefore, a study of mortality is unlikely to provide different results from a study of incidence. In a contrasting example, prostate cancer is fatal in a fairly small proportion of cases; incidence is 5 times higher, or more, than mortality (Merrill and Brawley, 1997). Therefore, a study of prostate cancer mortality would be less likely to detect the effect of a carcinogenic agent than would a study of prostate cancer incidence, unless the agent increased the severity of disease. But because prostate cancer is so common and occurs with increasing frequency as men age, any study of prostate cancer incidence should examine whether those exposed to the agent of interest develop the cancer at an earlier age than those not exposed. That type of analysis could be accomplished by using age-specific rates. Caution would have to be exercised in interpreting incidence studies because of the recent introduction of prostate-specific-antigen (PSA), a marker for prostate tumors that are not clinically detectable, as a screening tool. Differences among populations in the extent to which PSA is used could confound results (Gann, 1997).

In the investigation of cancer latency, changes in relative risk with time since exposure will occur later in mortality studies than in incidence studies by an amount approximately equal to the average time from cancer occurrence to death. Given the short survival of lung cancer patients, it is likely that the pattern with time since exposure will be similar in a mortality study, but the latent period will be longer than an incidence study. The same would be true of the presumptive period. As a result, at any given point in the follow-up period, a mortality study will record fewer events than a study of incidence and so will have lower statistical power even if the exposed and nonexposed cases have the same prognosis.

Similarly, if there is a substantial group in the population that is genetically susceptible to the effects of a carcinogen or has an acquired state of susceptibility, there may be a phenomenon similar to “exhaustion of susceptibles”, which is more commonly observed in infectious disease. In an infectious-disease outbreak, people lacking immunity or natural resistance develop the disease; when this pool of susceptible people is exhausted, the incidence in the population declines, perpetuated only by outbreaks among new entrants. In a chronic disease, such as cancer, there may be a pool of susceptible people who, when challenged by exposure to a carcinogen, get cancer at an earlier age than they would otherwise, and that can cause an apparent decline in incidence in the older age groups. However, one would expect conspicuous excess mortality in the younger groups for this effect to explain a later dip in incidence.

A further consideration is competing mortality. When people who are at risk

for a cancer die earlier than they otherwise might, they are not available for causes of death later. If the diseases are linked by an exposure, one disease may "hide" the other. For example, a person who smokes heavily may develop lung cancer or chronic obstructive lung disease. The two are related, and there is evidence that a common trait of individual susceptibly plays a role in both. A person who develops lung cancer, which is usually fatal, is not available later in life to develop chronic obstructive pulmonary disease, which is less often fatal in younger people.

The sparseness of empirical data available on Vietnam veterans makes it difficult to ascertain whether those complicated effects are occurring. Most of the relevant epidemiologic data for TCDD and herbicides reviewed to date have used the simplest models based on time since exposure.

LATENCY AND RESPIRATORY CANCER

As discussed in *Update 1998* (IOM, 1999), a substantial body of literature explores issues of timing of exposure and respiratory cancer, especially for some agents whose carcinogenic properties in the respiratory system are well studied. This section discusses briefly what is known about the latent period and presumptive period of well-studied respiratory carcinogens (gamma rays, radon daughters, smoking, arsenic, and asbestos) and about factors known to be confounders and effect modifiers for respiratory cancer.

Time Course for Respiratory Carcinogens Other Than TCDD

In an investigation of latency issues in radiation exposure of atomic-bomb survivors, it was found that the relative risk of lung cancer began to rise 5–10 years after exposure and reached a plateau about 15 years after exposure to gamma rays. Thirty years after exposure, there was no evidence of a decrease in relative risk (Land, 1987). In addition, the effects of age at exposure are quite pronounced for some sites, such as leukemia, digestive cancers, and breast cancer (NAS, 1990).

In miners exposed to radon daughters (radon decay products), the relative risk of lung cancer was seen to peak 5–10 years after first exposure and then to decline slowly, although the risk appears to be increased even 30 years after exposure (Lubin et al., 1994; Thomas et al., 1994). In addition, the effect of exposure varies with age at exposure: a given exposure results in a lower relative risk in older workers than in younger workers. Langholz et al. (1999) analyzed data on Colorado Plateau miners exposed to radon and concluded that the risk returns to the background value after 34 years. Hazelton et al. (2001) analyzed data from a historical cohort of Chinese tin miners, investigating the contributions of arsenic, radon, cigarette smoke, and pipe smoke to lung cancer risk. With respect to radon, their analyses indicate that the hazard posed by radon

increases sharply 45 years after first exposure and does not appear to decrease with increasing time since last exposure.

Analyses of lung cancer indicate that the relative risk posed by smoking begins to rise substantially about 20 years after the initiation of cigarette-smoking. Among ex-smokers, the relative risk declines to about half that of smokers by 12 years after cessation but then remains fairly constant—and higher than in those who never smoked (IOM, 2001). Analyses by Ockene et al. (1990) indicate that it takes as long as 20 years for the benefit of cessation of smoking (a decrease in risk of lung cancer) to be seen. Burns (2000) found that the risk of lung cancer remains increased up to 20 years after cessation of smoking, and Ebbert et al. (2003) found no decrease in risk 30 years after cessation. The analyses for smoking by Hazelton et al. (2001) of the Chinese tin miners show risk remaining increased for at least 30 years.

In a cohort of workers exposed to arsenic from a copper smelter in Montana, relative risk of lung cancer was observed to increase with time after exposure, reaching a maximum 15–20 years after first exposure, after which it slowly declined (Breslow and Day, 1987). There was little change in relative risk with age at first exposure. Brown and Chu (1983, 1987) observed a stronger effect of time since last exposure than of time since first exposure, although a model with both gave an excellent fit. The statistical models of arsenic exposure in Chinese tin miners were very similar to those of radon exposure, with a sharp rise in hazard 45 years after first exposure and no apparent drop in risk more than 50 years after last exposure (Hazelton et al., 2001).

In a cohort of workers exposed briefly to high concentrations of asbestos during World War II, the relative risk of lung cancer rose sharply 5–10 years after exposure, after which it remained constant up to 40 years after exposure (US EPA, 1986). Relative risk was independent of age at exposure. More recent data on asbestos confirm that the risk of lung cancer after asbestos exposure remains increased for many years, although the risk decreased to less than one-half of the peak 20 years after cessation of exposure (Hauptmann et al., 2002).

Thus, after some exposures, relative risks reached a plateau or peaked within 5–10 years; but after most exposures, it took at least 20 years after exposure began for relative risks to peak. In addition, most of the data on those exposures indicate that risks remain increased for many decades after cessation. Data on some of the better-studied lung carcinogens indicate that lung cancer might be attributable to exposure to them for 20, 30, 40, or even more than 50 years after exposure has ended.

Potential for Confounding and Effect Modification

In any person, multiple factors can contribute to or cause respiratory cancer. Those factors can include genes that confer a predisposition to cancer, age, and various exogenous factors, such as diet, smoking, and other environmental

chemical or physical agents. Substances known to be associated with lung cancer are nickel, chromium, arsenic, cadmium, polycyclic aromatic hydrocarbons, radon, gamma rays, and asbestos. There is great concern with smoking in connection with lung cancer, but it is important to remember that although it is estimated that about 90% of lung cancers in males are the result of smoking tobacco (ACS, 2003), only 10% of smokers will ever develop this cancer. Thus, smoking is not deterministic, and other factors clearly play a role in increasing the risk of cancer.

In estimating the risk of respiratory cancer associated with exposure to a given agent, ideally the extent of exposure to those other agents associated with respiratory cancer would be known. If any other such agents are associated with exposure to the herbicides used in Vietnam, they could confound the relationship with respiratory cancer unless adjusted for in statistical analysis. If such confounding exists, the risk of respiratory cancer associated with exposure to the herbicides or TCDD might be over- or under-estimated.

The most pertinent question for this report, however, is whether other respiratory carcinogens might affect the duration of latent periods and presumptive periods and, if so, how. Specifically, what is the effect of coexposures on the longest latency to be expected from TCDD? A cofactor, such as smoking, could have a different distribution of latencies; as a result, the apparent distribution of latencies associated with the exposure of interest would be distorted (it could be shorter or longer on the average, and it could show more or less variability). In addition, if the exposure to the cofactor was shorter or longer than the exposure to the main agent of interest, further distortion in the observed latent periods could take place.

To evaluate the length of time that a respiratory cancer might be presumed to be associated with exposure, it is necessary to address how coexposures might alter the presumptive period. If other factors alter the rate of cellular processes that affect carcinogenesis (apoptosis, cellular transformation, etc.) or alter the internal doses of herbicides or their contaminants (lengthening or shortening half-lives, blocking absorption), then latent periods or presumptive periods could be shortened or lengthened according to the extent of exposure to the co-factor and the strength of its association with either carcinogenesis or dose modification. That is, the other exposures could be modifiers of the latent period or presumptive period.

Whether smoking or other factors that contribute to respiratory carcinogenesis could modify the distribution of latent periods over which TCDD or herbicides used in Vietnam could cause respiratory cancer is unclear from the empirical evidence; much of the literature reviewed in Chapter 3 of this report regarding the carcinogenicity of TCDD, however, comes from studies in occupational settings or of the population exposed environmentally to TCDD after an industrial accident in Seveso, Italy (Bertazzi et al., 1989a,b).

It should also be recognized that the observed latent or presumptive periods

could be confounded. For instance, if people exposed to TCDD at the highest levels or for the longest time were also more highly exposed to cigarette smoke or other environmental agents, some of the earliest or latest effects could be mostly or wholly attributable to the other exposures. Since the specific causes of individual cases of disease are not easily identified, confounding of this type would be exceedingly difficult to assess.

To address the question of how coexposures alter the latent period and presumptive period, smoking data would be needed, in addition to detailed exposure histories. However, many studies of TCDD that are the most useful for examining the time between exposure and respiratory cancer appear not to include individual-level smoking data in their analyses. Therefore, the possibility that smoking could alter the presumptive period must be considered. Studies that conduct analyses of presumptive periods stratified by smoking status are needed to address that issue.

SUMMARY AND CONCLUSIONS

Of the chemicals sprayed in Vietnam, TCDD is of greatest concern for the development of respiratory cancer. In evaluating the time course between exposure to TCDD and respiratory cancer, it is important to differentiate between the true latent period (time from the induction of disease to disease detection), the latent period typically measured in epidemiologic studies (time from beginning of exposure to disease detection), and what can be referred to as the presumptive period (time from cessation of exposure to disease detection).

The presumptive period can be affected by the duration of exposure and the mechanism of carcinogenicity. The effects of chemicals that act early in the carcinogenic process (initiators) generally end earlier than the effects of chemicals that act later in the carcinogenic process (promoters or tumor-progression factors). Evidence indicates that TCDD is not an initiator but has tumor-promoting activity. Target organ exposure due to release of chemicals from stores in the body must be taken into account in considering the duration of exposure to chemicals, such as TCDD, that are not rapidly eliminated from the body. A number of statistical methods are available to assist in the analysis of the temporal relation between exposure and disease. If mechanistic data are available, models that incorporate them can be informative.

In general, data on chemicals other than TCDD that are known to be associated with respiratory cancer indicate presumptive periods of at least 20 years. In some studies, the risk of respiratory cancer had not dropped to background values even 50 years after cessation of exposure. It is possible that exposure to chemicals other than TCDD, such as by smoking, could modify the length of the presumptive period for TCDD and respiratory cancer, but there are no data on what any such modification might be.

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3

Epidemiologic Studies

To assess the presumptive period for the association between exposure to herbicides in Vietnam and their contaminants (2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T] and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD], cacodylic acid, and picloram) and increased risk of respiratory cancer, the epidemiology literature must be examined. *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994) and its updates (IOM, 1996, 1999, 2001, 2003) review the entire relevant literature on herbicide exposure, but this chapter discusses articles that the committee believes reflect, with reasonable accuracy, the length of time between herbicide or TCDD exposure and occurrence of respiratory cancer with sufficient respiratory-cancer cases to support some judgment about the patterns of relative risks reported. The committee searched the literature for epidemiologic studies on the presumptive period for exposure to TCDD or the herbicides used in Vietnam and the risk of respiratory cancer. No such studies were found. However, evidence regarding the latent period was found and, because that evidence can provide some information related to the presumptive period, the results of those studies are reviewed in detail.

The chemicals of interest that were sprayed in Vietnam were 2,4-D, 2,4,5-T and its contaminant TCDD, picloram, and cacodylic acid. No data are available that are relevant to the latent or presumptive periods that might exist if there were an association between 2,4,5-T or picloram and respiratory cancer. There are also insufficient data on humans to assess the latent period for cacodylic acid and respiratory cancer. Cacodylic acid is dimethylarsinic acid. In addition to being produced for use as a herbicide, dimethylarsinic acid is formed as a metabolite in humans after exposure to inorganic arsenic. Many epidemiologic stud-

ies have been conducted on populations exposed occupationally to inorganic arsenic. Although data indicate that dimethylarsinic acid might be the metabolite that mediates the carcinogenicity of inorganic arsenic, the dose-response and kinetics underlying the carcinogenicity of inorganic arsenic compared to exposure to dimethylarsinic acid are not characterized well enough to directly extrapolate epidemiologic data from inorganic arsenic exposure to dimethylarsinic acid exposure. Therefore, studies of inorganic arsenic exposure are not reviewed here. Of the chemicals, the most data are available on populations exposed to TCDD or 2,4-D. The relevant epidemiologic studies of those chemicals are described in this chapter. The pertinent discussion that appeared in *Update 1998* is included here for completeness.

Because respiratory cancer is fairly common, the committee has focused on studies with at least seven cases.

REVIEW OF STUDIES

The National Institute for Occupational Safety and Health (NIOSH) study of chemical-production workers gives the most detailed account of timing effects and exposure to TCDD (Fingerhut et al., 1991). Standardized mortality ratios (SMRs) for respiratory cancer (lung, bronchus, and trachea) were 0.8, 1.0, and 1.2 for 0–9, 10–19, and 20+ years, respectively, since first exposure to TCDD, on the basis of a total of 85 cases. SMRs for time since first exposure are further stratified by duration of exposure, as reproduced in Table 3-1. An association between TCDD exposure and respiratory cancer is not observed in years 0–9 after first exposure. Effects begin to be observed in the second decade after exposure began among those with at least 5 years of exposure, and they have not

TABLE 3-1 NIOSH Study: Respiratory-Cancer Relative Mortality, by Time Since First Exposure and Duration of Exposure to TCDD[a]

Time Since First Exposure (years)	Duration of Exposure to TCDD (years)									
	<1		1–4		5–14		15+		Overall	
	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
0–9	3	0.8	3	1.0	1	0.8	0	0.0	7	0.8
10–19	6	0.7	5	0.8	9	1.8	1	1.4	21	1.0
20+	17	1.0	17	1.3	14	1.5	9	1.6	57	1.2
Total	26	0.9	25	1.1	24	1.5	10	1.5	85	1.1

[a]Data from Fingerhut et al. (1991), Table 4. No confidence intervals were provided, but all p-values were greater than 0.05.

ABBREVIATIONS: NIOSH, National Institute for Occupational Safety and Health; Obs, observed; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

disappeared 20 or more years after first exposure. The latency may be longer for those with shorter exposure.

A later assessment of this cohort (Steenland et al., 1999) was based on an additional 6 years of follow-up and a job-exposure matrix that ranked 3,538 workers (69% of the cohort) on relative exposure to TCDD. An analysis using Cox regression models and an assumption of 15-year latency after initial employment found a statistically significant trend between exposure and lung cancer mortality among the workers, with highest mortality in the top two septiles of exposure (hazard ratios = 2.6 (1.3–5.0) and 1.6 (0.8–3.4) for septiles 6 and 7, respectively). Analyses were repeated with different values for latency (5, 10, and 20 years, in addition to 15 years). The authors reported that the model based on 15-year latency provided the best fit with the data for the analysis of all cancers combined. No information was provided on the alternative latency assumptions for the analysis of lung cancer alone, and goodness of fit in a limited set of models is not necessarily a reliable means of determining the appropriate latent period, which will vary across individuals.

One of the largest industrial accidents involving environmental exposure to TCDD occurred in Seveso, Italy, in July 1976 as a result of an uncontrolled reaction during trichlorophenol production. On the basis of soil sampling, three areas were defined about the release point: Zone A, the most heavily contaminated, from which all residents were evacuated within 20 days; Zone B, an area of less contamination that children and pregnant women in their first trimester were urged to avoid during the daytime; and Zone R, a region with some contamination in which consumption of local crops was prohibited. Data from Seveso in Bertazzi et al. (1989a,b) and summarized in Tables 3-2a and 3-2b indicate that lung cancer mortality was not increased among those in the exposed areas during the period from 0 to 5 years after the accident but was increased in years 6–10 for Zones A and B. In the 15-year follow-up of the Seveso cohort, no additional data are presented on latency for lung cancer (Bertazzi et al., 1997), but given the results from several publications, the committee has calculated the relative risk for years 11–15 as 1.0 in all three zones.

A report on the 20-year follow-up of the Seveso cohort (Bertazzi et al., 2001) is summarized in Table 3-2c. Data are shown for lung cancer (ICD-9 code 162) mortality in men of Zones A and B combined and for periods since exposure that are slightly different from the categories displayed in Table 3-2a. A modest increase in lung cancer mortality is observed for years 5–9 and 15–20, but there is no increase in the first period or in years 10–14. No latency analyses are presented for Zone R, and the number of lung-cancer deaths in women (four) is too small for an informative analysis of latency.

In an 18-year follow-up of Finnish herbicide appliers, Asp et al. (1994) gave the SMRs for respiratory cancer (lung, bronchus, and trachea) relative to the Finnish male calendar-year- and age-specific rates in such a way that SMRs could be calculated by time since first exposure for 0–9, 10–15, and >15 years.

TABLE 3-2a Seveso Study: Lung Cancer Mortality Risk Ratios in Men, by Calendar Period

Time Since Exposure (years)	Relative Risk		
	Zone A	Zone B	Zone R
0–5	0.0	1.1	0.7
6–10	2.0	1.8	0.9
11–15[a]	1.0	1.0	1.0

[a]Relative risks have been calculated by using data from the two published reports.
Data from Bertazzi et al., 1997, Table 3; Bertazzi et al., 1989b, Tables 4, 5, and 7.

TABLE 3-2b Seveso Study: Lung Cancer Mortality in Men for 15-year Follow-up

	Observed	Expected	Relative Risk	95% Confidence Interval
Zone A	4	4.2	1.0	(0.4–2.6)
Zone B	34	27.6	1.2	(0.9–1.7)
Zone R	178	194.4	0.9	(0.8–1.1)

Data from Bertazzi et al., 1997, Table 3.

TABLE 3-2c Seveso Study: Lung Cancer Mortality in Men, by Years Since First Exposure

Time Since First Exposure (years)	Zones A and B			
	Observed	Expected	Relative Risk	95% Confidence Interval
0–4	9	8.9	1.0	(0.5–2.0)
5–9	15	9.7	1.5	(0.9–2.6)
10–14	14	12.7	1.1	(0.6–1.9)
15–20	19	12.8	1.5	(0.9–2.4)

Data from Bertazzi et al., 2001, Table 7.

There is no clear pattern according to time since first exposure, but there also is no overall association with respiratory cancer, probably because the exposures averaged only 4 weeks.

Another study from Finland examined the incidence of cancer in a cohort of 152 male workers in a pulp and paper mill (Jappinen and Pukkala, 1991). The cohort was limited to workers employed in 1945–1961 in jobs with the greatest

respiratory or skin exposure to chlorinated organic compounds, including TCDD. The expected incidence of cancer was calculated from age- and calendar-specific rates for the mill district. During 34 years of follow-up (1953–1987), seven cases of lung cancer occurred (standardized incidence ratio, 3.0; 95% confidence interval (CI), 1.2–6.2). Six of the seven cases were diagnosed 15 years or more after initial employment in the mill. The authors acknowledged that company health records showed that six of the cases were in smokers.

In a report on four occupational cohorts involved in phenoxy herbicide and chlorophenol manufacturing in Germany, Becher et al. (1996) showed the relative risk to be highest in the first decade (SMR, 1.80) and to decline but remain elevated thereafter (SMR, 1.38 10–20 years after exposure, 1.35 thereafter). The chemicals produced included 2,4-D and 2,4,5-T, and exposure to TCDD was also likely in most of the cohorts. Those results are based on 47 lung cancer deaths, and the study had an overall SMR of 1.4. The data are presented in Table 3-3.

A different pattern of results was observed in a study of 549 men in the Netherlands employed during 1955–1985 in a factory whose main product was 2,4,5-T. Bueno de Mesquita et al. (1993) monitored cause-specific mortality for the same 30-year period and identified nine deaths from respiratory cancer (SMR, 1.0; bronchus, lung and trachea). In analyses stratified by time since first exposure, six of the respiratory cancer deaths occurred after 20 years of exposure (SMR, 1.7). Hooiveld et al. (1998) extended the follow-up by 6 years (through 1991) and reported SMRs of 1.0 overall (based on 14 deaths) and 1.3 for workers first exposed 20 years ago or earlier.

Coggon et al. (1991) examined cancer mortality in the male employees of four British factories that manufactured a variety of phenoxy herbicides. The cohort included 2,239 men who worked during 1963–1985, and follow-up for mortality was complete through 1987. Nineteen deaths were attributed to respiratory cancer (SMR, 1.3; lung, pleua, and mediastinum), but only six of the cases occurred more than 10 years after initial exposure to phenoxy compounds (SMR, 0.9).

TABLE 3-3 German Phenoxy Herbicide and Chlorophenol Manufacturing Workers Study: Observed and Expected Lung Cancer Deaths and SMRs for Men, by Time Since First Exposure

Time Since First Exposure (years)	Observed	Expected	SMR	95% CI
<10	8	4.4	1.8	(0.8–3.6)
10 to <20	14	10.1	1.4	(0.8–2.3)
20+	25	18.4	1.4	(0.9–2.0)

Data from Becher et al., 1996, Table 4.

TABLE 3-4 IARC International Study of Workers Exposed to TCDD or Higher Chlorinated Dioxins: Observed and Expected Lung Cancer Deaths and SMRs for Men, by Time Since First Exposure

Time Since First Exposure (years)	Observed	Expected	SMR	95% CI
0–9	34	27.9	1.2	(0.9–1.7)
10–19	64	61.5	1.0	(0.8–1.3)
≥20	127	110.4	1.2	(1.0–1.4)

Data from Kogevinas et al., 1997, Table 5.

The cohorts from Germany, the Netherlands, and England (and the aforementioned NIOSH study cohorts) were included in the much larger International Agency for Research on Cancer (IARC) multicohort occupational study (Kogevinas et al., 1997). The IARC study found a weak overall association between exposure to phenoxy herbicides or chlorophenols and lung cancer mortality (SMR, 1.1 based on 225 deaths). The SMRs for 0–9, 10–19, and 20+ years in the IARC study were 1.2, 1.0, and 1.2, respectively, on the basis of 34, 64, and 127 lung cancer deaths. The IARC results are shown in Table 3-4.

The study of Ranch Hands (Michalek et al., 1998) examines latency for several cancer sites but does not define whether it involves time since first service, since last service, since start of service in Vietnam, or since last service in Vietnam. This group of veterans experienced fewer respiratory cancer deaths than expected in the first 20 years (3 observed and 5.6 expected) and a slight excess after 20 years (9 observed and 7.2 expected).

A report on the Australian veterans who served in Vietnam provides additional information on the time since first year of service (Crane et al., 1997). The first year of service may have been earlier than the first year in Vietnam or the first year of exposure, so latency observed in these data would be longer than the actual latency. The pattern of SMRs for lung cancer deaths during 1980–1994 (no lung cancers were observed before 1980) was as follows: 2.5, 0.9, 1.3, 1.3, and 1.1 for the periods <10, 11–15, 16–20, 21–25, and >25 years, respectively, since the start of service. Note, however, that the SMR of 2.5 in the early period is based on only three lung cancer deaths, whereas the remaining periods had 17, 60, 95, and 35 lung cancer deaths, respectively. The results can be found in Table 3-5.

In addition, two recent studies have used toxicokinetic models to obtain a measure of cumulative dose and have used this as an exposure metric in analysis of increased cancer risk associated with TCDD exposure. Steenland et al. (2001) estimated cumulative dose from both estimated external exposure and known serum TCDD. The cumulative dose was calculated with a simple one-compartment first-order model, assuming a half-life of 7.1 years. The study

TABLE 3-5 Australian Vietnam Veterans Study: Observed and Expected Lung Cancer Deaths and SMRs for Men, by Time Since Start of Military Service

Time Since Start of Service (years)	Observed	Expected	SMR
<10	3	1.2	2.5
11–15	17	19.7	0.9
16–20	60	45.9	1.3
21–25	95	73.0	1.3
>25	35	32.2	1.1

Data from Crane et al., 1997, Table E-19.

assumed a background intake of 0.5 pg/kg of body weight per day, leading to a steady-state level of about 5 parts per trillion (ppt) in blood lipids. To estimate risk, the authors assumed an intake of 10 pg/kg per day. The exposure-response analysis used a cumulative TCDD dose and integrated time-specific serum concentrations over time to obtain a cumulative serum concentration for each person in the study. A similar cumulative dose was obtained from exposure scores at the end of exposure, and this did not differ much from the cumulative exposure based on serum concentrations. There was an increasing cancer risk with increasing cumulative TCDD dose in the serum, assuming a 15-year lag. The authors acknowledged limitations in their approach, one being the use of a constant estimated half-life; TCDD half-life may vary with body-mass index, initial body burden, and other factors. However, the cumulative dose (derived from serum concentrations) was judged to be a "reasonably good predictor" of cancer risk. The study by Steenland et al. dealt with all cancers, and although the analysis did not deal specifically with respiratory cancer, it does demonstrate a use of cumulative dose measures.

Salvan et al. (2001) also used a cumulative dose as an exposure metric to estimate cancer risk, for all cancers and for lung cancer specifically. They examined the NIOSH cohort data by using a minimal physiologic toxicokinetic model that assumes TCDD concentrations to be in dynamic equilibrium among three lipid compartments in the body—blood, liver, and adipose tissue—with assumptions about TCDD elimination and intake. The model used for analysis of the NIOSH cohort was developed with data on Ranch Hands, for whom serum concentrations were available at multiple times. The study used three methods to estimate elimination and input, including nonlinear least squares, a nonlinear mixed-effects model, and a hierarchic model with Bayesian analysis. The cumulative dose, expressed in ppt-years, was related to the all-cancer risk, assuming a 10-year lag from first exposure. The analysis showed an increase in risk ratio of

2 for exposures at 100 times background. The authors acknowledged limitations, including an inability to adjust for smoking. Despite the limitations, the value of using a cumulative dose as an exposure metric appears to be upheld.

When reviewing those two studies (Salvan et al., 2001; Steenland et al., 2001), however, it must be remembered that the relationships between cumulative dose and respiratory-system dose and between dose and response in the respiratory system are not clear. It is assumed that the continuing exposure estimated from serum concentrations indicates the degree to which the respiratory system is exposed. Whether the cumulative dose pertains to questions of latency when serum concentration has fallen to the background value is not clear.

SUMMARY

In reviewing the epidemiologic evidence on the timing of exposure to the chemicals of interest (2,4-D, 2,4,5-T and its contaminant TCDD, cacodylic acid, and picloram) and respiratory cancer, the relevant studies had exposure to either the herbicides and TCDD, or TCDD alone. There were no data available on the latent or presumptive period for the individual herbicides.

Despite a few suggestions in the literature, based on small numbers of deaths, that the highest risk is shortly after start of exposure, the preponderance of the evidence suggests that risk remains elevated at least 15 and probably more than 20 years after exposure. There is no indication that risks return to background levels during the entire length of follow-up, which in many studies is more than 25 years after exposure ends. Nevertheless, no data have been published at all regarding the time between cessation of exposure to TCDD and risk of respiratory cancer.

The NIOSH study (Fingerhut et al., 1991) does not begin to show an effect until 10 years after exposure, and risks were increased the most 20 years or more after exposure began. Six years later, a follow-up study of this cohort found a statistically significant trend between exposure and lung cancer mortality among workers; a 15-year latency period was the best fit for the study data (Steenland et al., 1999). The data on the Seveso cohort (Bertazzi et al., 1989a,b; 1997) show an increased occurrence of death from lung cancer beginning 6–10 years after initiation of an exposure. The 20-year follow-up of the Seveso cohort also showed similar elevations in risk for the periods 5–9 and 15–20 years since first exposure (Bertazzi et al, 2001). A study of workers involved in the manufacturing of phenoxy herbicide and chlorophenol showed the relative risk to be high in the first three decades after exposure begins (Becher et al., 1996). A mortality study of a different cohort of male factory workers employed by factories that manufactured phenoxy herbicides found nineteen deaths attributed to lung cancer (SMR, 1.3); 6 of these cases occurred more than 10 years after exposure in the factory (SMR, 0.9) (Coggon et al., 1991). The IARC cohort (Kogevinas et al., 1997) demonstrates elevations in lung cancer in the first and third decade after

exposure. Among Australian Vietnam veterans (Crane et al., 1997), risks were elevated 21–25 years, but not greater than 25 years, after exposure. The latest report on Ranch Hands (Michalek et al., 1998) shows a reduced risk of lung cancer death in the first 20 years after exposure and a slightly elevated risk after 20 years.

A study of Finnish pulp and paper mill workers found 7 cases of lung cancer (3.0; 95% CI, 1.2–6.2); 6 of the 7 cases were diagnosed 15 years or more after initial employment (Jappanin and Pukkala, 1991). Six out of 9 respiratory cancer deaths in a cohort of factory workers involved in the production of 2,4,5-T occurred after 20 years of exposure (Bueno de Mesquita et al., 1993). A follow-up study of this cohort reported 14 respiratory cancer deaths and SMRs of 1.0 overall (based on 14 deaths); workers first exposed 20 years or more earlier had an SMR of 1.3 (Hooiveld et al., 1998).

The committee finds evidence in the literature that the time between exposure and the detection of respiratory cancer depends on the duration of exposure; this evidence is in the Fingerhut et al. (1991) study, the only analysis that presented a cross-classification of time since first exposure with duration of exposure. With latency depending on the duration of exposure, one would not necessarily expect to see the same pattern for time since exposure in all studies. Nor would one expect the pattern of risk over time since exposure to be the same in Vietnam veterans as in those exposed in manufacturing plants or through accidental environmental releases of the same chemicals.

In summary, numerous studies have examined latency by stratifying on time since first exposure using the simplest approaches described in Chapter 2. Some of the data suggest that an increased risk of respiratory cancer occurs within 10 years of first exposure. No analyses examined the presumptive period for TCDD, that is, the time between termination of exposure and the end of an effect on the incidence of respiratory cancer. Data on latency in epidemiology studies provide a framework for the consideration of a presumptive period, but are not sufficient for drawing quantitative conclusions regarding the length of that period. The relationship between cumulative or peak dose in TCDD carcinogenesis is unknown, and the relative importance of the first or any specific window of exposures remains unclear because information from epidemiologic studies has not been sufficient to disentangle them. Although risk factors for cancer can be determined in a population, for any given individual who develops respiratory cancer, the exact exposures that contributed to the pathogenesis of that cancer cannot usually be determined with certainty. Therefore, there is no clear indication of the presumptive period; but in many of the studies, there also is no indication that the risk returns to background values during the entire length of follow-up, often more than 25 years. That is, some increased risk remains for at least 20 or 25 years after exposure began. Most of the studies, however, have not followed the cohort beyond 30 years, leaving no data with which to determine a latent or presumptive period beyond that time frame.

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4

Conclusions

This chapter summarizes the data that are available for estimating the presumptive period for respiratory cancer after exposure in Vietnam and the uncertainties that are inherent in the estimation, and it presents the overall conclusions of the committee on the latent period and the presumptive period.

DATA FOR ESTIMATION OF PRESUMPTIVE PERIOD

As discussed in Chapter 2, the main chemical used in Vietnam that is of concern for respiratory cancer is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin). The committee considered four types of data to evaluate the presumptive period, the period between cessation of exposure to TCDD and respiratory cancer: toxicokinetic data, mechanistic data, epidemiologic data, and data on the presumptive period for other respiratory carcinogens.

Toxicokinetic Data

TCDD is a highly hydrophobic chemical that readily crosses cell membranes and accumulates in lipid-rich organs. Mobilization of TCDD that accumulates in those organs results in continued target organ exposure after external exposure has ended. Estimates of the half-life of TCDD in humans have been consistent in confirming that TCDD is highly persistent in the body, with a half-life averaging about 7.5 years. That long half-life must be taken into consideration in determining cessation of exposure and the presumptive period. Although external exposure to herbicides in Vietnam was time-limited, elevated TCDD body burden could remain for many years after service in Vietnam. That pro-

longed elevation of body burden might result in respiratory cancers being linked to exposures in Vietnam at a later date than would be expected if the end of service in Vietnam was considered when TCDD could no longer have an effect. That is, the prolonged elevation of body burden would, in effect, lengthen the presumptive period for TCDD because the duration of the ongoing potential exposure of target organs from the elevated body burden is part of the presumptive period.

Mechanistic Data

To model and evaluate the carcinogenic properties of a chemical mechanistically, the multistage-carcinogenesis approach is often used (Pitot, 1986; Barrett, 1993). A chemical might initiate, promote, or alter the progression of a neoplasm. Latent periods and presumptive periods for different chemicals depend on differences in the mechanisms by which chemicals act, that is, on whether they are initiators or promoters. Furthermore, carcinogenic chemicals that are relatively persistent in the body may initiate or promote the carcinogenic process over a long period. In that case, latency may be either short or long from the time of initial exposure because it is possible that effects on the carcinogenic process may occur whenever body burden is increased and at multiple stages of the carcinogenic process.

TCDD is a known carcinogen in rats and mice and is considered to be a carcinogen in humans. All the available evidence indicates that it acts as a promoter by multiple pathways in the regulation of cell proliferation and differentiation (IOM, 2003). Given the tumor-promoting potential of TCDD and its persistence, it is possible that, as indicated above, the latent and presumptive periods could be altered because promotion of cells initiated by other chemicals after external exposure to TCDD has ended could occur whenever body burden is increased.

Epidemiologic Data

Studies have examined latency by stratifying on time since first exposure and through the simplest approaches described in Chapter 2. Some of the data suggest that an increased risk of respiratory cancer occurs within 10 years of first exposure. No analyses have examined the presumptive period for TCDD, that is, the time between termination of exposure and end of an association with respiratory cancer. Therefore, there is no clear indication of the presumptive period, and no upper limit on that period could be determined. Many of the studies also lack an indication that the risk returns to the background value for the entire length of follow-up; some increase in risk remains for 20 or 25 years, or more, after exposure began. Most of the studies, however, have not followed the cohort

beyond 30 years, leaving no data with which to determine a latent or presumptive period beyond that time frame.

Data on Other Respiratory Carcinogens

No epidemiologic studies have evaluated the time between cessation of exposure to TCDD and occurrence of respiratory cancer, but there is a substantial body of literature on timing of exposure and respiratory cancer for other carcinogens. Chapter 2 briefly reviews data on gamma rays, radon daughters, smoking, arsenic, and asbestos. Most of the data on those agents indicate that the risk of respiratory cancer remains increased for many decades after the end of exposure. For example, lung cancer risk posed by exposure to arsenic or radon remains increased in Chinese tin miners for more than 50 years after the end of exposure (Hazelton et al., 2001). Time courses cannot be directly extrapolated from other chemicals to TCDD, but those data do indicate that in many instances respiratory cancer can be associated with a chemical exposure that occurred many decades earlier.

UNCERTAINTY

There are two steps in the assessment of the presumptive period between an exposure and a given health outcome in a particular group, such as Vietnam veterans. The first step is to establish that the exposure in question is associated with the outcome, and the second is to evaluate how long the risk of the outcome remains increased after the cessation of the exposure. The overall uncertainty in the estimate of the presumptive period includes uncertainty in the association and uncertainty in the time course.

The *Update 2002* committee concluded that evidence remains limited but suggestive that there is an association between exposure to at least one of the chemicals of interest (2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid and its contaminant TCDD, picloram, and cacodylic acid) and respiratory cancer (cancer of the lung and bronchus, larynx, and trachea) (IOM, 2003). As is evident from the categorization of the evidence as limited/suggestive, uncertainty remains with regard to the association between the exposure of interest and respiratory cancer. Uncertainty can be introduced by the statistical error and potential biases that characterize any epidemiologic study. As discussed in *Update 2002* (IOM, 2003) and in Chapter 1 of the present report, for the chemicals of interest and respiratory cancer uncertainty in the strength of the evidence of an association and in whether the association is causal is a consequence of the absence, in available studies, of data on smoking, occupational exposure, and other confounding factors. As discussed in Chapter 2, however, the likelihood of confounding by smoking in studies that include internal comparisons (that is, that calculate relative risks rather than standardized mortality ratios) might be

low. Studies have shown that in large-scale occupational studies that conduct internal comparisons, smoking is not a confounder because there are not large variations in smoking within industrial cohorts (Bang and Kim, 2001). Studies that rely on standardized mortality ratios could be confounded.

Animal data that support the plausibility of an association between TCDD and respiratory cancer—studies indicate that TCDD can act as a promoter for lung cancer—also increase the committee's confidence in its conclusion of limited/suggestive evidence of an association between the exposure and respiratory cancer.

As mentioned above, there is also uncertainty in the time course of exposure and disease detection. Various statistical modeling techniques have been developed to evaluate latent periods and presumptive periods. Each model has limitations and is only as good as the available input data. The limitations of the various models must be kept in mind in evaluating the uncertainty surrounding a presumptive period. In estimating a latent period or presumptive period from epidemiologic data, errors in the assignment or timing of exposures could increase uncertainty. Other aspects of epidemiologic studies that might affect the presumptive period are whether a study evaluates cancer incidence or cancer mortality, whether competing mortality is affecting the results of a study, and whether there is a substantial population group that is genetically susceptible or has acquired a susceptibility to respiratory cancer. There is also the possibility that coexposure to effect modifiers has altered the presumptive period. As discussed in Chapter 2, other exposures, such as to smoking and other chemicals, can potentially modify the effects of TCDD on respiratory cancer; but no studies appear to have evaluated the impact of smoking on the latent or presumptive period associated with TCDD. The greatest source of uncertainty with respect to the presumptive period for TCDD and respiratory cancer, however, is the lack of data on the time between cessation of exposure and the manifestation of respiratory cancer in the epidemiologic literature. Such data are needed to provide an accurate estimate of the presumptive period. Data on latency in epidemiology studies provide a framework for the consideration of presumptive period, but are not sufficient for drawing quantitative conclusions regarding the length of that period. The relationship between cumulative or peak dose in TCDD carcinogenesis is unknown, and the relative importance of the first or any specific window of exposures remains unclear because information from epidemiologic studies has not been sufficient to disentangle them. For any given individual who develops respiratory cancer, the exact exposures that contributed to the pathogenesis of that cancer are unknown. The conclusions that the committee can draw, on the basis of the available data, are discussed below.

COMMITTEE'S CONCLUSIONS ON LATENT PERIOD AND PRESUMPTIVE PERIOD

Earlier Institute of Medicine reports on veterans and Agent Orange have looked at the question of the latent period between exposure to TCDD and respiratory cancer (IOM, 1996, 1999). The committees responsible for those reports concluded that no latent period could be estimated. Specifically, *Update 1998* concluded that "the evidence suggests that if respiratory cancer does result from exposure to the herbicides used in Vietnam, the greatest relative risk for lung cancer may be in the first decade after exposure, but until further follow-up has been carried out for some of the cohorts, it will not be possible to put an upper limit on the length of time these herbicides could exert their effect", that is, the presumptive period (IOM, 1999).

There are still few data on the latent period and no data on the presumptive period for TCDD and respiratory cancer. The available data on latency still suggest that an increased risk of respiratory cancer may occur within 10 years of exposure. The data also indicate that risk may remain elevated into at least the third decade after initiation of exposure.

The main question to the committee is whether it is possible to put an upper limit on the length of time that TCDD could exert its effect and, if so, what that limit would be. That is, the committee has tried to evaluate the presumptive period for exposure to the herbicides used in Vietnam and their contaminant TCDD and respiratory cancer. Because no epidemiologic studies have examined the time between cessation of exposure and the occurrence of respiratory cancer, the committee cannot determine a period beyond which the occurrence of respiratory cancer could no longer be presumed to be related to exposure to TCDD. However, given the long latent period seen in epidemiologic studies (increased risk remaining 20 or 25 years after first exposure), the persistence of TCDD in the body, the promoting activity of TCDD, and the fact that respiratory cancer risk posed by some other agents remains increased for many decades after exposure has ended (at least 50 years after cessation of exposure), the committee concludes that the risk of respiratory cancer posed by exposure to TCDD could last many decades.

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Appendix

Committee and Staff Biographies

Irva Hertz-Picciotto, PhD (*Chair*), is professor in the Department of Epidemiology and Preventive Medicine and deputy director of the Children's Center for Environmental Health at the University of California, Davis. She has published extensively on methods of epidemiologic data analysis, occupation-related cancer, environmental exposures, reproductive and developmental outcomes, and risk assessment. Dr. Hertz-Picciotto serves on editorial boards for *Epidemiology, American Journal of Epidemiology*, and *Environmental Health Perspectives,* as well as the Board of Scientific Counselors for the National Institute of Environmental Health Sciences, the Scientific Advisory Board for the US Environmental Protection Agency, and California Governor's Carcinogen Identification Committee. She is past president of the International Society for Environmental Epidemiology and was recently an invited delegate to the US–Vietnam Scientific Conference on the Environmental and Health Effects of the Vietnam War. Dr. Hertz-Picciotto also served as chair of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

Kiros T. Berhane, PhD, is an assistant professor in the Department of Preventive Medicine at the University of Southern California. He has conducted research on longitudinal time-series analysis, flexible-modeling techniques, modeling time-to-event data, and latency. Dr. Berhane received his PhD in biostatistics from the University of Toronto (Canada) and completed a postdoctoral fellowship in biostatistics at Johns Hopkins University (1994–1995). He is a member of a scientific advisory panel for an air-pollution study under the auspices of the Western Interprovincial Scientific Studies Association

(WISSA) in Canada. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Fourth Biennial Update).

Margit L. Bleecker, **MD, PhD**, is director of the Center for Occupational and Environmental Neurology in Baltimore. Her research interests are in clinical industrial neurotoxicology and occupational neurology. Dr. Bleecker recently served on the Institute of Medicine (IOM) Committee on the Safety of Silicone Breast Implants and has served on the IOM Committee on the Evaluation of the Department of Defense Comprehensive Clinical Evaluation Protocol and the IOM Committee on the Persian Gulf Syndrome Comprehensive Clinical Evaluation Program. She also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

Paul F. Engstrom, MD, is senior vice president of population science, overseeing Fox Chase programs in behavioral research, human genetics, epidemiologic research, and cancer-prevention research. He is also medical director of the Fox Chase Network and the International Programs for Fox Chase Cancer Center. Dr. Engstrom is a medical oncologist specializing in gastrointestinal cancers. He is a member of the National Cancer Institute (NCI) Cancer Epidemiology, Prevention and Control Review Committee and the American Cancer Society Council for Extramural Grants. He is former chair of the Board of Scientific Counselors for NCI's Division of Cancer Prevention and Control and former chair of NCI's Committee on Treatment Strategies to Cut Cancer-Death Rates in Half By the Year 2000. Dr. Engstrom is a member of the editorial board of *Cancer Epidemiology Biomarkers & Prevention*, *The Journal of Cancer Prevention* and *The Journal of Clinical Oncology*, and he is the author or coauthor of several texts and book chapters on cancer control and medical oncology. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Fourth Biennial Update).

Richard A. Fenske, PhD, is professor of environmental health in the Industrial Hygiene and Safety Program at the University of Washington School of Public Health and Community Medicine and is the director of the Pacific Northwest Agricultural Safety and Health Center. Dr. Fenske's work has focused on the evaluation of environmental health risks in special populations. His specialties include health risks posed by pesticide exposures, development of new exposure-assessment methods, and investigation of the role of skin exposure of workers and children. Dr. Fenske serves on the editorial review boards of *Applied Occupational and Environmental Hygiene* and the *Journal of Agricultural Safety and Health*. He also served as a member of the Committee to Review the

Health Effects in Vietnam Veterans of Exposure to Herbicides (Fourth Biennial Update).

Thomas A. Gasiewicz, PhD, is professor and chairman of the Department of Environmental Medicine and director of the Environmental Health Sciences Center at the University of Rochester School of Medicine. He serves on the editorial board of *Biochemical Pharmacology*, and *Toxicology and Applied Pharmacology*, as well as the National Toxicology Program Board of Counselors. He also is a peer reviewer for several other scientific journals, including *Cancer Research*, *Molecular Pharmacology*, *Carcinogenesis*, *Science*, *Toxicological Sciences*, and *Archives of Biochemistry and Biophysics*. Dr. Gasiewicz has published extensively on the toxicokinetics of dioxin, dioxin toxicity, and the role of the aryl hydrocarbon receptor in the molecular mechanism of dioxin toxicity. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

Tee L. Guidotti, MD, MPH, is the chair of the Department of Environmental and Occupational Health in the School of Public Health and Health Services of the George Washington University. He is also director of the Division of Occupational Medicine and Toxicology in the Department of Medicine of George Washington University School of Medicine and Health Science and is cross-appointed as professor of pulmonary medicine, health policy, and epidemiology. Dr. Guidotti is certified as a specialist in internal medicine, lung diseases, and occupational medicine. His primary research interests are air quality, inhalation toxicology, and occupational and environmental lung diseases. Dr. Guidotti is past president of the Association of Occupational and Environmental Clinics and sits on the Board of Directors of the American College of Occupational and Environmental Medicine and of the International Commission on Occupational Health. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

Loren D. Koller, DVM, PhD, served in academe for nearly 30 years, the last 16 as professor in the College of Veterinary Medicine of Oregon State University, Corvallis. For 10 of those years, he served as dean of the college. He operates a business in environmental health and toxicology. Dr. Koller pioneered the discipline now known as immunotoxicology with a research focus also in toxicology, pathology, carcinogenesis, and risk assessment. He is on the Institute of Medicine Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam and served for 6 years as a member of the National Research Council Committee on Toxicology. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

John J. Stegeman, PhD, is senior scientist and chair of the Biology Department at the Woods Hole Oceanographic Institution. He received his PhD in biochemistry, concentrating on enzymology, from Northwestern University. His research centers on metabolism of foreign chemicals in animals and humans and on the structure, function, and regulation of the enzymes that accomplish this metabolism. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

David S. Strogatz, PhD, MSPH, is associate professor and chair of the Department of Epidemiology of the University at Albany, State University of New York. He is also director of the Prevention Research Center of the School of Public Health of the University at Albany. Dr. Strogatz received his MSPH and PhD in epidemiology from the University of North Carolina, Chapel Hill. His research examines the epidemiology of cardiovascular disease and diabetes and the impact of socioeconomic status and race on health. He also served as a member of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third and Fourth Biennial Updates).

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Rose Marie Martinez, ScD, is director of the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. Before joining IOM, she was a senior health researcher at Mathematica Policy Research, where she conducted research on the impact of health-system change on the public-health infrastructure, access to care for vulnerable populations, managed care, and the health-care workforce. Dr. Martinez is a former assistant director for health financing and policy with the US General Accounting Office, where she directed evaluations and policy analysis in national and public-health issues. Dr. Martinez received her doctorate from the Johns Hopkins School of Hygiene and Public Health.

Michelle Catlin, PhD, is a program officer in the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. Before joining IOM, she served as a program officer with the Board on Environmental Studies and Toxicology of the National Research Council. She received her MSc in pharmacology and toxicology from Queen's University, Canada, and a PhD in environmental health (Toxicology Program) from the University of Washington. Dr. Catlin has worked on numerous National Academies reports, including *Copper in Drinking Water*, *Toxicological Effects of Methylmercury*, *Arsenic in Drinking Water: 2001 Update*, and *Veterans and Agent Orange: Update 2002*.

Jennifer A. Cohen is a research associate in the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. She received her undergraduate degree in art history from the University of Maryland. She has also been involved with the IOM committees that produced *Organ Procurement and Transplantation*; *Clearing the Air: Asthma and Indoor Air Exposures*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*; *Veterans and Agent Orange: Update 2000*; and *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans.*

Elizabeth J. Albrigo is a project assistant in the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. She received her undergraduate degree in psychology from the Virginia Polytechnic Institute and State University. She has been involved with the IOM Committee on the Review of the USDA *E. coli* O157: H7 Farm-to-Table Process Risk Assessment and the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam.

Joe A. Esparza is a senior project assistant in the Institute of Medicine (IOM) Board on Health Promotion and Disease Prevention. He attended Columbia University, where he studied biochemistry. Before joining IOM, he worked with the Board on Agriculture and Natural Resources of the National Research Council, where he was involved with the committees that produced *Frontiers in Agricultural Research: Food, Health, Environment, and Communities*; *Air Emissions from Animal Feeding Operations: Current Knowledge, Future Needs*; and *Publicly Funded Agricultural Research and the Changing Structure of US Agriculture*.