Minimum Latency & Types or Categories of Cancer

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Note for November 5, 2014 Revision: As new scientific information becomes available to the World Trade Center (WTC) Program Administrator on minimum latencies for the types of cancers on the List of WTC-Related Health Conditions found at 42 C.F.R. § 88.1, minimum latencies may be modified. This revision incorporates newly published scientific information, but does not change minimum latencies for any type or category of cancer.

Executive Summary

The WTC Program Administrator has determined minimum latencies for the following five types or categories of cancer eligible for coverage in the WTC Health Program:

(1) **Mesothelioma—11 years**, based on direct observation after exposure to mixed forms of asbestos;

(2) **All solid cancers (other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers)—4 years**, based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies;

(3) **Lymphoproliferative and hematopoietic cancers (including all types of leukemia and lymphoma)—0.4 years** (equivalent to 146 days), based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies;

(4) **Thyroid cancer—2.5 years,** based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies; and

(5) **Childhood cancers (other than lymphoproliferative and hematopoietic cancers)—1 year,** based on the National Academy of Sciences findings.

I. Introduction

According to the James Zadroga 9/11 Health and Compensation Act of 2010 ("Act") (42 U.S.C. §§ 300mm to 300mm-61), a determination that an individual's 9/11 exposure is substantially likely to be a significant factor in aggravating, contributing to, or causing an individual's health condition must be made based on an assessment of the following: (1) the individual's exposure to airborne toxins, any other hazard, or any other adverse condition resulting from the terrorist attacks; and (2) the type of symptoms and temporal sequence of symptoms (42 U.S.C. § 300mm-22(a)(2)). With regard to the temporal sequence of symptoms, cancers do not occur immediately after exposure to a causative agent and they usually take many years up to several decades to manifest clinically.

The formation of a tumor is a complex process, and tumor progression occurs by a sequence of randomly occurring changes in genetic material that alter cell functions such as proliferation, survival, and growth inhibition, as well as other cellular changes needed to overcome the normal barriers to becoming malignant. Nadler and Zurbenko (2013) used information from observed cancer incidence to construct models that estimate the period of time from malignant cancer initiation to diagnosis. For the 44 types of cancer they investigated, their model indicated that cancer latency ranged from 2.2 years (for chonric lymphocytic leukemia) to 57 years (for cancer of the transverse colon). For the solid cancers they found a range of latencies from 6.6 years up to 57 years. For the lymphoproliferative and hematopoietic cancers, they found a range of latencies from 2.2 years to 35.7 years. In addition, a study of genomic changes in non-small cell lung cancer found that tumors in former smokers suggested a long period of latency that preceded clinical detection (de Bruin et al. 2014). Furthermore, a DNA analysis of primary pancreatic cancers and their metastatic lesions showed that tumors of the pancreas take nearly 18 years to become clinically evident after the first cancer initiating mutations (Yachida et al. 2010).

Based on the requirement in the Act to consider the temporal sequence of symptoms, the Administrator determined that a minimum time period (i.e., latency) must have elapsed between the initial date of the individual's 9/11 exposure and the date of the initial diagnosis of the individual's cancer for the cancer to be certified.

The assessment of minimum latency periods for types of cancer is straightforward when exposures occur at a single point in time or regularly. However, most human exposures to carcinogens vary significantly over time, making a precise determination of minimum latency periods difficult.

The basis for selecting minimum latencies for specific types or categories of cancer is described in the sections below. However, at the outset it is important to understand that the scientific literature assessing minimum latency periods for specific types of cancer is scarce. Estimates of minimum latencies are available in the scientific literature for only a small number of the covered cancers associated with exposure to carcinogenic agents present in the aftermath of the 9/11 attacks (also referred to as "9/11 agents"). Similarly, observations of minimum latencies are available for only a few of the cancers that the Administrator added to the List of WTC—Related Health Conditions ("List") eligible for coverage under the WTC Health Program associated with other agents.

Therefore, the Administrator derived minimum latency estimates using several methods based on the best available scientific evidence for each type or category of cancer considered.

II. Methods Used to Determine Minimum Latency Estimates (*Latency Methods*)

The four specific methods used by the Administrator to select minimum latency estimates for types or categories of cancer are described below in order of the best available science, as judged by the Administrator. The methods are as follows:

Latency Method 1: Studies reporting minimum latency estimates for cancer from a 9/11 agent based on direct observation of latencies.

In this approach, the population studied must be large enough to develop a reasonable estimate of the lower bound of the distribution of latencies, which is the estimate of the minimum latency.

Latency Method 2: Authoritative Recommendations

When estimates of minimum latency are not available using *Latency Method 1*, the Administrator reviewed available recommendations on minimum latency from authoritative bodies, such as the National Academy of Sciences, and selected the shortest latency period.

Latency Method 3: Studies reporting observed latencies for a cancer from another agent, with preference given to agents chemically analogous to a 9/11 agent.

In this approach, the population studied must be large enough to develop a reasonable estimate of the lower bound of the distribution of latencies, which is the estimate of the minimum latency.

Latency Method 4: Statistical Modeling

When estimates of minimum latency are not available from studies with direct observations of minimum latencies [*Latency Methods 1 and 3*], or from authoritative recommendations [*Latency Method 2*], the Administrator looks to estimates of the minimum latency periods used in statistical models and published in the scientific literature. The two modeling approaches are described below.

4A: Estimates of cancer latency obtained by statistical modeling in epidemiologic studies of the association between exposure to an agent and a type of cancer.

Using this method, an investigator excludes exposure for some period of time (e.g., 10 or 20 years) before diagnosis is made. Exposure time is excluded because any exposure that occurs *after* a cancer develops in an individual does not contribute to the developmental time for that cancer. Several time periods may be tested, and the time period that yields the strongest association between exposure and the cancer is used as the estimate of the minimum latency period (Rothman and Greenland 1998).[1]

4B: Estimates of cancer latency obtained from statistical models used to estimate the lifetime risk of low-level ionizing radiation-related cancers.

[1] This procedure is referred to as "lagging" in epidemiologic studies.

The use of a radiation-induced cancer latency estimate is supported by scientific literature indicating shared mechanisms of carcinogenesis that apply to most solid tumors (Baba and Câtoi 2007). Furthermore, cancers that may develop as a result of radiation exposure are indistinguishable from those that occur as a result of exposure to other carcinogens (United States Nuclear Regulatory Commission 2011).

If multiple estimates of minimum latency based on statistical modeling in epidemiologic studies were available in the scientific literature, the Administrator's policy is to resolve any uncertainties inherent in this method [*Latency Method 4*] in favor of the WTC Health Program member by selecting the shortest latency period.

The strength of the available scientific evidence for estimates of minimum latency for each type of cancer or category of cancer was evaluated. The Administrator selected minimum latencies for use in the evaluation of a case of cancer for certification in the WTC Health Program based on that evaluation.

III. Basis for Selecting Minimum Latencies

A. Mesothelioma

The basis for adding mesothelioma to the List was exposure to chrysotile asbestos, which was the only form of asbestos identified in any of the settled surface dust samples in the New York City disaster area (New York City Department of Health and Mental Hygiene and Agency for Toxic Substances and Disease Registry 2002). However, a literature search did not identify any studies which reported a minimum latency that was specific for chrysotile exposure [*Latency Method 1*] for more than a few individuals. All reported latencies in these studies were greater than 20 years. Also, the Administrator was unable to find recommendations on minimum latency from other authoritative sources [*Latency Method 2*]. Therefore, the Administrator has decided to rely on estimates of latency in the scientific literature for exposures to mixed forms of asbestos [*Latency Method 3*].

A review of 21 studies by Lanphear and Buncher (1992) covered a large variety of occupations, and identified 1,105 cases of asbestos-related mesothelioma. The studies reported a median latency period of 32 years, with 96% of cases diagnosed at least 20 years following initial exposure and 33% of cases diagnosed 40 years after initial exposure. Lanphear and Buncher reported a minimum latency of 11 years. The minimum latencies of malignant mesothelioma reported in other studies of exposures to mixed forms of asbestos ranged from 13 to 15 years (Bianchi et al. 1997; Bianchi and Bianchi 2009; Kamp 2009; Linton et al. 2012; Selikoff et al. 1980).

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *Minimum Latency & Types or Categories of Cancer* policy, the Administrator maintains a minimum latency of 11 years for use in the evaluation of a case of mesothelioma for certification in the WTC Health Program. For a cancer occurring in a person less than 20 years of age, see Section III, E.

B. Solid Cancers (other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers)

Latency estimates based on a small number of individuals in direct observational studies have been reported for a few of the solid cancers included on the List. Those latency estimates are as follows:

- The minimum interval between the onset of gastro-esophageal reflux disease (GERD) and diagnosis of esophageal cancer (latency) has been reported to be 20 years (den Hoed et al. 2011). However, in individuals with GERD who have also been exposed to 9/11 agents acting as cancer initiators or promoters, the Administrator notes that the minimum latency may be significantly shortened;
- The minimum latency of 12 years has been reported for liver cancer associated with vinyl chloride exposure (Lelbach 1996). Additional 9/11 agents are known to cause liver cancer, however direct observations of latency [*Latency Methods 1 and 3*] or authoritative recommendations [*Latency Method 2*] are not available for those agents.
- Minimum latency estimates have been reported in the literature for lung cancer associated with exposure to asbestos (19 years) (Harding et al. 2009; Magnani et al. 2008; Selikoff et al. 1980), to chromium (5 years) (Harding et al. 2009), and to soot (9 years) (Barth and Hunt 1980). Additional 9/11 agents are known to cause lung cancer, however direct observations of latency [*Latency Methods 1 and 3*] or authoritative recommendations [*Latency Method 2*] are not available.

Latency estimates are available in the scientific literature for other covered solid cancers associated with exposures to agents not known to be present at the sites of the 9/11 terrorist attacks. For example, a minimum latency of 20 years has been reported for chlorinated biphenyl-related melanoma (Loomis et al. 1997) and a minimum latency of 4 years has been reported for urinary bladder cancer associated with aromatic amine exposure (Schulte et al. 1987). Specific 9/11 agents are known to cause melanoma and bladder cancer, however direct observations of latency [*Latency Methods 1 and 3*] or authoritative recommendations [*Latency Method* 2] are not available.

For some types of solid cancers on the List, estimates of minimum latency were found in the scientific literature based on statistical modeling in epidemiologic studies of associations between an exposure and cancer [*Latency Method 4A*]. Estimates of latency using this method have been reported for nasopharyngeal cancer associated with formaldehyde exposure (15 years) (Hauptmann et al. 2004) and for asbestos-related cancer of the pleura (30 years) (Magnani et al. 2008).

For solid cancers as a group, an estimate of minimum latency of 4 years is available from statistical modeling of risk between exposure to low-level ionizing radiation and solid cancers [*Latency Method 4B*] (Berrington de Gonzalez et al. 2012; National Research Council 2006).

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *Minimum Latency & Types or Categories of Cancer* policy, the Administrator maintains a minimum latency of 4 years for use in the evaluation of all types and categories of solid cancers other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers) for certification

in the WTC Health Program. For a cancer occurring in a person less than 20 years of age, see Section III, E.

C. Lymphoproliferative and Hematopoietic Cancers

Latency estimates vary widely for different lymphoproliferative and hematopoietic malignancies. For leukemia and lymphoma, direct observations of latency are not available in the literature for 9/11 agents [*Latency Method 1*]. Also, the Administrator was unable to find recommendations on minimum latency from other authoritative sources [*Latency Method 2*]. The only estimates of minimum latency found in the scientific literature were based on statistical modeling in epidemiologic studies of associations between an exposure and cancer [*Latency Methods 4A and 4B*]. The reported minimum latency estimate using statistical modeling in epidemiologic studies for acute non-lymphocytic leukemia and benzene exposure is 1.5 years (Hayes et al. 1997; Straube et al. 2010), and for lymphoproliferative and hematopoietic malignancies resulting from formaldehyde exposure is 2 years [*Latency Method 4A*] (Beane Freeman et al. 2009). For chronic lymphocytic leukemia, a minimum latency estimate of 15 years has been reported for ionizing radiation exposure [*Latency Method 4B*] (Richardson et al. 2005). A minimum latency period of 2 years has been reported for non-Hodgkin lymphoma (Bennett et al. 1991) following treatment of Hodgkin disease with chemotherapy and radiotherapy, which is similar to the latency for secondary acute leukemia [*Latency Method 3*] (Nadler and Zurbenko 2013; Tucker et al. 1988).

Evaluation of the latencies of leukemias, including chronic lymphocytic leukemia, and lymphomas from exposures to occupational and environmental agents is difficult for a number of reasons. First, the nomenclature used in the histological classification of these diseases is in flux. Second, a particular lymphoid neoplasm may manifest both lymphoid and leukemic features. Third, there is substantial overlap in the estimates of latency periods for lymphomas, which range from 2 to 10 years, and leukemias, which range from 1.5 to 35 years. This similarity in estimates of the minimum latencies for lymphoproliferative and hematopoietic malignancies is demonstrated as noted above and in risk models for radiation-induced leukemia and for chemotherapy-related acute myelocytic leukemia (National Research Council 2006). as well as acute non-lymphocytic leukemia from benzene exposure (Hayes et al. 1997). Moreover, leukemia that develops after exposure to benzene is similar to atomic bomb irradiation or therapy-induced leukemia (Larson et al. 1996).

Although latencies based on direct observations for some types of lymphomas and leukemias have been reported in the scientific literature, the nomenclature, classification, and latency overlap issues discussed above cast doubt on the reliability of these observations for use in the WTC Health Program. For these reasons, the Administrator has decided to rely on the estimate of minimum latency for all lymphoproliferative and hematopoietic malignancies of 0.4 years based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies for lymphomas and leukemias (Berrington de Gonzalez et al. 2012).

Therefore, based on the best available scientific evidence and following the methods presented in this revised *Minimum Latency & Types or Categories of Cancer* policy, the Administrator maintains a latency of 0.4 years or 146 days for use in the evaluation of cases of lymphoproliferative and hematopoietic cancers for certification in the WTC Health Program. For a lymphoproliferative or

hematopoietic cancer occurring in a person less than 20 years of age, the Administrator has also selected this minimum latency of 0.4 years, see Section III,E.

D. Thyroid Cancer

For thyroid cancer, direct observations or estimates of latency for 9/11 agents (*Latency Method 1*) or other agents (*Latency Method 3*) are not available in the literature. Also, the Administrator was unable to find recommendations on minimum latency from other authoritative sources [*Latency Method 2*]. Therefore, the Administrator has decided to rely on estimates of minimum latency based on the statistical modeling of risk for associations between exposure to low-level ionizing radiation and thyroid cancer of 2.5 years [*Latency Method 4B*] (Berrington de Gonzalez et al. 2012).

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *Minimum Latency & Types or Categories of Cancer* policy, the Administrator maintains a minimum latency of 2.5 years for use in the evaluation of a case of thyroid cancer for certification in the WTC Health Program. For a cancer occurring in a person less than 20 years of age, see Section III,E.

E. Childhood Cancers

The most common cancers in children are leukemia (34%), brain and nervous system tumors (34%), lymphomas (8%), Wilms tumor of the kidney (5%), bone cancers (4%), rhabdomyosarcoma (3%), and retinoblastoma (3%) (American Cancer Society 2013). One of the differences between childhood cancers and adult cancers is that childhood cancers typically have a shorter latency period. After reviewing the scientific literature, the Administrator has determined that estimates of minimum latency by *Latency Methods 1, 3, and 4* are not available for this broad category of cancer types. However, the National Academy of Sciences has reported that childhood cancers have a latency period of 1 to 10 years [*Latency Method 2*] (National Research Council 2003).

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *Minimum Latency & Types or Categories of Cancer* policy, the Administrator maintains a minimum latency of 1 year for use in the evaluation of cases of childhood cancer for certification in the WTC Health Program (excluding lymphoproliferative and hematopoietic cancers in children, for which the Administrator selected the minimum latency of 0.4 years). For purposes of the WTC Health Program, a childhood cancer means all types of cancer occurring in a person less than 20 years of age (42 C.F.R. §88.1).

IV. Summary

The Administrator has selected minimum latencies for the following five types or categories of cancer:

(1) **Mesothelioma—**11 years;

(2) **All solid cancers (other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers) —** 4 years;

(3) **Lymphoproliferative and hematopoietic cancers (including all types of leukemia and lymphoma) —** 0.4 years (146 days);

(4) **Thyroid cancer —** 2.5 years; and

(5) **Childhood cancers (other than lymphoproliferative and hematopoietic cancers)—**1 year.

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