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WTC Health Program Science Team Evaluation of Scientific Evidence Regarding the Addition of Amyotrophic Lateral Sclerosis to the List of WTC-Related Health Conditions

Assessment by the World Trade Center Health Program Science Team

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EXECUTIVE SUMMARY

As directed by the Administrator of the World Trade Center (WTC) Health Program, the WTC Health Program Science Team has reviewed four petitions (Petitions 031, 036, 039, and 053) requesting the addition of amyotrophic lateral sclerosis (ALS) to the List of WTC-Related Health Conditions (the List). ALS is a rare, heterogenous, and fatal disease that is mostly characterized by degenerative changes in upper and lower motor neurons. The WTC Health Program's Science Team evaluated the scientific evidence of a causal association between 9/11 exposure and ALS in accordance with the *Policy and Procedures for Adding Non-Cancer Health Conditions to the List of WTC-Related Health Conditions* (*Policy and Procedures*) [NIOSH 2024]. A literature review of peer-reviewed, published, epidemiologic studies of ALS in the 9/11-exposed population identified six high-quality studies for further evaluation and synthesis. The Science Team evaluated the information from these studies, individually and together, to characterize the available scientific evidence of a causal association between 9/11 exposures and ALS. Consideration was given to several aspects of association ("Bradford Hill Criteria"), namely: strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, and analogy [Hill 1965]. Study limitations and representativeness of findings were also assessed. Based on the weight of the evidence, the Science Team concludes that the available evidence was inadequate to draw any conclusion on the presence or absence of a causal association between 9/11 exposures and ALS.

BACKGROUND

On July 12, 2021, the Administrator of the World Trade Center (WTC) Health Program received a submission requesting the addition of amyotrophic lateral sclerosis (ALS) to the List of WTC-Related Health Conditions (the List), as promulgated in WTC Health Program regulations in Title 42 of the Code of Federal Regulations (CFR) Part 88 (42 C.F.R. § 88.15). Upon review, the submission was found to be valid and assigned an ordinal as Petition 031. Three additional petitions to add ALS to the List were subsequently received (Petition 036, received August 6, 2021; Petition 039, received April 14, 2022; and Petition 053, received January 30, 2024). In accordance with the WTC Health Program's *Policy and Procedures for Adding Non-Cancer Health Conditions to the List of WTC-Related Health Conditions* (*Policy and Procedures*), the Administrator directed the Program's Science Team to evaluate the scientific evidence of a causal association between 9/11 exposure and ALS. As permitted by WTC Health Program regulations (42 C.F.R. § 88.16(a)(4)), all four petitions are considered together in this evaluation.

PURPOSE

The purpose of this evaluation is to assess the scientific evidence from peer-reviewed, published, epidemiologic studies of ALS in the 9/11-exposed population to determine whether sufficient evidence of a causal association between 9/11-related exposures, including exposure to 9/11 agents, and ALS exists to support adding ALS to the List. This evaluation is being provided to the Administrator of the WTC Health Program to inform his determination regarding the Petitions in accordance with the *Policy and Procedures* [NIOSH 2024].

EVALUATED HEALTH CONDITION

In accordance with the *Policy and Procedures* [NIOSH 2024], the Science Team reviewed the information provided by the petitioners, including the medical basis, and determined that the health condition of interest for this evaluation is amyotrophic lateral sclerosis (ALS). ALS is a rare, heterogenous, and fatal disease that is characterized by degenerative changes in upper and lower motor

neurons [Kiernan et al. 2011; Rowland and Shneider 2001], although other neuronal populations may be affected [Gentile et al. 2019]. Mechanisms underlying neurodegeneration are not fully understood, although many cellular and molecular processes have been implicated [van Es et al. 2017]. ALS is the most common adult-onset motor neuron disease (MND), comprising about 70% of all cases. About 10–15% of ALS is familial, while cases without family history are classified as sporadic disease. Diagnosis relies on clinical findings sufficient to identify upper and lower motor neuron lesions and exclude alternative causes that mimic ALS. The disease is relentlessly progressive, but progression can be slow at disease onset, and clinical presentation is varied; therefore, differentiating ALS from other neurologic diseases can be difficult [Gentile et al. 2019; Kiernan et al. 2011; van Es et al. 2017]. There are no diagnostic tests available to definitively demonstrate ALS in every patient. A leading area of ALS research is the search for reliable diagnostic biomarkers [van Es et al. 2017].

The lifetime risk of ALS is estimated to be about 1 in 400 for women and 1 in 350 for men. For sporadic disease, onset appears most often between ages 58–63 years [Kiernan et al. 2011]. ALS risk is greater in men than in women and in White persons more than in other races [van Es et al. 2017]. The sex difference has decreased over time, suggesting that socioeconomic factors may be at play [Logroscino et al. 2008]. Using 2016 information from the U.S. National ALS Registry, the age-adjusted annual incidence and prevalence rates are 1.6 and 5.2 per 100,000 persons, respectively [Mehta et al. 2022a; Mehta et al. 2022b]. These estimates are compatible with values observed in other developed countries [Chio et al. 2013]. The median survival among ALS patients is 2–4 years after onset, with only 5–10% of patients surviving beyond 10 years. Respiratory failure is the most common cause of death. Between 2011–2014, the age-adjusted annual mortality rate per 100,000 persons in the United States (U.S.) was 1.70 [95% confidence interval (CI): 1.68, 1.72] [Larson et al. 2018]. Given that the number of persons aged 60 or more years is increasing rapidly in developing nations, ALS cases worldwide have been projected to increase nearly 70% by 2040 [Arthur et al. 2016].

Evidence on the effects of comorbidities on ALS onset and progression is equivocal. Much of the inconsistency stems from ALS heterogeneity in terms of sex, age at disease onset, body site of onset, speed of symptom progression, site of motor neuron involvement, and the occurrence of cognitive and behavioral changes [Bendotti et al. 2020]. For example, there is evidence that cardiovascular diseases and associated risk factors lower ALS risk. Conversely, risk appears greater among patients diagnosed with dementia, parkinsonism, and depressive symptoms [Korner et al. 2013; Zarei et al. 2015]. Other studies have challenged these results with conflicting findings across different populations and ALS phenotypes [Pereira et al. 2021; Xu et al. 2022].

The etiology of sporadic ALS is unknown. However, it is generally considered to be a multifactorial disease involving complex interactions between genetic susceptibility and environmental factors [Kiernan et al. 2011; Logroscino et al. 2008; Rowland and Shneider 2001]. The disease is characterized by relatively lengthy and varied pathological pathways from onset to clinical presentation. Population and geographic variations in ALS risk suggest roles for genetic, social, and environmental factors [Luna et al. 2017]. However, sufficient evidence to establish a causal relationship between ALS and suspected environmental factors is lacking [Newell et al. 2022]. Several potential risk factors have been investigated, such as smoking, education, physical activity, and other lifestyle factors; head injury; trauma; occupation and military experience; and exposures to chemicals such as pesticides, solvents, metals, silica, and particulate matter. For example, a recent comprehensive review and synthesis of 173 articles evaluated 83 potential environmental factors and found that exposures to β-N-methylamino-L-alanine (BMAA), formaldehyde, selenium, and heavy metals including manganese, mercury, zinc, and copper were among those deemed most likely to be determinants of ALS [Newell et al. 2022]. Of these, all but BMAA are listed as 9/11 agents in the *Inventory of 9/11 Agents* [NIOSH 2018].

Although there are reports of modest associations between ALS and a wide array of risk factors, findings among studies have been inconsistent [Longinetti and Fang 2019; Luna et al. 2017; Zarei et al. 2015]. Clear causal associations are elusive given limitations in identifying causal links between an agent

and a multifactorial disease in which contributions from individual factors appear relatively small. Moreover, in addition to several weaknesses attributable to studies of rare outcomes, researchers have faced other challenges specific to ALS observational studies, such as uncertainty in onset and clinical diagnosis, absence of standardized reporting, and the lack of ICD classification specific to ALS until 2017. Unlike communicable diseases and cancer in the U.S., ALS is not required to be reported to state, local, or federal health agencies; therefore, ascertainment of ALS cases for incidence and prevalence measures is less certain [Mehta et al. 2022a; Mehta et al. 2022b].

EVALUATION APPROACH

This Science Team evaluation was carried out in accordance with the *Policy and Procedures* [NIOSH 2024]. The evaluation followed these key steps:

1) Develop a literature search protocol and conduct the search for peer-reviewed, published, epidemiologic studies of ALS in 9/11-exposed populations, as directed by the *Policy and Procedures*, Section III. B. [NIOSH 2024].
2) Review identified studies and determine which studies are high-quality studies according to validity indicators, as described in the *Policy and Procedures*, Section III. C. [NIOSH 2024]. These high-quality studies comprise the set of studies that are identified for further evaluation.
3) Evaluate and integrate the evidence across the identified high-quality studies to characterize the evidence of a causal association between 9/11 exposures and ALS. As outlined in the *Policy and Procedures*, Section IV. [NIOSH 2024], this evaluation includes:
    a) An application of the aspects of a causal association referred to as 'Bradford Hill criteria' [Hill 1965] or weight of evidence criteria. The Bradford Hill criteria include: strength of the association between a 9/11 exposure and the health condition under consideration and precision of the risk estimate; consistency of the association across multiple studies; specificity observed in the cause and effect; temporality of the cause and effect; biological gradient, or exposure-

response, relationships between 9/11 exposures and the health condition under consideration; biological plausibility of the studies with known facts about the biology of the health condition under consideration; coherence between a causal association and known disease etiology; and analogy with an established causal relationship. Assessing biological plausibility, coherence, and analogy refer to a determination of whether the proposed (i.e., hypothesized) causal relationship between the 9/11 exposure and the adverse health condition is consistent with existing biological and medical knowledge. Biological plausibility of an association is necessary but not sufficient to conclude that the observed association is causal. *See Policy and Procedures*, Section IV. A. 1. [NIOSH 2024].

b) Consideration of study limitations, such as the potential for residual confounding of effect measures from incomplete information on other risk factors and major sources of selection or information biases, such as healthy worker effects, adequacy of the control group, ascertainment errors, exposure misclassification, and any conflicts of interests. See *Policy and Procedures*, Section IV. A. 2. [NIOSH 2024].

c) Consideration of the representativeness of the body of evidence to assess whether the studies, taken together, represented both WTC responder and survivor populations or, if only a subgroup of 9/11-exposed population is represented. If the 9/11 population is only partially represented, then the Science Team considered whether the results can reasonably be extrapolated to the 9/11-exposed population. See *Policy and Procedures*, Section IV. A. 3. [NIOSH 2024].

4) Synthesize and interpret findings to categorize the weight of evidence of a causal association between the health condition (i.e., ALS) and 9/11 exposure and advise the Administrator of evaluation findings, as directed by the *Policy and Procedure*s, Sections V. and VI. [NIOSH 2024].

REVIEW OF LITERATURE

Literature Search

To identify potentially relevant studies, the Science Team periodically searched abstracts and titles from peer-reviewed English language literature. In addition to search terms used to identify epidemiologic studies of the 9/11-exposed population, keywords used to uncover potentially informative studies included: 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. Diseases of the nervous system and nervous system disorders were also included to capture mortality studies of 9/11-exposed populations. The databases searched were APA PsycInfo®, CINAHL (EBSCOhost), Embase Classic+Embase, Health & Safety Science Abstracts (ProQuest), NIOSHTIC-2, Ovid MEDLINE®, Scopus, and Toxicology Abstracts (ProQuest).

Periodic follow-up searches were conducted using the WTC Health Program Bibliographic Database, a database of relevant WTC-related research maintained by the Program and updated at least weekly using a standing search of the previously mentioned databases. The last follow-up search was conducted in December 2024. This two-pronged approach ensures all relevant and up-to-date literature is available for the evaluation. The Science Team also reviewed the medical basis provided by each petitioner as well as a recently published comprehensive review of 9/11-related research for information germane to this evaluation [Mears et al. 2022].

The searches yielded 85 unique references for detailed review and quality assessment by the Science Team. Among these, there were **no** studies identified that directedly examine ALS or MND risk separately in the 9/11-exposed population. Although lacking studies explicitly examining ALS risk, the Science Team identified six analytic epidemiologic studies as potentially informative regarding mortality due to nervous systems disorders, including ALS, in the 9/11-exposed population. Thus, studies identified for this evaluation were limited to longitudinal studies examining cause-specific mortality patterns in the 9/11-exposed population using composite outcomes of nervous system disorders that included ALS.

These grouped disorders were defined by Major 15 and Minor 52 of the 119-cause rate file used in the NIOSH Life Table Analysis System (LTAS) [Bertke and Kelly-Reif 2022; Robinson et al. 2006; Schubauer-Berigan et al. 2011].[1] LTAS was used in the external comparisons reported in studies under evaluation. Hereafter, these composite outcomes are referred to as either 'Major 15' or 'Minor 52', corresponding to the major and minor categories originally defined in NIOSH LTAS as shown in Table 1.

Table 1. Major 15 category from the NIOSH Life Table Analysis System (LTAS): minor categories and ICD codes for disorders of the nervous system and sensory organs.[1]

Minor Description	Minor ID	ICD Revision 10 code[2]
Multiple sclerosis	51	G35
Other diseases of the nervous system and sensory organs	52	E75.1, E75.4, G08, G10-G30, G31.0-G31.1, G31.8–G31.9, G36–G43, G45.3, G47.3, G47.8, G50–G70, G71.0–G71.3, G71.9, G72–G92, G93.0–G93.2, G93.4–G93.9, G95–H01, H02.0–H02.5, H02.7–H02.9, H04–H93, H95, R44.1

1. Abstracted from NIOSH LTAS 119-cause map.
2. Amyotrophic lateral sclerosis (ICD10 G12.21) falls within motor neuron diseases (ICD10 G12.2).

Abbreviations: ICD 10, International Classification of Diseases, 10th Revision.

Identified High-Quality Studies

Six studies were identified as high-quality studies (Table 2) according to an assessment of validity indicators, as defined per NIOSH *Policy and Procedures* [NIOSH 2024]. Among these six, no study directly examined ALS risk in the 9/11-exposed population. Instead, all six studies examined a 9/11-exposed population by comparing the number of deaths within a group of causes including ALS with expected deaths in that group that were calculated from rates in a reference population (e.g., the U.S. or New York State populations). This is sometimes referred to as an 'external' analysis. One study also examined the exposure-response relationship between a composite outcome (i.e., Minor 52) and categories of self-reported 9/11 exposure. This is sometimes referred to as an 'internal' analysis [Jordan et al. 2018]. Overlapping information between selected studies of the same targeted group is unavoidable.

[1] NIOSH LTAS is computer software commonly used to conduct comparisons of cause-specific incidence and mortality rates by age, sex, race, calendar time, and duration or level of exposure. LTAS software was used in the external comparisons reported in studies under evaluation. LTAS support was discontinued in 2022, but its functionality was retained in software available on another platform. See Bertke SJ, Kelly-Reif K. Introducing LTASR, a new R package based on the NIOSH Life Table Analysis System. Occup Environ Med. 2022 Sep 20:oemed-2022-108462. doi: 10.1136/oemed-2022-108462. Epub ahead of print. PMID: 36126975; PMCID: PMC10041408.

For example, there are firefighters and rescue and recovery (rescue/recovery) workers included in responder studies who were also enrolled in the WTC Health Registry. The studies reviewed are presented in Table 2 and described below in descending chronologic order.

Table 2. Identified high-quality studies for evaluation.[1]

Author	Follow-up	Outcome[2]	Population	Person-years	Characteristics
Singh et al. (2023)	2001–2016	Mortality (Major 15 and Minor 52), records-based	FDNY	163,583	19,599 male firefighters (10,786 FDNY) followed through 2016; median age on 9/11: 40.4 years FDNY, 43.9 years non-FDNY; SMRs with U.S. population rates referent.
Li et al. (2023)	2002–2016	Mortality (Major 15), records-based	FDNY, GRC, WTCHR	697,943	60,631 rescue/recovery workers followed through 2016; 15.9% female; median age on 9/11: 39.0 years; SMRs with U.S. population rates referent.
Colbeth et al. (2020, 2023)	2001–2017	Mortality (Major 15), records-based	FDNY	248,665	15,431 responders; 3.2% female; median age on 9/11: 39.9 years; 87.2% non-Hispanic White; 3.5% deceased; SMRs with U.S. population rates referent.
Jordan et al. (2018)	2003–2014	Mortality (Major 15 and Minor 52), records-based	WTCHR Rescue & Recovery	308,340	29,280 rescue/recovery registrants; 21.9% female; 70.9% non-Hispanic White; 3.0% deceased; SMRs with New York City and U.S. population rates referent.
			WTCHR Community Members	416,448	39,643 community member registrants; 53.3% female; 56.8% non-Hispanic White; 4.3% deceased; SMRs with New York City and U.S. population rates referent. Cox proportional regression for exposure-response across ordinal categories of exposure intensity (low, intermediate, and high exposure).
Stein et al. (2016)	2002-2011	Mortality (Major 15), records-based	GRC	164,563	28,918 general responders; 14.2% female; 63.3% non-Hispanic White; 1.1% deceased; SMRs and PMRs with U.S. population rates and deaths referent.
Jordan et al. (2011)	2003–2009	Mortality (Major 15), records-based	WTCHR Rescue & Recovery	74,697	13,337 rescue/recovery registrants; 24% female; 57% non-Hispanic White; 1.1% deceased; SMRs with New York City rates referent.
			WTCHR Community Members	161,519	28,593 community member registrants; 59% female; 50% non-Hispanic White; 2.2% deceased; SMRs with New York City rates referent.

1. Studies within the identified peer-reviewed, published, epidemiologic studies of the health condition of interest in the 9/11-exposed population that the Science Team has determined are informative regarding the causal association between 9/11 exposure and the health condition of interest and of appropriate study quality based on an assessment of validity indicators to merit further evaluation [NIOSH 2024].
2. As defined in the NIOSH LTAS 119-cause map (*See* Table 1).

Abbreviations: FDNY, Fire Department of the City of New York; EMS, emergency medical services; GRC, General Responders Cohort; PMR, proportional mortality ratio; SMR, standardized mortality ratio; WTCHR, World Trade Center Health Registry

Singh et al. [2023] examined 10,786 male WTC-exposed FDNY firefighters and 8,813 male non-WTC-exposed firefighters from other urban fire departments who were employed on 9/11. The firefighters were followed beginning on September 11, 2001, and continuing through 2016, resulting in 163,583 person-years. Death information was obtained from the National Death Index (NDI) managed by the Centers for Disease Control and Prevention (CDC). Standardized mortality ratios (SMRs) by firefighter cohort were estimated using U.S. national mortality rates, with Minor 52 as the outcome of interest. The FDNY cohort was mostly non-Hispanic White (93.8%) and never smokers at enrollment (66.4%). Among FDNY firefighters, nearly all (99.8%) had at least one WTC Health Program visit during the study period, with a median of 10 visits per person. There were ≤5 deaths listing other diseases of the nervous system (Minor 52) as the underlying cause. For FDNY firefighters, the SMR was 0.17 (95% CI: 0.03, 0.49), compared with 0.63 (95% CI: 0.35, 1.05) among the non-WTC-exposed non-FDNY firefighters (n = 14 deaths). Methods used were appropriate for the available data. Important limitations included the lack of ALS-specific analyses. Evidence suggests that the sensitivity of death certificates for ascertaining ALS may be relatively high (85%); therefore, using death certificates for case information may be a reasonable approach for ALS-specific analyses moving forward [Stickler et al. 2012].

Li et al. [2023] examined mortality among 60,631 rescue/recovery workers from FDNY (n = 15,887), General Response Cohort (GRC; n = 25,657), and WTC Health Registry enrollees (n = 19,087). The pooled cohort was restricted to workers who were 18 years or older on 9/11 and had complete information on race and ethnicity. To reduce the potential for selection bias, the study also excluded persons enrolled after 2010 or had died or reached their 85th birthday during the first year of enrollment. To avoid duplication of subjects, pooling began with FDNY members first, followed by GRC then WTC Health Registry members. Follow-up was between 2002–2016 resulting in 697,943 person-years. Vital status and the underlying cause of death were ascertained via linkage with NDI. Major 15 was the outcome of interest. The cohort was mostly male (84.2%), non-Hispanic White (71.3%), and never smokers at enrollment (59.5%). There were 30 deaths observed listing a Major 15 code as the underlying

cause. Within this category, the number of deaths was significantly less than expected when using U.S. (SMR = 0.25; 95% CI: 0.17, 0.36) or New York State rates (SMR = 0.39; 95% CI: 0.26, 0.55). Study strengths included large sample size and lengthy follow-up. Methods used were appropriate for the available data. An important limitation was the lack of ALS-specific analyses.

Colbeth et al. [2020, 2023] examined mortality patterns in a longitudinal study of 15,431 FDNY responders (i.e., firefighters and emergency medical service providers) who worked at the WTC site between the morning of September 11, 2001, and July 25, 2002, were actively employed by FDNY for at least 18 months, and were followed through 2017 (248,665 person-years). The underlying cause of death was identified via linkage to NDI. The SMR and its 95% CI were calculated for Major 15 outcomes combined, controlling for age, sex, race, and calendar period using U.S. general population rates as referent. The number of deaths in the Major 15 category was significantly below expectation (SMR = 0.21; 95% CI: 0.10, 0.40; $n = 9$) suggesting a strong healthy worker effect. The large study of exposed firefighters and relatively long follow-up (16 years) are notable study strengths. There are also important limitations, such as using a composite outcome that is a poor proxy for ALS or MND risk, conducting comparisons with a reference group that demonstrated the potential for strong selection bias, and the absence of an exposure-response investigation within the group of interest.

Jordan et al. [2018] extended follow-up of the previous longitudinal mortality study [Jordan et al. 2011], adding five years through 2014. The study population comprised WTC Health Registry 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). The latter group comprised lower Manhattan area residents, area workers, school students and staff, and passers-by as well as commuters through lower Manhattan on September 11, 2001. In all analyses, rescue/recovery participants were analyzed separately from community members. Mortality risk for Major 15 was assessed by SMRs using New York City rates as referent. The exposure-response association was examined using Minor 52 (i.e., Major 15, excluding multiple sclerosis). In that analysis, the potential for exposure to 9/11 agents

was categorized as high, intermediate, or low (Table 3) and the exposure-response was investigated among community members, but not rescue/recovery workers, using proportional hazards regression with the low exposure category referent. Model specifications were not provided. The model was described as 'unadjusted'; therefore, it was presumed to control only time on study as the timescale. Other factors (e.g., age, sex, race, heritable factors, and smoking) were not considered.

Table 3. Exposure level definitions for the 9/11-exposed population of community members and rescue/recovery workers. Adapted from Jordan et al. [2018].

Category	Community members	Rescue/recovery workers
Low	Reported no injuries related to 9/11 and: for area residents, also evacuated home, or for area students/school staff, also were not present at school on 9/11	Began work after 9/17/2001, did not work on pile, worked <30 days, and were not present south of Chambers Street between the first plane impact and noon on 9/11.
Intermediate	Exposure level fell between high and low	Exposure level fell between high and low
High	Reported ≥ two injuries related to 9/11 and: for area residents, also did not evacuate home, or for area students/school staff, also were present at school on 9/11	Worked in Manhattan south of Chambers Street between the time of the first plane impact and noon on 9/11 (encompassing the WTC towers' collapse) and (a) worked on the dust and debris pile on 9/11 or (b) worked for >90 days starting before 9/18/2001.

For Major 15 external analyses, there was no evidence of excess mortality among rescue/recovery workers (SMR = 0.94; 95% CI: 0.53, 1.55; n = 15 deaths). In contrast, the number of Major 15 deaths was significantly greater than expected among community members (SMR = 1.84; 95% CI: 1.38, 2.41; n = 54 deaths), which was a marked increase in the SMR compared to the initial 2011 study (SMR = 1.09; 95% CI: 0.58, 1.86; n = 13 deaths), when using the New York City population as the reference population [Jordan et al. 2011]. Similar patterns were observed when excluding multiple sclerosis deaths, with a slight increase in the SMR for community members (SMR = 1.96; 95% CI: 1.47, 2.57; n = 52 deaths). Within this Minor 52 category, there were 24 deaths among community members that were attributed to Alzheimer's disease, nine MND deaths, seven Parkinson's disease deaths, and 12 deaths that were unspecified. Based on exposure-response modeling using 51 of these deaths (the reason for excluding one death was not specified), the excess was not exposure-related (Table 4); however, results were presented

from unadjusted models, which may not adequately control for important risk factors. The authors acknowledged that most Minor 52 deaths were attributable to Alzheimer's disease at advanced ages; however, they also stated that there were nine deaths from unspecified MND. They did not report risk estimates restricted to MNDs but stated that existing information was insufficient to attribute MND risk to 9/11 exposure. It was also notable that SMRs for Major 15 were markedly decreased when using U.S. population rates as referent, indicating lower baseline death rates in the New York City population compared to national rates. For example, the excess mortality in community members observed using New York City rates was no longer observed when using U.S. population rates (Major 15 SMR = 0.47; 95% CI: 0.35, 0.61), indicating a strong vulnerability to bias from a reference group that differs from the study group (i.e., a selection bias). Investigating subgroups of the 9/11-exposed population is a notable strength of this study. Other strengths include a large study size and long follow-up. Another strength is the investigation of exposure-response, although the models appear crude. There were notable limitations, such as using a composite outcome and conducting comparisons with reference groups that demonstrated a potential for strong selection bias.

Table 4. Exposure-response among community members[1] for other diseases of the nervous system and sensory organs (*see* Minor 52, Table 1).[2]Adapted from Jordan et al. [2018].

Exposure Intensity	Deaths	Hazard ratio (CI)
Low	20	Reference
Intermediate	28	1.03 (0.58, 1.83)
High	3	0.56 (0.17, 1.91)

1. WTC Health Registry enrollees of lower Manhattan area residents, area workers, school students and staff, and passers-by as well as commuters through lower Manhattan on September 11, 2001.
2. As defined in the NIOSH LTAS 119-cause map.

Abbreviations: CI, confidence interval.

Stein et al. [2016] examined mortality in rescue and recovery workers (*n* = 28,918) in the general responder cohort who were followed between 2002–2011 (164,563 person-years). The cohort comprised rescue, recovery, clean-up, and related support workers enrolled from all WTC General Responder Clinical Centers of Excellence (i.e., Icahn School of Medicine at Mount Sinai; New York University Grossman School of Medicine; Northwell Health; State University of New York, Stony Brook; and Rutgers, State University of New Jersey). The underlying cause of death was identified via linkage to

NDI. The SMR for Major 15 was calculated, controlling for age, sex, race, and calendar period. Proportionate mortality ratios (PMRs) were also calculated with similar standardization. There were significantly fewer deaths than expected based on reference rates (Major 15 SMR = 0.18; 95% CI: 0.04, 0.53; *n* = 3 deaths). The PMR for Major 15 also provided no evidence of increased risk (PMR = 0.41; 95% CI: 0.08, 1.21). This is the only study of mortality in the GRC, and it covered a relatively short period of observation. Continued follow-up of cohort members may provide additional information. Other notable limitations include the use of a composite outcome with few observed deaths and the use of an external reference group demonstrating strong selection bias. Another limitation is the use of a PMR as a risk measure, which given the absence of denominator data for the population at risk, relies heavily on strong assumptions that may not be valid for this population [Miettinen and Wang 1981].

Jordan et al. [2011] conducted the first study of mortality among members of the WTC Health Registry (2003–2009). Registrants comprised rescue and recovery workers (*n* = 13,337; 74,967 person-years), and community members (*n* = 28,593; 161,519 person-years). Contrary to Jordan et al. [2018], the study sample was restricted to participants residing in New York City at the time of Registry enrollment (*n* = 41,930). The underlying cause of death was obtained from New York City vital records for decedents residing in the city at the time of death, and linkage to NDI through 2007 for deaths occurring outside of the city. The cause of death among decedents outside New York City after 2007 (estimated at 24 deaths) was not ascertained. All persons not linked to a death certificate were assumed alive at study end. As in other studies, Major 15 was the outcome of interest. SMRs were calculated with New York City rates referent adjusted for age, race, sex, and calendar period. There was no evidence of excess mortality from Major 15 outcomes in the total study population (SMR = 0.93; 95% CI: 0.51, 1.55; *n* = 14 deaths) or when restricting to rescue/recovery workers (SMR = 0.31; 95% CI: 0.01, 1.75; *n* = 1 death) or community members (SMR = 1.09; 95% CI: 0.58, 1.86; *n* = 13 deaths). In addition to the limitations previously described for the update [Jordan et al. 2018], this study had limited statistical power due to small numbers of deaths and few years of observation.

An important limitation shared by all these studies is the absence of risk estimates pertaining to ALS or MND exclusive of other nervous system disorders. The large group of health conditions examined comprised a wide array of outcomes with varying etiology. Within this group, the expected contribution to mortality from MNDs including ALS (~1.6 deaths per 100,000) is small relative to more common outcomes, such as Parkinson's disease (~4.9 deaths per 100,000) and Alzheimer's disease (~38.5 deaths per 100,000) [Feigin et al. 2021]. Although risk factors may be shared by some outcomes, causes can vary widely among them. Thus, the quality of causal inference regarding ALS based on the evidence of an association between the full group of neurologic diseases is poor. Furthermore, the study populations were all relatively young (<5% deceased); therefore, follow-up may lack enough ALS-related deaths to observe an exposure effect, given deaths are typically diagnosed at older ages. Finally, all studies conducted comparisons using external reference groups that indicated strong selection bias in a downward direction. For example, estimates of the all-cause mortality risk in the 9/11-exposed populations were well below that in the reference groups in all studies, and strong differences in risk measures were observed by choice of reference group (e.g., differences in New York City and U.S. rates used by Jordan et al. 2018).

In summary, the identified studies examining mortality among the 9/11-exposed population provided no evidence of increased ALS risk among responders or rescue and recovery workers. The lack of specific information on ALS risk was common to all studies evaluated, resulting in reliance on composite outcomes. Thus, uncertainties associated with this approach are a prominent limitation in evaluating a potential causal association between ALS and 9/11 exposure. There was evidence suggesting greater than expected mortality from disorders of the nervous system and sensory organs in the most recent study of community members enrolled in the WTC Health Registry [Jordan et al. 2018]; however, the excess largely depended on the choice of referent rates used in comparisons. There was no evidence of an exposure-response in internal comparisons. Finally, among the Minor 52 deaths used in external comparisons, only nine (17%) were attributed to unspecified MNDs that may include ALS.

Review of Medical Basis Information Provided by Petitioners

The validity of the four petitions was previously established based on a review of the submitted information supporting a medical basis, as per 42 C.F.R. § 88.16(a)(1)(iv) and the NIOSH *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions* [NIOSH 2014]. The Science Team reviewed this submitted information for peer-reviewed evidence that may support the current evaluation in accordance with the *Policy and Procedures* [NIOSH 2024]. The intent of the review is to 1) uncover any high-quality studies that may have been missed in the literature review, and 2) uncover any information that might additionally inform on biological plausibility of the casual relationship. For these reasons, the Science Team focuses on peer-reviewed literature. For brevity, the Science Team describes the submitted literature based on its contribution to the evaluation; therefore, all studies reviewed might not be described in this section.

A total of 10 published studies were submitted as part of the medical basis in support of Petitions 031, 036, 039, and 053 and reviewed by the Science Team. There were five peer-reviewed, published epidemiologic studies submitted with Petition 031 [Beard and Kamel 2015; Colbeth et al. 2019; Genuis and Kelln 2015; Schulte et al. 1996; Vanacore et al. 2010]. Two of these studies were literature reviews providing evidence summaries of potential occupational and environmental risk factors for ALS, including 9/11 agents [Beard and Kamel 2015; Genuis and Kelln 2015]. The medical basis for Petitions 036 and 039 addressed findings from analysis of a large cohort study prospectively examining the association between MND mortality and self-report of exposures [Weisskopf et al. 2009]; this study was an update to a previous examination [Weisskopf et al. 2005], both studies are discussed below for completeness. The medical basis for Petition 053 included four studies [Ash et al. 2019; Gunnarsson and Bodin 2019; Keir et al. 2020; Peters et al. 2021], of which one was a review article discussing links between occupational exposures and neurodegenerative diseases [Gunnarsson and Bodin 2019]. The remaining three articles provided mechanistic [Ash et al. 2019], epidemiologic [Peters et al. 2021], and exposure science [Keir et al. 2020] information that collectively provided evidence on the plausibility of a

causal association between 9/11 agents, such as metals and polycyclic aromatic hydrocarbons (PAHs), and ALS. Thus, these10 studies provided as medical basis for the four petitions supplied useful information on potential risk factors for neurologic disorders, including ALS, which potentially informs consideration of the plausibility and uncertainty of a causal association between 9/11 exposure and ALS. However, these studies did not examine the association between 9/11 exposure and ALS in 9/11-exposed populations; therefore, they were not evaluated further. These studies are briefly described in more detail below.

Peters et al. [2021] conducted a nested case-control study within the prospective European Prospective Investigation into Cancer and Nutrition cohort (EPIC) to examine the association between metal levels in blood and MND deaths (ICD 10 G12.2). MND deaths (*n* = 107, 65% female) were ascertained from death certificates as the underlying cause and matched to 319 controls on age, sex, and participating study center. Odds ratios (ORs) were calculated using conditional logistic regression comparing tertiles of blood metal (i.e., arsenic, cadmium, copper, lead, manganese, mercury, selenium, and zinc) concentrations taken at least one year prior to death. Potential confounders, such as cigarette smoking, body mass index, physical activity, alcohol consumption, and education were considered; however, none were found to significantly affect estimates, and all were excluded from final models. The median time between blood collection and MND death was 8 years (range 1–15 years). The study reported evidence suggesting cadmium and lead may be associated with an increased MND risk, although the exposure-response trend was not statistically significant for either agent. An important study limitation was the lack of information on disease onset; therefore, given a potential long latency between onset and death it was possible for MND to precede the exposure indicated by blood sample collection.

Keir et al. [2020] examined a relatively small sample of Ottawa firefighters (*n* = 28) selected from four fire stations to quantify occupational exposures to PAHs, antimony, cadmium, and lead. The study reported evidence of firefighter exposures to these combustion by-products during on-shift fire suppression. Although demonstrating occupational exposures to PAHs, antimony, cadmium, and lead

through dermal and inhalation pathways, Keir et al. [2020] did not provide any information on associated health effects, including ALS; therefore, this study was generally uninformative for this evaluation.

Ash et al. [2019] conducted a toxicological study involving a series of *in vitro* and *in vivo* animal experiments to examine possible molecular mechanisms linking heavy metal neurotoxicant exposures to ALS. The study provided evidence of a direct mechanistic link between heavy metals and molecular changes in TDP-43, the primary pathological insoluble protein accumulating in many ALS cases. This information was considered preliminary, although it supported the biological plausibility of a causal relationship between heavy metals and ALS.

Gunnarsson and Bodin [2019] conducted a systematic review and meta-analysis of publications examining associations between occupational exposures to electromagnetic fields (EMFs), metals, and pesticides and neurodegenerative diseases, including ALS. The authors considered relative effect measures, (e.g., ORs, HRs, and RRs) to be equivalent. The meta-relative risk (mRR) was estimated in inverse-variance weighted random-effects models. Methods used to estimate the between-study variance (τ^2) were not specified; however, heterogeneity was measured with the I^2 statistic. Among 9/11 agents, modest excess ALS risk was indicated for pesticides and metals. For pesticides, the mRR from aggregating six studies (1991–2010) was 1.35 (95% CI: 1.012, 1.59; I^2 = 57.8%). For metals, the mRR was 1.45 (95% CI: 1.07, 1.96; I^2 = 61.1%) from aggregating six studies (1992–2017). Among limitations, few studies were available for aggregating, significant between-study variance was evident in all models, the definitions of exposure and ALS varied between studies, and publication bias was indicated. Furthermore, given few studies for aggregating, the choice of τ^2 estimator, as well as the approach for calculating confidence intervals are important considerations. For example, there is evidence of poor coverage when between-study variance is large or when there are few studies available [Inthout et al. 2014; Veroniki et al. 2019].

Colbeth et al. [2019] examined FDNY firefighters and emergency medical service workers (n = 9,239) in a cross-sectional study of self-reported peripheral neuropathy symptoms. The researchers

stratified the study population into two groups comprising those with conditions known to be linked to peripheral neuropathy, such as diabetes, cancer, and autoimmune disease (indicated group) and those without these conditions (non-indicated group). The level of WTC exposure was categorized (high, moderate, and low) by time of arrival at the disaster site. Comparisons were made, restricted to the non-indicated group (n = 7,180), in multivariable regression using the low exposure group and the National Health and Nutrition Examination Survey (NHANES) 2003–2004 non-diabetic cohort as reference groups. Models controlled for work assignment, sex, race, smoking history, alcohol abuse, and age at exam. The study found that the highest level of WTC-exposure was significantly associated with increased positive indications of peripheral neuropathy. Trend tests between WTC exposure level and paresthesias of the arms and all extremities, respectively, were significant (p for trend = 0.036; 0.006). The authors concluded that their study suggested symptoms of peripheral neuropathy and paresthesias are common in the study population and may be causally associated with WTC-exposure intensity. The authors made no connection between their findings and ALS risk.

Although this study suggests an exposure-response association between 9/11 exposure and paresthesias in the FDNY 9/11-exposed population, it does not provide evidence of a causal association between ALS and 9/11 exposure. Sensory nerve conduction is typically normal in patients with ALS, which is key to differentiation from demyelinating neuropathies [Kiernan et al. 2011]. Symptoms of peripheral neuropathy and paresthesias appear rarely (1–10%) among ALS patients [Stetkarova and Ehler 2021; Weis et al. 2011]; therefore, there is no clear evidence of a shared etiology and having these conditions is not predictive of ALS risk.

Beard and Kamel [2015] reviewed the evidence on military service-related ALS and MNDs (ALS/MND) from peer-reviewed epidemiologic studies published through 2013. After identifying nearly 1,000 potential articles in a literature search, synthesis was limited to 30 studies meeting inclusion criteria. In general, findings were inconsistent, although loosely supportive of an association between military service and ALS/MND risk. For example, among six studies reporting associations between

military service overall and ALS/MND risk, three reported positive associations, two reported negative associations, and one study reported no association. Similar findings were observed among the remaining studies. The authors attributed the inconsistency to several study limitations, such as control selection, statistical power, and incomplete and varied information on exposure and outcome. The authors found the evidence to be too limited to draw firm conclusions regarding associations between military service and ALS etiology or survival or point to any specific military exposures as a risk factor for ALS/MND. This study provided no evidence of a causal association between ALS and 9/11 exposure. The military exposures reviewed (e.g., military status, deployment to the Gulf War, prisoner of war) were not related to WTC-exposure.

Genuis and Kelln [2015] reviewed the literature on bioaccumulation following exposure to toxicants and increased risk of cognitive dysfunction and dementia. The search methods used were poorly described; however, keywords included terms related to chemical exposure and dementia, toxicants, Alzheimer's disease, pollutants and neurodegenerative disease, environmental health sciences and the elderly, neurotoxicity with poisoning, and detoxification. No terms specific to MND or ALS were reported. Several classes of toxicants believed to be associated with neurogenerative diseases are generally discussed, including metals, pesticides, solvents, and air pollutants. The review included a case history of a lead-exposed individual who was later diagnosed with dementia. The review focused on the associations between accrual of toxicants over time and cognitive conditions, offering no discussion on the effects of acute exposures or the potential for exposure-related MND, such as ALS. In general, the review summarizes evidence supporting the hypothesis that exposures and subsequent bioaccumulation of certain toxicants may be a determinant of neurodegenerative diseases, such as Alzheimer's disease; however, it provides no evidence of a causal association between ALS and 9/11 exposure.

Vanacore et al. [2010] used information from death certificates from a large publicly available national database to conduct a registry-based case-control analysis of 14,628 ALS deaths. Controls comprised 58,512 deaths from causes other than ALS that were frequency matched to cases by age,

gender, and broad geographic area. Exposure was defined from death certificate information about the usual occupation and industry over the decedent's lifetime. There was no information on possible modifiable risk factors. The study found increased mortality among firefighters compared to non-firefighters (OR = 1.96; 99% CI: 1.22–3.23; *n* = 45 exposed deaths). However, among fire service occupations, the greatest risk was observed among fire inspection and fire prevention (OR = 2.70; 99% CI: 0.59–12.49; *n* = 5 exposed deaths). Increased risk was also observed among professional athletes but not among occupations with increased physical activity at work. The authors concluded that occupational conditions leading to intermittent hypoxia might be an ALS risk factor in subjects genetically prone to an abnormal response to hypoxia.

Vanacore et al. [2010] did not provide direct evidence of a causal association between ALS and 9/11 exposure. The 9/11 exposed population was not examined. Intermittent hypoxia is not an experience listed among 9/11 agents. Nor has intermittent hypoxia been established as a risk factor for ALS. The study is supported by an earlier finding of increased MND risk among firefighters compared to other occupations [Schulte et al. 1996]. However, this finding has not been replicated in other studies of ALS in occupations [Dickerson et al. 2018; Farrugia Wismayer et al. 2021; Peters et al. 2017]. If ALS risk is related to firefighting exposures generally, then studies of ALS among 9/11-exposed firefighters would potentially need to account for an increased baseline risk to isolate any additional contribution specifically from 9/11 exposure.

The study by Vanacore et al. [2010] has several notable limitations. First, the study lacked information on the population of interest (i.e., denominator data). The control events were deaths due to causes other than ALS. Although useful for cancer surveillance, these studies offer a valid measure of risk only when the rate of control events among the exposed is the same in the exposed and unexposed groups. In the absence of such parallel rates of control events, a serious bias in either direction can occur. This limitation is common among studies lacking denominator data (e.g., PMRs). Second, information on exposure was based solely on the occupation listed on the death certificate. This provides no information

on duration or intensity of exposure. Also, there is a potential for incomplete or erroneous occupational information from death certificates, which may be differential by occupation, leading to bias in either direction [Bidulescu et al. 2007; Olsen et al. 1990; Turner et al. 1987].

Weisskopf et al. [2009] examined MND mortality among persons enrolled in the American Cancer Society's Cancer Prevention Study II (CPS-II). The prospective study included over one million participants followed between 1989–2004, accruing 13.5 million person-years. MND (ICD-9 335.2) was ascertained from the NDI as either the underlying or contributing cause of death. Exposure and other risk factor information was assessed by a baseline questionnaire administered in 1982; no follow-on occurred until seven years later in 1989. Chemical exposures were defined as having ever been regularly exposed to one of 11 hazardous substances, namely: pesticides/herbicides, asbestos, acids/solvents, coal dusts, diesel exhaust, coal tar/pitch/asphalt, dyes, formaldehyde, gasoline exhausts, textile fibers and dust, wood dust, and X-rays. Non-responses were considered unexposed. Participants were also asked to provide the years of exposure for positive responses. Hazard ratios (HRs) were calculated using Cox regression [Cox 1972] adjusting for age, calendar period, sex, smoking, military service, education, alcohol intake, occupation, vitamin E use, and all other chemical classes. The study identified 617 deaths from MND among men and 539 among women. There was evidence of excess MND mortality associated with exposure to formaldehyde (HR = 1.34; 95% CI: 0.93, 1.92), which is listed as a 9/11 agent. This association was strengthened when excluding persons with missing information on the duration of formaldehyde exposure (HR = 2.47; 95% CI: 1.58, 3.86) and there was an exposure-response association across increasing categories of years of exposure ($p = 0.0004$). However, there were only 36 MND deaths among persons with formaldehyde exposure. There was no evidence of an association between MND and any other self-reported exposure.

The CPS-II study population was previously examined by Weisskopf et al. [2005] with follow-up through 2002 (11,994,938 person-years). That study identified 937 deaths with MND listed as either the underlying or contributing cause. Exposure was assessed based on self-reported occupation, which was

determined at baseline as the longest held job. In Cox regression stratified by sex, there was excess ALS mortality among men employed as programmers (HR = 4.55; 95% CI: 1.46, 14.2; *n* = 3 deaths) and laboratory technicians (HR = 1.96; 95% CI: 1.04, 3.66; *n* = 10 deaths). Among women, there was evidence of increased MND mortality among machine assemblers (HR = 2.81; 95% CI: 1.05, 7.53; *n* = 4 deaths) and nurses (HR = 1.40; 95% CI: 0.96, 2.04; *n* = 30 deaths). There was no evidence of increased MND mortality for either sex in other occupations, including electrician, welder, or farmer, each of which has been associated with ALS in previous studies; nor among persons working in construction trades, production, or the services sector, which best aligned with WTC responders and recovery workers.

The large study size and prospective design were notable strengths of the CPS-II study [Weisskopf et al. 2009], which updated a previous study [Weisskopf et al. 2005], also discussed herein. Significant limitations include the reliance on incomplete self-reported exposure information and occupational histories. Another limitation was the use of mortality as an endpoint, which was not specific to ALS. Overall, these two analyses of the CPS-II cohort reported a few significant positive associations between MND mortality and occupations that were based on multiple comparisons of small numbers. There was also evidence of an exposure-response association between MND mortality and self-reported formaldehyde exposure, but not with any other exposure, including exposures to chemicals, solvents, asbestos, and several dusts, also considered 9/11 agents. Findings between men and women within these analyses were largely inconsistent, as were findings in the analyses compared with findings reported in other studies; therefore, alternative explanations cannot be ruled out.

Schulte et al. [1996] conducted a study of occupation and neurodegenerative diseases using death certificate data in a national mortality surveillance database. The study calculated age-standardized PMRs for neurodegenerative disease deaths in 27 states between 1982–1991. PMRs were stratified by sex and race. The outcomes comprised underlying and contributing causes of death from presenile dementia, Alzheimer's disease, Parkinson's disease, and MND. Occupation was used as a proxy for exposure and was determined from death certificates as the usual occupation as listed by next-of-kin at the time of

death. Among occupations associated with MND, significantly increased PMRs were observed for firefighters, teachers, machinists, military personnel, veterinarians, excavation machine operators, janitors, packaging machine operators, technical support, and mail distribution workers. The number of deaths in these occupations was small, ranging between 2–27 across all categories. The PMRs also varied widely by race and sex. Among significant findings, the greatest PMR was observed among black male commodity sales representatives (PMR = 20.51; 95% CI: 2.48, 74.1; *n* = 2). Overall, Schulte et al. [1996] found that neurodegenerative diseases appeared to occur more frequently in certain occupations. It is uncertain whether this variation is attributable to occupational exposures or other causes. This study does not provide evidence of a causal association between ALS and 9/11 exposure. The risk measure was derived from case data only (i.e., a PMR), which relied on strong assumptions that may be invalid given survival differences by occupation [Miettinen and Wang 1981].

Related Research on the 9/11 Population

The literature search also revealed six peer-reviewed, published, epidemiologic studies of 9/11-exposed populations that provided information on exposure-related neurodegenerative diseases [Clouston et al. 2020; Marmor et al. 2017; Marmor et al. 2020; Stecker et al. 2016; Thawani et al. 2019; Wilkenfeld et al. 2016]. However, these studies did **not** examine the association between 9/11 exposure and ALS in 9/11-exposed populations; therefore, they were not further evaluated. They are discussed below for completeness of information.

Four studies examined paresthesias or peripheral neuropathies in 9/11-exposed populations [Marmor et al. 2017; Marmor et al. 2020; Thawani et al. 2019; Wilkenfeld et al. 2016]. Like the previously described study by Colbeth et al. [2019], these studies provide evidence suggesting a potential association between 9/11-exposure and peripheral neuropathy; however, they all lacked information on ALS in the 9/11-exposed population. Another study provided information from a neurologic case-series that included two MND patients [Stecker et al. 2016]. Although descriptive of MND among a unique small group of 9/11-exposed persons, that study did not estimate exposure-related MND or ALS risks.

Previous literature reviews by Daniels et al. [2021] and Clouston et al. [2022a] have suggested a potential association between WTC-dust exposure and cognitive impairment based largely on studies examining patterns of neurodegenerative disease in brain imaging studies. For example, Clouston et al. [2020] found reduced cortical thickness among responders in regions often observed in neurodegenerative diseases. The reduction appeared greatest among those with cognitive impairment compared to unimpaired responders. A follow-up study further examined cerebellar atrophy among the sample of responders, including attempts to differentiate between ALS and common neurodegenerative diseases—such as Alzheimer's disease, frontotemporal dementia, and multiple system atrophy—while excluding other diseases such as Huntington's and Parkinson's diseases [Clouston et al. 2022b]. That study reported an average reduction of cerebellar cortical thickness of 0.17mm in responders with cognitive impairment. However, the reduced cerebellar cortical thickness did not match patterns for known neurodegenerative conditions, including ALS. Therefore, the study could not establish a causal link between 9/11 exposure and ALS in the 9/11-exposed population.

SYNTHESIS OF EVIDENCE FOR CATEGORIZATION

The Science Team evaluation of evidence is a qualitative assessment of risk estimates and associated uncertainty in the identified high-quality studies. A "qualitative assessment" refers to descriptive methods used to categorize the likelihood of an adverse effect under specified conditions of exposure, as opposed to a "quantitative assessment" which provides numerical estimates of the exposure-related risk [NIOSH 2020]. The weight of the evaluated scientific evidence is assigned to one of the following five categories of likelihood of causal association between 9/11 exposure and the health condition of interest: (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. This information is used by the Administrator to inform the decision on whether there is *sufficient evidence of causal association* between 9/11 exposures and the health condition to propose adding the health condition to the List, according to

the *Policy and Procedures* [NIOSH 2024]. The Administrator may determine that there is sufficient evidence of causal association between 9/11 exposures and the health condition based on the evaluation of scientific evidence supporting that the 9/11 exposures are substantially likely to be causally associated with the health condition; which may be established through the scientific evaluation of evidence in high-quality, peer-reviewed, published, epidemiologic studies of the health condition in 9/11-exposed populations or, in certain instances, following a discretionary secondary evaluation of additional highly-relevant scientific information regarding non-9/11 exposures.[2]

In accordance with the *Policy and Procedures*, the Science Team utilizes several aspects of association ("Bradford Hill Criteria") to describe and evaluate the evidence across the high-quality epidemiologic studies identified in the literature search [Hill 1965]. The criteria of strength of association, consistency, temporality, and biological gradient are directly applicable to the evaluation of the available epidemiologic evidence from identified studies, and each criterion is addressed in the synthesis of the specific evidence from these studies. As such, these criteria are given the most weight. In contrast, 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; therefore, it is not further discussed.

Biological plausibility, coherence, and analogy are related criteria that require reasonable knowledge of the biology of the health condition of interest, including facts about disease etiology and any established direct or analogous causal relationships [NIOSH 2024]. Although previous biological evidence may have motivated the high-quality epidemiologic studies identified for evaluation, these studies themselves may not provide sufficient information to evaluate biological plausibility, coherence, and analogy criteria. To address any concerns regarding incomplete information in the identified studies,

[2] If the Science Team's evaluation characterizes the evidence available from high-quality, peer-reviewed, published epidemiologic studies of the health condition in 9/11-exposed populations as demonstrating a high, but not substantial, likelihood of causal association between 9/11 exposures and the health condition (Category II), the Administrator may, at their discretion, direct the Science Team to evaluate additional highly-relevant scientific information regarding exposures to known 9/11 agents in non-9/11 exposure scenarios. Based upon its evaluation of the available highly-relevant scientific information about 9/11 agents in non-9/11 exposure scenarios, together with its findings from the evaluation of high-quality, peer-reviewed, published, epidemiologic studies of the health condition in 9/11-exposed populations, the Science Team will determine whether the totality of the evidence and information supports characterizing the support for causal association as either Category I (substantial likelihood) or Category II (high likelihood).

the Science Team exercises scientific and medical judgment to refer to additional information from biologic, toxicologic, and epidemiologic research, usually from references cited in the identified studies or medical basis, or from a limited review of the literature to assess biological plausibility, coherence, and analogy. This approach permits a more complete analysis of these criteria, offsetting the likelihood of reaching a default decision that there is inadequate information to evaluate the likelihood of a causal association.

The Science Team considers study limitations that may affect the validity of findings from the identified high-quality studies. These limitations may include the potential for residual confounding of effect measures from incomplete information on risk factors and major sources of selection or information biases, such as healthy worker effects, adequacy of the control group, ascertainment errors, exposure misclassification, and conflicts of interest, among others. Study limitations are integral to assessing aspects of association, such as strength of association, consistency, temporality, and biological gradient. For example, large effects (strength of association) are generally less vulnerable to study biases. Likewise, cross-sectional studies, by design, generally offer little information on temporality compared with longitudinal studies.

The Science Team considers the representativeness of the body of evidence to assess whether the high-quality studies, taken together, represent both WTC responder and survivor populations or, if only a subgroup of 9/11-exposed population is represented. If the 9/11 population is only partially represented, then the Science Team considers whether the results can reasonably be extrapolated to the full 9/11-exposed population. Representativeness is linked to consistency such that similar findings observed in multiple populations are generally weighted more heavily than findings observed in one population.

Due to the interrelatedness of certain aspects of association (e.g., "Bradford Hill Criteria," such as strength of association, consistency, temporality, and biological gradient) and consideration of study limitations and representativeness, those aspects are grouped together for evaluation. The evaluation and synthesis of the evidence is provided in two parts: 1) consideration of the strength of association,

consistency, temporality, and biological gradient in the identified high-quality studies, including assessment of study limitations and representativeness of study populations; and 2) consideration of biological plausibility, coherence, and analogy that combines information from the identified high-quality studies with additional information, as necessary. A summary of the synthesis is provided in Table 5 at the end of this section.

Consideration of the Strength of Association, Consistency, Temporality, and Biological Gradient, including an Assessment of Limitations and Representativeness

As discussed above, six studies were identified as high-quality studies for evaluation [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] (Table 2). The Science Team determined that the six studies demonstrated representation of both responder and survivor groups.

With respect to strength of association, Jordan et al. [2018], found twofold greater than expected deaths from diseases of the nervous system and sensory organs (Minor 52) among community WTC Health Registry members when compared with the New York City population referent. Jordan et al. [2018] attributed the greater than expected excess Minor 52 deaths to Alzheimer's disease, not ALS. With respect to consistency of findings between studies, similar evidence of association was not found in any other study or among other 9/11-exposed populations. The lack of reproducible results is an important consideration in assessing the likelihood of a causal association.

Regarding temporality, all studies were longitudinal cohort designs with the at-risk period beginning on 9/11; therefore, 9/11 exposure was presumed to precede ALS onset, meeting minimal temporal requirements. However, none of the identified high-quality studies specifically examined temporal variations in risk. Moreover, given the lack of knowledge regarding the biologically relevant period between exposure and onset, preexisting conditions or prior exposures cannot be ruled out as possible sources of bias.

None of the evaluated studies provided evidence of a biological gradient. Investigating an exposure-response association was limited to one study of WTCHR community members that found no evidence of increasing risk with 9/11 exposure. [Jordan et al. 2018]. Future research that examines exposure-response associations between measures or indices of 9/11-exposure and ALS **is needed** to support causal inference.

Study limitations were considered in the evaluation of strength of association, consistency, temporality, and biological gradient. In addition to limited information on strength of association, consistency, temporality, and biological gradient described in this section, other important limitations in the design and available information of each identified high-quality study are found in section "Identified High-Quality Studies". All six of the identified high-quality studies share two notable limitations that greatly diminished their usefulness for providing evidence of a causal association:

a) None of these six studies directly examined ALS risk in 9/11-exposed populations. The synthesis of the evidence from the identified studies was restricted to study designs using large, heterogenous groups of nervous system disorders in which the contribution from ALS is not clear. Future research that examines ALS risk separately and specifically in the 9/11 population **is needed** to elucidate a causal association between 9/11 exposure and ALS.

b) Findings stemmed primarily from external comparisons of observed deaths with expected deaths calculated from rates in a reference population (e.g., U.S. or New York State populations). Statistical comparisons between the 9/11-exposed population and an external reference group, such as the New York State population are limited by a strong potential for selection bias given known differences in populations, as evidenced by less than expected deaths among the 9/11 population in all studies examined. For example, some persons participating in identified studies may also be enrolled in the WTC Health Program; therefore, these persons may have important differences in health screening compared with the general population. Furthermore, this bias may be greater in working populations, such as WTC responders and rescue/recovery workers due to

health qualifications for employment and improved lifestyle. Study designs aimed to reduce the potential for bias from differences in comparisons groups **is needed** to improve internal validity of the research findings.

Consideration of Biological Plausibility, Coherence, and Analogy

As previously discussed, the etiology of ALS is largely unknown and information on environmental factors associated with ALS is equivocal [Newell et al. 2022]. Thus, it is difficult to evaluate with certainty the reasonableness (plausibility) of a proposed agent-disease association or the coherence of the association with known disease etiology. Therefore, the Science Team evaluation of biological plausibility, coherence, and analogy looked beyond studies within the 9/11 exposed population to determine whether there is reasonable evidentiary support of the proposed causal association between ALS and 9/11 agents. For this evaluation, the Science Team searched the literature for existing information that either supported or refuted a causal association between ALS and 9/11 agents. To identify literature for this purpose, the Science Team examined the bibliographies of the identified high-quality studies, the medical basis provided by the petitioners, as well as recently published information from peer-reviewed systematic reviews and meta-analyses found in keyword searches of the Scopus database.

This evaluation of literature identified studies of associations between exposures to metals (e.g., lead and cadmium), silica, and formaldehyde, all of which are 9/11 agents, as potentially providing evidence of biologic plausibility for ALS associated with 9/11 exposures. While the identified agents (metals, silica, and formaldehyde) should not be construed as a comprehensive list of 9/11 agents potentially associated with ALS, they may represent the most likely candidates for an association between 9/11 exposures and ALS based on current literature.

Following the Science Team's evaluation of the information briefly described below, the Science Team concluded that evidence was available identifying at least three 9/11 agents (i.e., metals, such as lead and cadmium, silica, and formaldehyde) as possible ALS risk factors. Ultimately, none of the

evidence was sufficient to conclude that a causal association existed between these 9/11 agents and ALS; however, the Science Team did not find compelling evidence refuting a causal association between these 9/11 agents and ALS.

Metals

Given their ubiquitous nature and known neurotoxicity, there have been several studies examining the relationship between ALS and metals [Belbasis et al. 2016; Callaghan et al. 2011; Dickerson et al. 2020; Meng et al. 2020; Sutedja et al. 2009; Wang et al. 2014]. Findings have been largely inconsistent, due in part to methodological limitations in study design and exposure assessment. For example, a recent meta-analysis found that just three of 50 studies of metals and ALS had sufficient methodological and exposure assessment quality for aggregation [Sutedja et al. 2009]. Among metals, the evidence appears strongest for chronic occupational exposures to lead (a known motor neuron toxin and listed 9/11 agent), where multiple epidemiologic studies have found an association with ALS [Belbasis et al. 2016; Farace et al. 2020; Meng et al. 2020; Wang et al. 2014]. Data from a recent meta-analysis of nine case-control studies was used to estimate that about 5% of all sporadic ALS cases may be attributable to occupational exposure to lead. Although lead exposures from the 9/11 attacks are likely to be much lower than those experienced in most occupational settings involving lead products, the exposure-response characteristics, especially at low doses, have not been elucidated. Evidence is emerging that supports an association between low-level environmental lead exposures and ALS [Andrew et al. 2022; Belbasis et al. 2016; Wang et al. 2014]. Causal mechanisms remain largely unknown; however, recent findings from molecular research suggest that lead-induced promotion of TDP-43 protein aggregation and mislocalization may have an important role in lead-mediated development of ALS [Farace et al. 2020].

There is much less information on other 9/11 metals, and findings among studies have been inconsistent. Among candidate metals, there is a suggested link between cadmium, a known neurotoxicant, and ALS [Oggiano et al. 2021; Peters et al. 2021]. For example, a recent case-control

study, nested within a large prospective cohort, examined MND mortality from metals using blood level measurements collected at baseline years prior to diagnosis [Peters et al. 2021]. The median time between blood collection and MND death was 8 years. Comparing the highest with the lowest tertile blood levels, MND mortality appeared to be associated with concentrations of cadmium (OR = 2.04; 95% CI: 1.08–3.87; *p* for trend = 0.122) and lead (OR = 1.89; 95% CI: 0.97–3.67; *p* for trend 0.153), but not arsenic, copper, manganese, mercury, selenium, or zinc. Other studies have not found similar evidence of a positive association between cadmium and ALS. A recent review of the evidence concluded that current information is insufficient to show direct involvement of cadmium in ALS or to rule it out as a risk factor [Oggiano et al. 2021].

Silica

Silica is listed as a 9/11 agent [NIOSH 2018]. Crystalline silica mass concentrations found in bulk samples of undisturbed settled WTC debris ranged from not detected to 18%, with a median of 3.2%, [Wallingford and Snyder 2001]. Personal and area monitoring data collected during cleanup and recovery of the WTC site has shown elevated levels of respirable dust and silica [Pavilonis and Mirer 2017].

Information on silica and ALS is sparse; however, a recent large, multicenter, population-based case–control study found an association between ALS and occupational silica exposure, which appeared independent of the other occupational exposures studied [Visser et al. 2019]. In a model adjusting for age, gender, education, smoking, alcohol, and data collection center, the odds of ALS among those in the highest cumulative exposure category (> median among exposed controls) were significantly greater than that in those without silica exposure (OR = 1.73; 95% CI: 1.28, 2.33). There was a monotonic exposure-response trend in risk with increasing exposure (*p* for trend 0.01). This is the only known study directly examining ALS risk from silica exposure. There are studies reporting increased ALS risk among construction workers [Andrew et al. 2017; Dickerson et al. 2018; Fang et al. 2009] and glass and tile workers [Peters et al. 2017], who may be occupationally exposed to silica. Still, other studies of occupations have reported conflicting results [Peters et al. 2017; Weisskopf et al. 2005]. Respirable silica,

and other particulate matter, may reach the brain by translocation through the systemic circulation following deposition in the lung or across olfactory epithelium and along olfactory and sensory neuronal pathways (nose-to-brain route)[Block et al. 2012; Clouston et al. 2022a; Daniels et al. 2021]. Although causal mechanisms are unknown, it is plausible that silica and other particulates may be neurotoxic through oxidative stress and neuroinflammation [Block et al. 2012].

WTC dust is a complex mixture of potential toxins that includes silica among other agents [Lioy et al. 2002]. Whether these toxins may work independently or synergistically to contribute to ALS is not known. The unique nature of the 9/11 exposure is a strong limitation to external validity shared by existing studies of environmental factors. Observed associations between suspect agents and ALS have been strongest in occupational settings generally involving chronic exposures to a reasonably defined agent that is delivered at relatively low-dose rates over long periods (e.g., a working lifetime). Complementary information stemmed from protracted environmental exposures delivered at even lower dose rates compared to workers. These exposures are in stark contrast to the acute WTC dust exposures experienced by 9/11-exposed populations during and immediately after the terrorist attacks [Lioy and Georgopoulos 2006; Lioy et al. 2002]. Thus, there is large uncertainty in extrapolating exposure-induced risks among non-9/11 exposed workers and the public to the 9/11-exposed population given widely disparate exposure profiles.

Formaldehyde

Formaldehyde is an environmentally ubiquitous carcinogen that is also endogenously produced through multiple biologic mechanisms. It is a byproduct of several combustion processes and can also be released from building materials. Concentrations in outdoor air are generally below 20 $\mu g/m^3$ in urban settings and typically between 20–60 $\mu g/m^3$ indoors [IARC 2012]. Given a wide variety of potential sources, formaldehyde was reasonably assumed to have been present at the 9/11 disaster sites during the attack, response, or recovery and therefore included in the *Inventory of 9/11 Agents* [NIOSH 2018]. Actual measurement data are sparse. The environmental data compiled in the Environmental Protection

Agency's New York City Response Monitoring Data Retrieval database (RMDR) included 16 air and 16 personal samples collected in 2001 between October 16 and December 16 that were analyzed for formaldehyde. There were 11 personal detects from 0.007–0.061 ppm and 15 air detects from 1.5–13.5 $\mu g/m^3$.

There is inconsistent evidence of formaldehyde exposure as a determinate of ALS and the literature addressing any potential association is sparse. Rana et al. [2021] conducted a recent meta-analysis examining the association between formaldehyde exposure and ALS. In an inverse variance random-effect model, they estimated the meta-relative risk (meta-RR) of ALS from high levels of formaldehyde exposure at 1.78 (95% CI: 1.20, 2.65) using information from six occupational studies [Fang et al. 2009; Peters et al. 2017; Pinkerton et al. 2013; Roberts et al. 2016; Seals et al. 2017; Weisskopf et al. 2009]. "High level" exposures were described as the highest exposure category assigned in the study based on duration (e.g., > 10 years), concentration (e.g., >28 ppm), or intensity. Five of these studies indicated excess ALS risk from formaldehyde exposure; however, specific risk measures, study populations, and exposures varied markedly among studies. There was significant between-study heterogeneity ($p < 0.01$) in the main model. In further examination, the authors found that removing the study by Weisskopf et al. [2009], which contributed the most weight (32%), reduced the summary estimate (meta-RR = 1.31; 95% CI: 1.08, 1.59), as well as the residual heterogeneity ($p = 0.29$). There was no evidence of association in models aggregating ever-exposed estimates or when including studies with proxy exposures ($n = 11$). The funnel plot provided evidence of publication bias. Given few studies for aggregation, the mixing of risk measures, and varied definitions of exposure, interpretation of the summary estimate merits caution.

Summary of Synthesis

The evaluation and synthesis weighted the evidence of a causal association between 9/11 exposure and ALS based on an assessment of the strength of association, consistency, temporality, and biological gradient using information on the findings, strengths, and limitations in the six identified high-

quality studies. The evaluation also assessed the biological plausibility, coherence, and analogy of the proposed causal association based on information from the identified high-quality studies and supplemental information, as necessary. The Science Team found there was representation of all groups of 9/11-exposed population. The Science Team's synthesis findings are summarized in Table 5 below.

Table 5. Summary of synthesis of the aspects of association and representativeness.

Aspect of Association ("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.
Biological Plausibility, Coherence, and Analogy	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. The assumption that the risk observed in a composite outcome is analogous to ALS risk is unsubstantiated, which is an important study limitation.
Representativeness	There was representation of all groups of 9/11-exposed populations.

Abbreviations: ALS, amyotrophic lateral sclerosis; MND, motor neuron disease.

CONCLUSION

Six high-quality studies were identified for evaluation. These studies employed longitudinal designs that began the at-risk period at a time preceding the outcome; therefore, minimally satisfying the temporality criterion. However, no study specifically examined temporal effects and there is large uncertainty in the relevant biologic period. Findings among these studies were largely imprecise and inconsistent. Evidence suggestive of a causal association was limited to one WTC Health Registry study of community members that reported significantly increased mortality from nervous system disorders including ALS; however, subsequent exposure-response analyses did not reveal increasing risk with 9/11 exposure [Jordan et al. 2018]. The study authors attributed the excess to disorders other than ALS. There was no evidence available from studies that specifically examined ALS risk.

Based on its evaluation, the Science Team concludes that a causal association between 9/11-exposures and ALS appears plausible; however, the current evidence is not sufficient to support a reasonable conclusion that there is a *substantial* or *high likelihood* of a causal association. Given inconsistent findings among the six identified studies, sparse evidence of a positive association from one study, and no studies that specifically investigated ALS exposure-related risk, the available evidence is deemed *inadequate* to determine the likelihood of causal association (Category V), as described in Section V. E. of the *Policy and Procedures* [NIOSH 2024].

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