



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

[NIOSH Docket 094]

World Trade Center Health Program; Petitions 031, 036, 039, and 053—

Amyotrophic Lateral Sclerosis; Finding of Insufficient Evidence

AGENCY: Centers for Disease Control and Prevention, Health and Human Services (HHS).

ACTION: Denial of petitions for addition of a health condition.

SUMMARY: The Administrator of the World Trade Center (WTC) Health Program received four petitions (Petitions 031, 036, 039, and 053) to add amyotrophic lateral sclerosis (ALS) to the List of WTC-Related Health Conditions (List). Upon reviewing the scientific and medical literature, including information provided by petitioners, the Administrator determined that there is insufficient evidence to support taking further action at this time regarding ALS. The Administrator also finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a proposed rule, or to publish a determination not to publish a proposed rule.

DATES: The Administrator of the WTC Health Program is denying these petitions for the addition of a health condition as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER].

ADDRESSES: Visit the WTC Health Program website at

<https://www.cdc.gov/wtc/received.html> to review Petitions 031, 036, 039, and 053.

FOR FURTHER INFORMATION CONTACT: Rachel Weiss, Program Analyst, 1090 Tusculum Avenue, MS: C-48, Cincinnati, OH 45226; telephone (404) 498-2500 (this is not a toll-free number); email NIOSHregs@cdc.gov.

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A. WTC Health Program Statutory Authority

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 (Pub. L. 111-347, as amended by Pub. L. 114-113, Pub. L. 116-59, Pub. L. 117-328, and Pub. L. 118-31), added Title XXXIII to the Public Health Service (PHS) Act,¹ thereby establishing the WTC Health Program within HHS. The WTC Health Program provides medical monitoring and treatment benefits for health conditions on the List² to eligible firefighters and related personnel, law enforcement officers, and rescue, recovery, and cleanup workers who responded to the September 11, 2001, terrorist attacks in New York City, at the Pentagon, and in Shanksville, Pennsylvania (responders). The Program also provides benefits to eligible persons who were present in the dust or dust cloud on September 11, 2001, or who worked, resided, or attended school, childcare, or adult daycare in the New York City disaster area³ (survivors).

All references to the Administrator of the WTC Health Program (Administrator) in this document mean the Director of the National Institute for Occupational Safety and Health (NIOSH) or his designee.

Pursuant to section 3312(a)(6)(B) of the PHS Act, interested parties may petition the Administrator to add a health condition to the List in 42 CFR 88.15. Within 90 days

¹ Title XXXIII of the PHS Act is codified at 42 U.S.C. 300mm to 300mm-64. Those portions of the James Zadroga 9/11 Health and Compensation Act of 2010 found in Titles II and III of Public Law 111-347 do not pertain to the WTC Health Program and are codified elsewhere.

² The List of WTC-Related Health Conditions is established in 42 U.S.C. 300mm-22(a)(3)–(4) and 300mm-32(b); additional conditions may be added through rulemaking and the complete list is provided in WTC Health Program regulations at 42 CFR 88.15.

³ See 42 U.S.C. 300mm-5(7); 42 CFR 88.1.

after receipt of a valid petition to add a condition to the List, the Administrator must take one of the following four actions described in section 3312(a)(6)(B) of the PHS Act and § 88.16(a)(2) of the WTC Health Program regulations: (1) Request a recommendation of the STAC; (2) publish a proposed rule in the **Federal Register** to add such health condition; (3) publish in the **Federal Register** the Administrator's determination not to publish such a proposed rule and the basis for such determination; or (4) publish in the **Federal Register** a determination that insufficient evidence exists to take action under (1) through (3) above.

More information about the WTC Health Program, including the List and the petition process, is available at www.cdc.gov/wtc/.

B. Procedures for Evaluating a Petition

In addition to the regulatory provisions, the WTC Health Program has developed policies to guide the review of submissions and petitions,⁴ as well as the evaluation of evidence supporting the potential addition of a non-cancer health condition to the List.⁵

A valid petition must include sufficient medical basis for the association between the September 11, 2001, terrorist attacks and the health condition to be added. In accordance with WTC Health Program *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions*, reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11-exposed populations or to clinical case reports of health conditions in WTC responders or survivors may demonstrate the required medical basis. In accordance with 42 CFR 88.16(a)(5), the Administrator is required to consider a new petition for a previously-evaluated health condition determined not to qualify for addition to the List

⁴ See WTC Health Program [2014], *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions*, May 14, 2014, <http://www.cdc.gov/wtc/pdfs/WTCHPPPPetitionHandlingProcedures14May2014.pdf>.

⁵ See WTC Health Program [2024], *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*, October 18, 2024, https://www.cdc.gov/wtc/pdfs/policies/WTCHP_PP_Adding_NonCancer_Health_Conditions_20241018.pdf.

only if the new petition presents a new medical basis for the association between 9/11 exposures and the condition to be added. A new medical basis is evidence not previously reviewed by the Administrator.

After the Program has determined that a petition is valid, and in accordance with the *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions (Policy and Procedures)*, the Administrator directs the WTC Health Program Science Team (Science Team) to conduct a review of the scientific literature to determine if the available scientific information has the potential to provide a basis for a decision on whether to add the health condition to the List.⁶ The literature review is a keyword search of relevant scientific databases intended to identify peer-reviewed, published, epidemiologic studies about the health condition among 9/11-exposed populations.

Using validity indicators detailed in the *Policy and Procedures*, the Science Team evaluates the scientific quality of each peer-reviewed, published, epidemiologic study of the health condition that exhibits the potential to provide a basis for deciding whether to propose adding the health condition to the List identified in the literature search. The Science Team then evaluates the studies, individually and together, to characterize the evidence of a causal association between 9/11 exposures and the health condition. The Science Team's evaluation includes consideration of the Bradford Hill weight of evidence criteria,⁷ study limitations, and whether the studies are representative of the 9/11-exposed population of responders and survivors. After assessing the degree to which the evidence supports a causal association between 9/11 exposures and the health

⁶ *Id.* at 6.

⁷ Hill AB [1965], *The Environment and Disease: Association or Causation?* Proc R Soc Med 58(5):295–300. According to the *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*, the “Bradford Hill criteria are a leading weight of evidence framework which comprises nine aspects of association. These aspects comprise strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.” See *supra* note 5 at 9, footnote 21.

condition, the Science Team will assign the evidence to one of the following five categories:

- (1) substantial likelihood of causal association,
- (2) high likelihood of causal association,
- (3) limited likelihood of causal association,
- (4) no likelihood of causal association, or
- (5) inadequate evidence to determine the likelihood of causal association.

The Science Team provides the outcome of its evaluation to the Administrator. A health condition may be added to the List if peer-reviewed, published, epidemiologic studies provide support that there is a substantial likelihood of a causal association between the health condition and 9/11 exposures (Category 1).⁸ If the evaluation of evidence provided in peer-reviewed, published, epidemiologic studies of the health condition in 9/11 populations demonstrates a high, but not substantial, likelihood of a causal association between the 9/11 exposures and the health condition (Category 2),⁹ then the Administrator may consider additional highly relevant scientific evidence regarding exposures to 9/11 agents in non-9/11 exposure scenarios. If that additional assessment establishes that there is now sufficient evidence to support the conclusion that a causal association between the 9/11 exposures and the health condition is substantially likely among 9/11-exposed populations (Category 1), the health condition may be proposed for addition to the List.

More information about the WTC Health Program, including the List and the petition process, is available at www.cdc.gov/wtc/.

C. Petitions 031, 036, 039, and 053

⁸ *Substantial likelihood of causal association* means that the association is strongly supported by evidence from high-quality, peer-reviewed, published epidemiologic studies of the health condition in 9/11-exposed populations and there is high confidence that the association cannot be explained by chance, bias, confounding, or any other alternative explanation. *See supra* note 5 at 12.

⁹ *High likelihood of causal association* means that the scientific evidence, taken as a whole, demonstrates that the likelihood of a causal association is less than substantial, but definitively more than limited. Therefore, there is some meaningful likelihood that the association can be explained by chance, bias, confounding, or another alternative explanation. *See supra* note 5 at 12.

The Administrator of the WTC Health Program received four petitions requesting the addition of amyotrophic lateral sclerosis to the List of WTC-Related Health Conditions between 2021 and 2024. Of the scientific references provided in each petition, six were found to meet the validity requirement of being peer-reviewed, published, epidemiologic studies about the health condition among 9/11-exposed populations or to clinical case reports of health conditions in WTC responders or survivors. Each petition and its medical basis is described below.

On July 12, 2021, the Administrator received a petition (Petition 031) from a WTC responder requesting the addition of “Amyotrophic Lateral Sclerosis (ALS)” to the List.¹⁰ The petition’s validity was established by references to three peer-reviewed, published, epidemiologic studies that demonstrate a medical basis for the association between 9/11 exposures and ALS. The referenced studies and literature reviews each individually establishing a medical basis are as follows:

- *Neurodegenerative Diseases: Occupational Occurrence and Potential Risk Factors, 1982 through 1991*, by Schulte et al. [1996],¹¹ is a peer-reviewed, published case-control study of occupational exposures and neurodegenerative diseases, including ALS, using death certificate data in a national mortality surveillance database.
- *Toxicant Exposure and Bioaccumulation: A Common and Potentially Reversible Cause of Cognitive Dysfunction and Dementia*, by Genuis and Kelln [2015],¹² is a peer-reviewed, published review article of the literature on bioaccumulation following exposure to toxicants, some of which are 9/11

¹⁰ See Petition 031, WTC Health Program: Petitions Received, <http://www.cdc.gov/wtc/received.html>.

¹¹ Schulte PA, Burnett CA, Boeniger MF, Johnson J [1996], *Neurodegenerative Diseases: Occupational Occurrence and Potential Risk Factors, 1982 through 1991*, Am J Public Health 86(9):1281–8.

¹² Genuis SJ and Kelln KL [2015], *Toxicant Exposure and Bioaccumulation: A Common and Potentially Reversible Cause of Cognitive Dysfunction and Dementia*, Behav Neurol 2015:620143.

agents, and increased risk of cognitive dysfunction and dementia resulting from neurodegenerative diseases including ALS.

- *Military Service, Deployments, and Exposures in Relation to Amyotrophic Lateral Sclerosis Etiology and Survival*, by Beard and Kamel [2015],¹³ is a peer-reviewed, published review of the evidence associating ALS and motor neuron diseases (MNDs) with military service, deployments, and exposures, from peer-reviewed epidemiologic studies published through 2013.

These three studies suggest a potential association between exposure to 9/11 agents (specifically experiences that might cause psychological harm, physical hazards, and chemical hazards, including heavy metals) and ALS, and thus provided a sufficient medical basis to consider the submission a valid petition.

On April 7, 2022, the Administrator received a petition (Petition 039), requesting the addition of “Amyotrophic Lateral Sclerosis (ALS), Lou Gehrig’s disease,” to the List.¹⁴ A second petition (Petition 036), submitted by the same petitioner, was received by the Administrator on April 14, 2022.¹⁵ The petitions’ validity was established by references to one peer-reviewed, published, epidemiologic study that demonstrates a positive association between 9/11 exposures and ALS:

- *Prospective study of chemical exposures and amyotrophic lateral sclerosis*, by Weisskopf et al. [2009],¹⁶ is a peer-reviewed, published prospective cohort study of the relationship between exposure to chemicals, including formaldehyde (a 9/11 agent), and ALS in over 1 million cancer prevention study participants.

¹³ Beard JD and Kamel F [2015], *Military Service, Deployments, and Exposures in Relation to Amyotrophic Lateral Sclerosis Etiology and Survival*, *Epidemiol Rev* 37(1):55–70.

¹⁴ See Petition 039, WTC Health Program: Petitions Received, <http://www.cdc.gov/wtc/received.html>.

¹⁵ NB: The petition numbers are out of order because the WTC Health Program processed the second submission first.

¹⁶ Weisskopf MG, Morozova N, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Ascherio A [2009], *Prospective Study of Chemical Exposures and Amyotrophic Lateral Sclerosis*, *J Neurol Neurosurg Psychiatry* 80(5):558–61.

This study suggests a potential association between exposure to formaldehyde, a 9/11 agent, and ALS, and thus provided a sufficient medical basis to consider the submission a valid petition.

On January 30, 2024, the Administrator received a petition (Petition 053), requesting the addition of “Amyotrophic Lateral Sclerosis (ALS)” to the List.¹⁷ The petition’s validity was established by references to two peer-reviewed, published, epidemiologic studies that demonstrate a medical basis for the association between 9/11 exposures and ALS. The studies establishing a medical basis are as follows:

- *Occupational Exposures and Neurodegenerative Diseases—A Systematic Literature Review and Meta-Analyses*, by Gunnarsson and Bodin [2019], is a peer-reviewed, published review article discussing the links between occupational exposures and neurodegenerative diseases.
- *Blood Metal Levels and Amyotrophic Lateral Sclerosis Risk: A Prospective Cohort*, by Peters et al. [2021], is a prospective cohort study comparing metal levels in blood samples for ALS patients and controls, to investigate whether metals such as arsenic, cadmium, copper, and lead are associated with ALS mortality.

These studies suggest a potential association between cadmium, lead, and zinc and ALS, and thus provided a sufficient medical basis to consider the submission a valid petition.

D. Review of Scientific Evaluation

In response to Petitions 031, 036, 039, and 053, and pursuant to the *Policy and Procedures*, the WTC Health Program conducted a systematic literature search to identify peer-reviewed, published, epidemiologic studies of ALS or motor neuron disease (MND) in 9/11-exposed populations.¹⁸

¹⁷ See Petition 053, WTC Health Program: Petitions Received, <http://www.cdc.gov/wtc/received.html>.

¹⁸ The complete list of search terms is as follows: amyotrophic lateral sclerosis, motor neuron disease, motor neuron syndrome, lateral sclerosis, Lou Gehrig’s disease, neurodegenerative disorder, amyotrophy, progressive muscular atrophy, ALS, and motor neuropathy.

The literature search conducted by the WTC Health Program found no studies that directly examined ALS or MND risk in the 9/11-exposed population. However, the search identified six peer-reviewed, published, epidemiologic studies of mortality from nervous systems disorders, including ALS¹⁹ in 9/11-exposed populations:

- *A 15-Year Follow-Up Study of Mortality in a Pooled Cohort of World Trade Center Rescue and Recovery Workers*, by Li et al. [2023],²⁰ examined mortality among 60,631 Fire Department of New York (FDNY) responders, including firefighters and emergency medical service providers ($n = 15,887$), the WTC Health Program general responder cohort (GRC) ($n = 25,657$), and the WTC Health Registry (WTCR) ($n = 19,087$).
- *All-Cause and Cause-Specific Mortality in a Cohort of WTC-Exposed and Non-WTC-Exposed Firefighters*, by Singh et al. [2023],²¹ examined mortality patterns in male FDNY firefighters ($n = 10,786$) followed through 2016 (163,583 person-years²²).
- *Mortality among Fire Department of the City of New York Rescue and Recovery Workers Exposed to the World Trade Center Disaster, 2001–2017*, by Colbeth et al. [2020; 2023],²³ examined mortality patterns in 15,431 FDNY responders followed through 2017 (248,665 person-years).

The following databases were searched: APA PsycInfo®, CINAHL (EBSCOhost), Embase Classic+Embase, Health & Safety Science Abstracts (ProQuest), NIOSHTIC-2, Ovid MEDLINE®, Scopus, and Toxicology Abstracts (ProQuest).

¹⁹ All six of the studies examined mortality patterns in the 9/11-exposed population using composite outcomes that included ALS along with other disorders of the nervous system and sensory organs. The six studies all used composite outcomes grouped together in the “NIOSH-119 Death Categories and Corresponding International Classification of Disease Codes for 1960 through 2004,” available at <https://www.cdc.gov/niosh/ltas/pdf/Rate-Info-Table-1.pdf>. Diseases of the nervous system and sense organs, categorized by NIOSH as “Major 15,” includes such health conditions as ALS, Parkinson’s disease, hereditary and idiopathic neuropathy, and many other nervous system disorders.

²⁰ Li J, Hall CB, Yung J, Kehm RD, Zeig-Owens R, Singh A, Cone JE, Brackbill RM, Farfel MR, Qiao B, Schymura MJ, Shapiro MZ, Dasaro CR, Todd AC, Prezant DJ, Boffetta P [2023]; *A 15-Year Follow-Up Study of Mortality in a Pooled Cohort of World Trade Center Rescue and Recovery Workers*, *Environ Res* 219:115116.

²¹ Singh A, Zeig-Owens R, Cannon M, Webber MP, Goldfarb DG, Daniels RD, Prezant DJ, Boffetta P, Hall CB [2023], *All-Cause and Cause-Specific Mortality in a Cohort of WTC-Exposed and Non-WTC-Exposed Firefighters*, *Occup Environ Med* 80(6):297–303.

²² Person-years means the cumulative sum of time that all study participants are under observation.

²³ Colbeth HL, Zeig-Owens R, Hall CB, Webber MP, Schwartz TM, Prezant DJ [2020], *Mortality among Fire Department of the City of New York Rescue and Recovery Workers Exposed to the World Trade Center Disaster, 2001–2017*, *Int J Environ Res Public Health* 17(17):6266. Colbeth HL, Zeig-Owens R, Hall CB, Webber MP, et al. [2023]. *Correction: Colbeth et al. Mortality among Fire Department of the City of New York rescue and recovery workers exposed to the World Trade Center disaster, 2001–2017*, *Int J Environ Res Public Health* 2020, 17, 6266, *Int J Environ Res Public Health* 20(16):6585.

- *Mortality among Rescue and Recovery Workers and Community Members Exposed to the September 11, 2001 World Trade Center Terrorist Attacks, 2003–2014*, by Jordan et al. [2018],²⁴ examined WTCHR enrollees categorized as rescue/recovery workers ($n = 29,280$; 308,340 person-years) and lower Manhattan area community members ($n = 39,643$; 416,448 person-years).
- *Mortality among World Trade Center Rescue and Recovery Workers, 2002–2011*, by Stein et al. [2016],²⁵ examined mortality in GRC responders ($n = 30,947$; 164,563 person-years).
- *Mortality among Survivors of the Sept 11, 2001, World Trade Center Disaster: Results from the World Trade Center Health Registry Cohort*, by Jordan et al. [2011],²⁶ conducted the first study of mortality among members of the WTCHR (2003–2009). Registry participants comprised responders ($n = 13,337$; 74,967 person-years), and community members ($n = 28,593$; 161,519 person-years); however, the study sample was restricted to participants residing in New York City at the time of Registry enrollment ($n = 41,930$).

Pursuant to the WTC Health Program's *Policy and Procedures*, the Program conducted an evaluation of the six studies identified in the literature search to determine the likelihood of a causal association between 9/11 exposures, including exposures to 9/11 agents,²⁷ and the petitioned health condition.²⁸ The systematic literature search, the

²⁴ Jordan HT, Stein CR, Li J, Cone JE, Stayner L, Hadler JL, Brackbill RM, Farfel MR [2018], *Mortality among Rescue and Recovery Workers and Community Members Exposed to the September 11, 2001 World Trade Center Terrorist Attacks, 2003–2014*, *Environ Res* 163:270–279.

²⁵ Stein CR, Wallenstein S, Shapiro M, Hashim D, Moline JM, Udasin I, Crane MA, Luft BJ, Lucchini RG, Holden WL [2016], *Mortality among World Trade Center Rescue and Recovery Workers, 2002–2011*, *Am J Ind Med* 59(2):87–95.

²⁶ Jordan HT, Brackbill RM, Cone JE, Debchoudhury I, Farfel MR, Greene CM, Hadler JL, Kennedy J, Li J, Liff J, Stayner L, Stellman SD [2011], *Mortality among Survivors of the Sept 11, 2001, World Trade Center Disaster: Results from the World Trade Center Health Registry Cohort*, *Lancet* 378(9794):879–887.

²⁷ 9/11 agents are chemical, physical, biological, or other hazards reported in a published, peer-reviewed exposure assessment study of responders, recovery workers, or survivors who were present in the New York City disaster area, or at the Pentagon site, or the Shanksville, Pennsylvania site, as those locations are defined in 42 CFR 88.1, as well as those hazards not identified in a published, peer-reviewed exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. See WTC Health Program [2018], *Development of the Inventory of 9/11 Agents*, July 17, 2018, https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf.

²⁸ None of the studies provided to establish medical basis were found to meet the criteria for further evaluation, although they are discussed briefly in the Scientific Evaluation, *infra* note 28.

WTC Health Program Science Team’s evaluation and synthesis of the available literature, and the Science Team’s conclusions regarding the association between 9/11 exposure and ALS are described in full in the *WTC Health Program Science Team Evaluation of Scientific Evidence Regarding the Addition of Amyotrophic Lateral Sclerosis to the List of WTC-Related Health Conditions* (Scientific Evaluation) found in the docket for this notice.²⁹

The six studies identified as high-quality and summarized in the Scientific Evaluation were evaluated individually and together to determine whether they provide a basis to support the addition of ALS to the List based on a causal relationship between 9/11 exposures to WTC dust, injury, or experiences and ALS. As described in the *Policy and Procedures*, the WTC Health Program uses the following Bradford Hill criteria to evaluate studies of 9/11-exposed populations: strength of association³⁰ and precision of the risk estimate,³¹ consistency of association,³² specificity,³³ temporality,³⁴ biological gradient,³⁵ and plausibility,³⁶ coherence,³⁷ and analogy.³⁸ In addition to the Bradford Hill

²⁹ World Trade Center Health Program Science Team [2024], *WTC Health Program Science Team Evaluation of Scientific Evidence Regarding the Addition of Amyotrophic Lateral Sclerosis to the List of WTC-Related Health Conditions*, November 20, 2024.

³⁰ It is generally thought that strong associations are more likely to be causal than weak associations; however, a weak association does not rule out a causal relationship.

³¹ Precision of the risk estimate describes the random error (“chance”) inherent in estimating the strength of association (the effect size) between exposure and the health condition. It is often expressed as a confidence interval illustrating a range of plausible values of the effect estimate given sampling error. A narrow confidence interval indicates a more precise measure of the effect and a wider interval indicates greater uncertainty. While precision is not a Bradford Hill criterion, the Science Team takes it into consideration to evaluate the extent of random error in study estimates.

³² Consistent findings are demonstrated when they have been repeatedly reported by multiple studies. When assessing consistency, the Science Team also considers differences in study quality that could explain inconsistent study findings. If only a single study is available for evaluation, the Science Team will place more emphasis on evaluating the strength of the association and precision of the risk estimate.

³³ Specificity is the premise that an association is more likely to be causal if it is observed between one cause and one effect. In practice, epidemiologic examinations of health conditions in the 9/11-exposed population involve complex exposures to multiple 9/11 agents suspected of causing multifactorial diseases; therefore, specificity has a limited role in Science Team evaluations. Specificity has been given no weight in this evaluation due to the complexity of the proposed association between multiple 9/11 agents and ALS, a multifactorial disease.

³⁴ Temporality is the condition that the 9/11 exposure must precede the health condition of interest and is typically assessed when considering aspects of exposure in the study design.

³⁵ Studies establish an exposure-response relationship by demonstrating that increases in exposure (i.e., exposures of greater intensity and/or longer duration) are associated with a greater incidence of disease. A thorough evaluation of exposure-response requires analysis of multiple levels of exposure such that the investigator can demonstrate that the risk increases with increasing levels of exposure.

³⁶ Study findings demonstrate a basis in scientific theory that supports the relationship between the exposure and the health effect, and do not conflict with known facts about the biology of the health condition.

³⁷ Coherence implies that the interpretation of a causal association agrees with known disease etiology.

³⁸ Analogy is used to inform on biological plausibility and coherence by contrasting the evidence on the suspected causal association with that from an established association between similar (analogous) causes or effects.

criteria, the Science Team also considered the limitations of the evaluated evidence and whether the evidence represents the 9/11-exposed population.

The Science Team discussed its evaluation in full in the Scientific Evaluation, and summarized its findings in table 5, which is reproduced here:

Aspect of associative causal inference (“Bradford Hill Criteria”) [Hill 1965]	Evaluation findings
Strength of association (and estimate precision)	Among six high-quality studies identified for evaluation, none examined ALS risk separately in 9/11-exposed populations [Colbeth et al. 2020, 2023; Jordan et al. 2011; Jordan et al. 2018; Li et al. 2023; Singh et al. 2023; Stein et al. 2016]. Among the six studies, only one reported a statistically significant positive association of indicating modest excess of mortality from nervous system disorders, including ALS, among WTC Health Registry community members [Jordan et al. 2018]. The authors attributed the observed excess to Alzheimer’s disease, not ALS. The finding strongly depended on the choice of control group, indicating a potential for strong selection bias. The use of composite outcomes, external reference groups, and lack of exposure information are important study limitations common to all studies evaluated.
Consistency	All but the study by Jordan et al. [2018] reported less than expected deaths from nervous disorders when using an external reference population. Results supporting a causal association between 9/11 exposure and composite outcomes of neurologic diseases including ALS were not reproduced in different 9/11-exposed populations (e.g., firefighters, general responders, and community members). The lack of reproducible results is a strong limitation of causal inference.
Temporality	9/11 exposure was presumed to precede ALS onset because all studies were longitudinal and began observation on or after 9/11. However, no studies specifically examined temporal variations in risk.
Biological gradient	One study examined the exposure-response between categories of 9/11 exposure and mortality from a composite of other nervous system disorders (including ALS) in community members [Jordan et al. 2018]. That study found no evidence of increasing risk with 9/11 exposure.

Aspect of associative causal inference (“Bradford Hill Criteria”) [Hill 1965]	Evaluation findings
Plausibility, Coherence, and Analogy	<p>There are no established environmental factors that are causal for ALS; therefore, no 9/11 agent has been identified as a contributing cause. However, the literature supports a general conclusion that a causal association between a 9/11 agent (e.g., metals, silica, formaldehyde) and ALS is plausible, although unproven.</p> <p>The assumption that the risk observed in a composite outcome is analogous to ALS risk is unsubstantiated, which is an important study limitation.</p>
Representativeness	There was representation of all groups of 9/11-exposed populations.

Upon review of the evidence available in peer-reviewed, published, epidemiological studies regarding ALS among 9/11-exposed populations, the Science Team has assessed the degree to which the evidence supports a causal association between 9/11 exposures and ALS and has determined that the available evidence is inadequate to determine the likelihood of a causal association³⁹ between 9/11 exposures and ALS (Category 5). The Science Team’s evaluation and categorization of the evidence has been provided to the Administrator.

E. Administrator’s Final Decision on Whether to Propose the Addition of Amyotrophic Lateral Sclerosis to the List

Based on the Scientific Evaluation and the Science Team’s finding that there is inadequate evidence to determine whether a causal association exists between 9/11 exposures and ALS, the Administrator has determined that there is insufficient evidence of causal association between 9/11 exposures and ALS to propose adding the condition to the List.⁴⁰ Pursuant to PHS Act, sec. 3312(a)(6)(B)(iv) and 42 CFR 88.16(a)(2)(iv), and

³⁹ See *Policy and Procedures* supra note 5 at Sec. V.E.—Evidence is Inadequate to Determine a Causal Association.

⁴⁰ See *Policy and Procedures* supra note 5 at Sec. VIII.B, proposed additions to the List are made pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.16(a)(2)(ii). The Administrator has also determined that insufficient evidence is available to publish a determination not to publish a proposed rule in the *Federal Register* (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR 88.16(a)(2)(iii)); nor is requesting a recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.16(a)(2)(i)) warranted.

in accordance with Sec. IX.B. of the *Policy and Procedures*, the Administrator is publishing this notice of his determination of insufficient evidence.

For the reasons discussed above, the request of Petitions 031, 036, 039, and 053 to add ALS to the List of WTC-Related Health Conditions is denied.

F. Approval to Submit Document to the Office of the Federal Register

The Secretary, HHS, or his designee, the Director, Centers for Disease Control and Prevention (CDC) and Administrator, Agency for Toxic Substances and Disease Registry (ATSDR), authorized the undersigned, the Administrator of the WTC Health Program, to sign and submit the document to the Office of the Federal Register for publication as an official document of the WTC Health Program. Mandy Cohen M.D., M.P.H., Director, CDC, and Administrator, ATSDR, approved this document for publication on January 6, 2025.

John J. Howard,
Administrator,
World Trade Center Health Program and Director,
National Institute for Occupational Safety and Health,
Centers for Disease Control and Prevention,
Department of Health and Human Services.

[FR Doc. 2025-00692 Filed: 1/17/2025 11:15 am; Publication Date: 1/22/2025]