9.11 World Trade Center Health Program

Evaluation of Scientific Evidence Supporting the Addition of Peripheral Neuropathy to the List of WTC-Related Health Conditions

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I. EXECUTIVE SUMMARY

At the direction of the Administrator of the World Trade Center (WTC) Health Program (Administrator), the WTC Health Program's Science Team (Science Team) reviewed three petitions — **Petitions 032, 033,** and **068** — requesting the addition of peripheral neuropathy to the List of WTC-Related Health Conditions (the List). The Administrator previously evaluated two petitions regarding "peripheral neuropathy" and "neuropathy" in **Petition 010**[1] and **Petition 015,**[2] respectively; both evaluations resulted in findings of *insufficient evidence* to add their respective health conditions.

The Science Team evaluated the scientific evidence of a causal association between 9/11 exposures and peripheral neuropathy 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 published between September 2001 and April 2026 identified three studies not previously evaluated by the Science Team reporting on the risk of paresthesia — a symptom of peripheral neuropathy — in 9/11-exposed populations.

The Science Team evaluated the information from the three studies identified in the review of the literature in addition to three studies identified in the previous literature reviews conducted for **Petition 010** and **Petition 015**, individually and together, to characterize the available scientific evidence of a causal association between 9/11 exposures and peripheral neuropathy. The Science Team concludes that there is *inadequate evidence* to determine the likelihood of a causal association between 9/11 exposures and peripheral neuropathy (Category V).[3]

II. BACKGROUND

Pursuant to the James Zadroga 9/11 Health and Compensation Act of 2010,[4] an interested party may petition the Administrator of the WTC Health Program for the addition of a health condition to the List of conditions eligible for treatment in the Program.[5,6] To petition the Program, petitioners must submit, in writing, their name, contact information, and signature of the interested party requesting the addition of a health condition to the List; a statement of intent to petition for the addition of a health condition to the List; the name or description of the health condition; and reasons for adding the health condition to the List, including the medical basis for the association between the September 11, 2001, terrorist attacks and the health condition.[7] These requirements are further explained in the *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions (Policy and Procedures for Handling Submissions and Petitions)* [NIOSH 2026a]. Submissions that meet all requirements are considered valid petitions.

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1 *See* Federal Register, Vol. 81, No. 64, Monday, April 4, 2016, 10908-10910. https://www.govinfo.gov/content/pkg/FR-2016-04-04/pdf/2016-07567.pdf.

2 *See* Federal Register, Vol. 82, No. 90, Thursday, May 11, 2017, 22004-22006. https://www.govinfo.gov/content/pkg/FR-2017-05-11/pdf/2017-09551.pdf.

3 *See Policy and Procedures*, Section V.E. [NIOSH 2024].

4 Title I of Pub. L. 111-347, as amended by Pub. L. 114-113, Pub. L. 116-59, Pub. L. 117-328, Pub. L. 118-31, and Pub. L. 119-75; codified at 42 U.S.C. §§ 300mm – 300mm-64.

5 42 U.S.C. § 300mm-22(a)(6)(B).

6 The current List of WTC-Related Health Conditions is found in WTC Health Program regulations in Title 42 of the Code of Federal Regulations (CFR) Part 88 (42 C.F.R. § 88.15).

7 *See* 42 C.F.R. § 88.16(a)(1).

A. Petition 032

On July 29, 2021, the Administrator received a submission requesting that "neuropathy and paresthesia" be added to the List. Upon review, the submission was found to be a valid petition and assigned an ordinal number as **Petition 032**.

B. Petition 033

On September 2, 2021, the Administrator received a second submission requesting that "peripheral neuropathy" be added to the List. Upon review, the submission was found to a valid petition and assigned an ordinal number as **Petition 033**.

C. Petition 068

On September 3, 2025, the Administrator received a third submission requesting that "bilateral neuropathy" be added to the List. Upon review, the submission was found to be a valid petition and assigned an ordinal number as **Petition 068**.

The scientific evaluations for these three petitions are considered jointly in this evaluation for the health condition "peripheral neuropathy," as permitted by Program regulations.[8] In accordance with the *Policy and Procedures* [NIOSH 2024], the Administrator directed the Science Team to evaluate the scientific evidence of a causal association between 9/11 exposure and peripheral neuropathy. *See* **Tables 1a** and **1b**.

D. Previous Petitions

The Administrator previously evaluated peripheral neuropathy for potential addition to the List. **Petition 010**, requesting the addition of "peripheral neuropathy," was received on January 5, 2016. The Administrator's determination that the available evidence did not have the potential to provide a basis for a decision on whether to add peripheral neuropathy to the List was published on April 4, 2016.[9] A second petition, **Petition 015**, requesting the addition of "neuropathy," was received on November 25, 2016. The Administrator's determination that the available evidence did not have the potential to provide a basis for a decision on whether to add neuropathy to the List was published on May 11, 2017.[10] The findings from these previous evaluations are discussed in Section VIII.B.1. below.

III. PURPOSE

The purpose of this evaluation is to assess the scientific evidence from peer-reviewed, published, epidemiologic studies of peripheral neuropathy in the 9/11-exposed population,[11] to determine whether sufficient evidence of a causal association between 9/11-related

8 *See* 42 C.F.R. § 88.16(a)(4).

9 *See supra*, note 1.

10 *See supra*, note 2.

11 9/11-exposed population means those persons who can reasonably be assumed to have been exposed to hazards resulting from the September 11, 2001, terrorist attacks, including those 9/11 agents identified in the Program's *Development of the Inventory of 9/11 Agents (Inventory)*, within the geographic areas identified in the WTC Health Program's eligibility criteria; such populations may include, but are not limited to, WTC Health Program members. The *Inventory* includes a catalog of chemical, physical, biological, and other hazards that may have been present at the disaster areas. *See* NIOSH [2018].

exposures, including exposure to 9/11 agents,[12] and the requested health condition exists to support adding the condition to the List. This evaluation is being provided to the Administrator to inform the Administrator's determination regarding **Petitions 032, 033,** and **068**, in accordance with the WTC Health Program's *Policy and Procedures* [NIOSH 2024].

IV. REVIEW OF MEDICAL BASIS INFORMATION PROVIDED BY THE PETITIONERS

The validity of each petition was established by the Program in accordance with Program regulations and the *Policy and Procedures for Handling Submissions and Petitions* [NIOSH 2026a]. The Program examined the references provided with the submissions to determine whether they provided a medical basis for an association between the September 11, 2001, terrorist attacks and the health condition to be added to the List. *See* **Table 1a**. Across the three petitions, five distinct studies provided by the petitioners were determined to provide sufficient medical basis for the petitions. *See* **Table 1b**.

A. Petition 032

Petition 032 provided four studies as medical basis. One of the studies, Marmor et al. [2020], a peer-reviewed, published case-control study finding "increased prevalence of clinical and laboratory-test abnormalities indicative of neuropathy among individuals with WTC exposure and paresthesia of the lower extremities," provided sufficient medical basis for the petition. Marmor et al. [2020] was also identified in the literature review and is further discussed in Section VIII.B.2.c. The other three studies submitted were found not to provide sufficient medical basis for the petition because they were previously provided as medical basis and evaluated in **Petitions 010** and **015** [Stecker et al. 2016; Wilkenfeld et al. 2016; Marmor et al. 2017]. *See* Section VIII.B.1.

B. Petition 033

Petition 033 provided ten studies as medical basis. Five of the ten studies provided sufficient medical basis for the petition [Chia and Chu, 1984; Thomke et al. 1999; Staff and Windebank 2014; Colbeth et al. 2019; Marmor et al. 2020]. Colbeth et al. [2019] is a peer-reviewed, published cross-sectional study finding increased reporting of peripheral neuropathy symptoms among 9/11-exposed responders. Colbeth et al. [2019] and Marmor et al. [2020] were both also identified in the literature review and are further discussed in Section VIII.B.2.a. and c., respectively.

Chia and Chu [1984] examined neurological symptoms in a case series of 35 Taiwanese patients who were admitted for treatment following inadvertent chronic ingestion of polychlorinated biphenyl (PCB)-contaminated cooking oil in the late 1970s. PCBs are listed as a 9/11 agent in the *Development of the Inventory of 9/11 Agents (Inventory)* [NIOSH 2018].[13] Chia and Chu [1984] did not examine

12 9/11 agents are chemical, physical, biological, or other agents or hazards reported in a peer-reviewed, published, 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 C.F.R. § 88.1, as well as those hazards not identified in a peer-reviewed, published, exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. Known 9/11 agents are established in the *Inventory* [NIOSH 2018].

13 *See supra*, note 12.

health conditions in a 9/11-exposed population and did not examine exposure conditions experienced on September 11, 2001, therefore this study was not considered further in this evaluation.

Thomke et al. [1999] is a cross-sectional study that examined chloracne, a common symptom of acute dioxin intoxication, and peripheral neuropathy in a group of 121 workers who were chronically exposed to dioxin while employed in a pesticide producing plant. Thomke et al. [1999] reported an association between exposure to 2,3,7,8-polychlorinated dioxins and furans (PCDD/F) and toxic neuropathy in exposed workers. PCDDs and PCDFs are listed as 9/11 agents in the *Inventory* (e.g., 2,3,7,8-tetrachlorodibenzodioxin, and 2,3,7,8-tetrachlorodibenzofuran) [NIOSH 2018]. Although the study provided sufficient medical basis, it did not report on 9/11 exposed populations and was not further considered in this evaluation.

Staff and Windebank [2014] is a literature review describing the relationship between peripheral neuropathies and vitamin deficiencies, medications, and toxins, such as heavy metals (e.g., lead, arsenic, thallium, and mercury), hexacarbons (e.g., n-hexane, methyl n-butyl ketone), and organophosphates. Overall, the review demonstrated the wide array of potential causal agents potentially linked to toxic neuropathies. Many of the heavy metals reviewed, as well as some of the hexacarbons, are included in the *Inventory* as 9/11 agents. Since some of the studies included in the review assert a causal relationship between 9/11 agents and peripheral neuropathy, Staff and Windebank [2014] provides sufficient medical basis, however it is not a study of 9/11-exposed populations and therefore was not further considered in this evaluation.

Five of the ten studies submitted with **Petition 033** were found not to provide sufficient medical basis [Lioy et al. 2002; Stecker et al. 2014; Wilkenfeld et al. 2016; Stecker et al. 2016; Marmor et al. 2017]. Lioy et al. [2002] characterized the dust/smoke that settled in lower Manhattan after the collapse of the WTC on September 11, 2001, but did not examine any health conditions related to 9/11-exposures; therefore, it was not further considered in this evaluation. The other four studies provided [Stecker et al. 2014; Wilkenfeld et al. 2016; Stecker et al. 2016; Marmor et al. 2017] were previously provided as medical basis and evaluated in **Petitions 010** and **015**, therefore they were not found to provide sufficient medical basis for the petition.

C. Petition 068

Petition 068 provided one study as medical basis [Colbeth et al. 2019], which was sufficient medical basis for the petition. For a discussion of Colbeth et al., see Section VIII.B.2.a.

V. EVALUATED HEALTH CONDITION

In accordance with the *Policy and Procedures* [NIOSH 2024], the Science Team reviewed the information provided by the petitioners, including medical basis information and determined that the health condition of interest for the evaluation is peripheral neuropathy (e.g., ICD-10 G60.3, G60.9, G62.2, G62.9).

Neuropathy is a broad term to describe nerve damage while peripheral

neuropathy refers to damage to nerves that lie outside the brain and spinal cord, chiefly nerves that innervate the arms, hands, legs, and feet. The two terms are used interchangeably [Hammi and Yeung 2022]. Since the term "neuropathy" is frequently used interchangeably with the term "peripheral neuropathy," the Administrator understands the term "neuropathy" to include the health condition referred to as "peripheral neuropathy." Nerve damage to the central nervous system (i.e., the brain and spinal cord) is not considered peripheral neuropathy for this evaluation.

Peripheral neuropathy is a term describing any reversable, persistent, or progressive damage to the peripheral nervous system. Peripheral neuropathies can manifest as symmetric polyneuropathy or as asymmetric neuropathy involving a single or multiple nerves [Mauermann and Staff 2026]. Given this broad definition, it is a common health condition with widely varying etiology, pathology, and symptomology. Peripheral neuropathy is often a component of another disease, such as cancer, atherosclerosis, autoimmune disease, and diabetes mellitus [Martyn and Hughes 1997]. Peripheral neuropathy is relatively common, affecting 2% to 11% of the general population, and increases in frequency with age [Hughes 2002; Hanewinckel et al. 2016a; Hicks et al. 2021].

Symptoms of peripheral neuropathy are diverse — ranging from mild to disabling — and are largely dependent on the types of nerves affected (i.e., sensory, motor, or autonomic nerves) and the degree of nerve damage. Peripheral neuropathy can present with unilateral or bilateral symptoms [Mauermann and Staff 2026]. Accurate diagnosis can be difficult and typically involves taking a careful medical history, evaluation of clinical signs and symptoms that are compatible with peripheral neuropathy, followed by validated objective measures from electrodiagnostic studies, such as nerve conduction studies and needle electromyography (EMG). Electrodiagnostic studies are necessary to determine whether the neuropathy is primarily demyelinating (degeneration of myelin surrounding axons of neurons) or axonal (degeneration and loss of axons), which is critical to establishing cause and treatment. Additional studies, e.g., magnetic resonance imaging (MRI), may also be necessary. Taken together, clinical evaluation and results from objective measures are best able to accurately diagnose and classify peripheral neuropathy, determine possible causes, and suggest treatment options [England and Asbury 2004].

There are several types of peripheral neuropathies described in the scientific literature. In addition to several diseases and disorders, acquired forms have been linked to infection, inflammation, environmental toxins, physical trauma, and life-style factors [Kelly 2004, 2005]. Among causes, diabetic peripheral neuropathy occurs most often in developed countries, with prevalence estimated between 6% to 51% among adults with diabetes mellitus, depending on age, duration of diabetes, glucose control, and type 1 versus type 2 diabetes [Hicks and Selvin 2019]. Hereditable neuropathies are rare [Martyn and Hughes 1997], although genetic and epigenetic factors might have roles in susceptibility to acquired forms.

It is estimated that 25% to 33% of all cases of peripheral neuropathy lack a known cause [Smith and Singleton 2006; Brannagan 2012; Singer et al. 2012; Hanewinckel et al. 2016b]. The high prevalence of idiopathic (i.e., condition

without a known cause) peripheral neuropathy may result, in part, from difficulties in recognizing treatable causes. For example, a study reexamining a group of patients previously diagnosed with idiopathic peripheral neuropathy found that 67% actually had an identifiable etiology [Farhad et al. 2016]. Among likely causes of idiopathic neuropathy, there is emerging evidence suggesting that impaired glucose tolerance and metabolic syndrome, in particular dyslipidemia and obesity, may be important risk factors [Farhad et al. 2016; Smith and Singleton 2006; Smith 2012]. Except for diabetic neuropathy and Guillain-Barre syndrome, relevant population-based epidemiologic studies investigating peripheral neuropathy are sparse [Martyn and Hughes 1997].

Neuropathies, when caused by trauma, are not considered peripheral neuropathy for this evaluation. Many such trauma-caused mononeuropathies may be eligible for treatment coverage by the Program as musculoskeletal disorders (MSDs), acute traumatic injuries, or health conditions medically associated with a WTC-related health condition (i.e., potentially related to a certified acute traumatic injury).[14] WTC-related MSDs manifesting as mononeuropathies include carpal tunnel syndrome (CTS) and ulnar neuropathy. Similarly, radiculopathies (i.e., nerve root compressions) that arise from back injury caused by acute or repetitive trauma are excluded from peripheral neuropathy for purposes of this evaluation.

Although **Petition 032** requests paresthesia be added to the List (along with neuropathy), the Science Team determined that paresthesia is not a health condition of interest. This is because paresthesia is a symptom and not a health condition.

VI. RISK FACTORS FOR EVALUATED HEALTH CONDITION

A. General Risk Factors

Peripheral neuropathy can arise from a variety of origins, including metabolic, systemic, and toxic causes, although in many patients with chronic peripheral neuropathy, the etiology is unknown. Underlying etiologies that place an individual at risk of peripheral neuropathy include: (1) diabetes mellitus; (2) chronic alcoholism; (3) nutritional deficiencies (e.g., vitamins B1, B6, B12, and E); (4) inflammatory conditions (e.g., vasculitis); (5) hypothyroidism; (6) autoimmune disease (e.g., Sjögren syndrome, lupus, rheumatoid arthritis); (7) infections (e.g., Lyme disease, Epstein-Barr virus, hepatitis C, shingles, leprosy, HIV); (8) Guillain-Barre syndrome; (9) toxins (heavy metals, chemicals); (10) chemotherapy agents; (11) medications (antibiotics, cardiovascular medications); (12) tumors (secondary to compression or associated paraneoplastic syndromes); (13) inherited conditions (e.g., Charcot-Marie-Tooth disease, familial amyloidosis); (14) trauma or injury; (15) multiple myeloma and its treatments; and (16) monoclonal gammopathy of undetermined significance (MGUS) [Hammi and Yeung 2022].[15]

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14 *See* 42 C.F.R. § 88.15(c) and (e).

15 Although not a direct cause of peripheral neuropathy, post-traumatic stress disorder (PTSD) may place an individual at risk for peripheral neuropathy. This is because PTSD increases the risk of conditions that can cause peripheral neuropathy, e.g., diabetes mellitus. In addition, PTSD is associated with a wide range of somatic symptoms (i.e., physical sensations or bodily complaints — such as pain, fatigue, or dizziness — that cause significant distress or daily disruption, regardless of whether a clear medical cause exists) and the broad spectrum of neurological and autonomically-mediated symptoms associated with PTSD includes “ill-defined” or “medically unexplained” somatic syndromes such as unexplained dizziness, tinnitus, and blurry vision, including paresthesia. *See* Boscarino [2004].

B. 9/11 Risk Factors

Responders to and survivors of the September 11, 2001, terrorist attacks experienced a variety of exposures to environmental toxicants. The collapse of the World Trade Center towers resulted in a massive and dense cloud of suspended toxic dusts, gases, and smoke that engulfed the highly populated areas of southern Manhattan and Brooklyn [Lioy and Georgopoulos 2006]. The bulk (about 80 to 90%) of the aerosolized dust resulted from the cascading impacts of concrete floor slabs that crushed the building materials and contents into a dispersible powder [Lippmann et al. 2015]. The six-story pile of debris at Ground Zero burned intermittently for more than three months [Landrigan et al. 2004]. Exposures continued in the days and months that followed; initially mostly from burning jet fuel and building fires, and later by the resuspension of dusts during the many months of cleanup and recovery. Clean-up activities may also have led to exposure to neurotoxins present in cleaning fluids, solvents or paints, including n-hexanes and 2-hexanone.

In 2018, the WTC Health Program published the *Inventory*, a catalog of chemical, physical, biological, and other hazards that may have been present at the disaster areas [NIOSH 2018]. The over 350 hazards referenced in the *Inventory* are recognized as "9/11 agents."[16] Peripheral neuropathy is linked to exposures to toxicants identified as 9/11 agents in the *Inventory* [NIOSH 2018]. The 9/11 agents linked to peripheral neuropathy include n-hexane, arsenic, 2-hexanone, 3-chloropropylene, polychlorinated biphenyls, arsenic, thallium, and lead [Staff 2020].

VII. SCIENTIFIC EVALUATION APPROACH

The Science Team evaluation was carried out in accordance with the *Policy and Procedures* [NIOSH 2024] and includes the following steps: (1) develop a literature search protocol and conduct a search for peer-reviewed, published, epidemiologic studies of the health condition being evaluated among 9/11-exposed populations;[17] (2) review identified studies to determine which studies are high-quality studies for further evaluation;[18] (3) evaluate and integrate the evidence of a causal association between 9/11 exposures and the health condition being evaluated;[19] and (4) synthesize and interpret all findings to categorize the weight of evidence of a causal association between 9/11 exposures and the health condition evaluated.[20] The Science Team then advises the Administrator of its findings.[21]

VIII. REVIEW OF THE LITERATURE

A. Literature Search

The literature search identifies peer-reviewed, published, epidemiologic studies that provide evidence on the likelihood of a causal relationship between 9/11 exposures and the health condition under consideration — peripheral neuropathy. To identify potentially relevant studies, the Science Team searched abstracts

16 *See supra*, note 12
17 *See Policy and Procedures*, Section III.B. [NIOSH 2024].
18 *See Policy and Procedures*, Section III.C. [NIOSH 2024].
19 *See Policy and Procedures*, Section IV. [NIOSH 2024].
20 *See Policy and Procedures*, Section V. [NIOSH 2024].
21 *See Policy and Procedures*, Section VI. [NIOSH 2024].

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: peripheral neuropathy, polyneuropathy, nerve injury, neuropathy, neuropathies, paresthesia, mononeuropathy, neuronopathy, polyradiculoneuropathy, nerve disease, nerve entrapment, CTS, neuropathic, neurologic problem, autonomic dysfunction, palsy, and nerve syndrome. 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 9/11-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 April 2026. This two-pronged approach ensures all relevant and up-to-date literature is available for the evaluation.

The literature search identified six peer-reviewed, published, epidemiologic studies relating to peripheral neuropathy among 9/11-exposed populations for full review as potential studies for evaluation [Stecker et al. 2016; Wilkenfeld et al. 2016; Marmor et al. 2017; Colbeth et al. 2019; Thawani et al. 2019; Marmor et al. 2020].

Three of the six studies were previously reviewed as part of the scientific evaluation for **Petitions 010** and **015** [Stecker et al. 2016; Wilkenfeld et al. 2016; Marmor et al. 2017]. After evaluation, these three studies were found to be inadequate to provide a basis for a causal association between exposure to 9/11 agents and peripheral neuropathy.[22,23] While these studies are not further considered, the findings of the previous scientific evaluations regarding the studies are summarized in Section B.1. below for completeness. *See* **Table 2**.

The three remaining studies identified in the literature search [Colbeth et al. 2019; Thawani et al. 2019; Marmor et al. 2020] examined the "symptoms of peripheal neuropathy" [Colbeth et al. 2019] or "paresthesia" [Thawani et al. 2019; Marmor et al. 2020], a common symptom of peripheral neuropathy among 9/11-exposed populations, but not peripheral neuropathy itself.[24] Paresthesia is also a common symptom of other medical conditions, including several currently covered by the Program such as depression [Benavidez et al. 2020], back injury, and mononeuropathy arising from repetitive trauma. The Science Team determined that these three studies [Colbeth et al. 2019; Thawani et al. 2019; Marmor et al. 2020] do not have sufficient validity indicators to be high-quality studies due to various limitations and because they only examine non-specific symptoms of peripheral neuropathy and do not directly examine the risk of 9/11 exposure and peripheral neuropathy.[25] Thus, the studies were removed from further consideration; however, they are discussed in Section B.2. below for completeness.

22 *See supra*, note 1.
23 *See supra*, note 2.
24 Paresthesia is a neurological symptom of different health conditions that is described as abnormal sensations, such as feelings of pins and needles, tingling, and pricking of the skin, usually felt in extremities (e.g., fingers, hands, toes, and feet). *See* Kleiner [2017].
25 *See Policy and Procedures*, Section III.C. [NIOSH 2024].

B. Studies Removed from Further Consideration

1. Previously Reviewed Studies Removed from Further Consideration

Three of the six studies identified in the literature review were previously reviewed by the Administrator in the evaluation of **Petitions 010** and **015** [Stecker et al. 2016; Wilkenfeld et al. 2016; Marmor et al. 2017]. *See* **Table 2**. The findings and notable limitations were discussed in the published decisions on **Petitions 010** and **015**. The evaluations found these three studies to be inadequate to provide a basis for a causal association between exposure to 9/11 agents and peripheral neuropathy.[26,27,28] Those findings are summarized below for completeness.

a. Stecker et al. [2016]

Stecker et al. [2016] is a cross-sectional study that included 16 patients with WTC exposures who were evaluated at a neurology clinic in Long Island, New York (10 responders and 6 survivors). The control population consisted of patients undergoing outpatient electromyogram (EMG)/nerve conduction studies at a hospital in Long Island between December 8, 2015, and May 1, 2016. The control sample consisted of 174 patients with a clear neurophysiologic diagnosis and no WTC exposures. The evaluation included a neurologic examination, and most patients also received EMG and nerve conduction studies as well as appropriate imaging and blood tests. Among patients who received EMG, 9/11-exposed patients were more likely to have EMG findings that were consistent with axonal polyneuropathy (9 out of 14, 64%) versus control patients (59 out of 174, 34%) (relative risk [RR] = 1.9; 95% CI = 1.0, 2.7). There was no difference in CTS prevalence in the two groups (WTC-exposed = 21%, controls = 24%, RR = 0.89; 95% CI = 0.23, 2.3). Some findings from the nerve conduction studies were also significantly different between the 9/11 exposed group versus the control group. These included the WTC-exposed group having shorter sural sensory amplitudes; longer sural sensory durations (measured in milliseconds); slower peroneal motor velocity; shorter tibial motor amplitudes; and slower tibial motor velocity. This study has several limitations including lack of information for how persons with 9/11 exposure were selected for study participation (e.g., it is not clear if 9/11-exposed persons with certain symptoms were preferentially enrolled). Also, there was a lack of consistency in the type of neuropathy assigned to WTC-exposed participants. For example, in Table 1 of the study, among the 14 WTC-exposed participants who received EMG, none were reported to have radiculopathy based on EMG findings. However, in Table 3 of the study, two WTC-exposed participants were reported to have radiculopathy on EMG, and in Table 4 of the study, six had magnetic resonance

26 *See supra*, note 1.
27 *See supra*, note 2.
28 Previous versions of the *Policy and Procedures* were in effect at the time the evaluations of **Petitions 010** and **015** were published [NIOSH 2014; 2017]. However, even under the current *Policy and Procedures* [NIOSH 2024], these three studies are not considered high-quality and, as a result, would not be further evaluated.

imaging (MRI) findings that were consistent with radiculopathy (e.g., spinal stenosis, root compression, disc herniation). In addition, no comparison of demographics between 9/11-exposed versus controls was provided, so it is not clear if they differed in age, sex, or risk factors for neuropathy. Finally, no dose-response analyses involving 9/11 exposures were provided.

Upon review, Stecker et al. [2016] exhibited significant limitations, including flawed study design and selection bias. The study did not include appropriate population sampling criteria and although it used an objective measure of neuropathy, the comparison group was inadequate. The small exposure group and multiple statistical tests in Stecker et al. [2016] may have limited the study power. Moreover, it did not address potential exposures to toxins outside of 9/11 exposures and other confounders that could explain the findings. As a result of these limitations, Stecker et al. [2016] was found not to provide a basis for deciding whether to propose adding neuropathy to the List.[29]

b. Wilkenfield et al. [2016]

Wilkenfeld et al. [2016] is a cross-sectional study that assessed self-reported neuropathic symptoms among a small convenience sample of subjects ($n = 255$) who completed an online survey. Those with 9/11 exposures ($n = 139$) were compared to those without 9/11 exposures ($n = 116$). Participants were administered the Michigan Neuropathy Screening Instrument (MNSI), which is a questionnaire consisting of 15 questions about various neuropathic symptoms. MNSI scores were used to define "clinical neuropathy." Those with WTC exposures were significantly more likely to have clinical neuropathy, whether defined as an MNSI score of 4 or greater (WTC exposure = 66%, no WTC exposure = 11%, $p < 0.001$) or an MNSI score of 7 or greater (WTC exposure = 21%, no WTC exposure = < 1%, $p < 0.001$). Linear regression analyses assessing continuous MNSI scores (and controlling for diabetes mellitus, severe stress and lung disease), predicted that participants with the highest WTC exposures (i.e., those who were both caught in the dust cloud and worked on the ‘‘pile'') would have average neuropathy scores 2.5 points higher than people without WTC exposure ($p < 0.001$). Those with moderate WTC exposures (i.e., those who either were caught in the dust cloud or who worked on the ‘‘pile'') were predicted to have scores that were an average of 2 points higher than people without WTC exposure ($p < 0.001$).

Wilkenfeld et al. [2016] had several limitations including the lack of information on date of symptom onset, so it was not clear if neuropathic symptoms had a pre-9/11 onset. The outcome was based on subjective self-report and was not clinically verified. Participants with known back or nerve injury arising from repetitive trauma were not excluded. The study was a convenience sample, participation rates were not reported, and it is not known if the sample is representative of the entire 9/11-exposed population. Finally, it is not clear if the

29 *See supra*, note 2.

authors sufficiently controlled for other neuropathic risk factors (e.g., alcohol use disorder, nutritional deficiencies, use of certain medications, trauma, or repetitive trauma). Wilkenfeld et al. [2016] included both responders and survivors, but the authors did not report how many of each participated. Based on the numerous limitations of the study, Wilkenfeld et al. [2016] was found insufficient to provide the Administrator with a potential basis for deciding whether to propose adding peripheral neuropathy to the List.[30]

c. Marmor et al. [2017]

Marmor et al. [2017] is a cross-sectional study of self-reported paresthesia among survivors attending the Bellevue Hospital EHC. Paresthesias were dichotomized to "never" versus "sometimes" through ''almost continuously'' to capture paresthesia of either the upper or lower extremities as self-reported to have occurred in the year before interview. Among the study sample of 3,141 participants, a total of 1,793 (57%) reported paresthesia. Similar percentages reported paresthesia of the upper (46%; 1,446 participants) or lower (44%; 1,383 participants) extremity. Most of those reporting paresthesia had paresthesia of both extremities (33%; 1,033 of all participants), 11% (346) of patients reported isolated paresthesia of the lower extremities and 13% (407) reported isolated paresthesia of the upper extremities. When all paresthesia was combined, the odds of paresthesia were significantly increased among those who were heavily covered in WTC dust after adjustment for diabetes, cancer, depression, anxiety, and PTSD checklist score > 44, compared to those with no dust exposure (OR = 1.30; 95% CI = 1.08, 1.57). Similarly, among those who reported cleaning WTC dust at work compared to those without such exposure, the odds of paresthesia were significantly increased (OR = 1.69; 95% CI = 1.32, 2.18). Exposure to light amounts of WTC dust was not associated with paresthesia. When those with isolated upper or lower extremity paresthesia were examined separately, the odds of paresthesia were also significantly increased among those who were heavily covered in WTC dust, but not for the other two WTC exposures.

There were several limitations of the Marmor et al. [2017] study. Participants with paresthesia that commenced pre-9/11 were not excluded. There was no clinical confirmation that the paresthesia was caused by peripheral neuropathy. Participants with paresthesia arising from back injury or repetitive trauma were not excluded. Analyses controlled for some important confounders (e.g., diabetes and cancer) but not always for others (e.g., age; mental health outcomes such as depression, anxiety, and PTSD), which were shown by the authors to be independently associated with paresthesia. When evaluating Marmor et al. [2017] for **Petition 015**, the Program found that because the study reported on paresthesia — a condition related to and at times a symptom of neuropathy — it ultimately was not a "relevant" study and

30 *See supra,* note 1.

could not provide potential support for deciding whether to propose adding neuropathy to the List.[31]

2. Newly Identified Studies Removed from Further Consideration

The three studies newly identified in the literature search [Colbeth et al. 2019; Thawani et al. 2019; Marmor et al. 2020] examined paresthesia as a proxy[32] for peripheral neuropathy in 9/11-exposed populations. *See* **Table 3**.

a. Colbeth et al. [2019]

Colbeth et al. [2019] was identified in the literature search and also provided as medical basis for **Petitions 033** and **068**. It is a cross-sectional study of self-reported symptoms of peripheral neuropathy among 9/11-exposed responders (n = 9,239) employed by the Fire Department of the City of New York (FDNY). Study participation required: (1) arrival at the disaster site between the morning of 9/11/2001 and 9/24/2001; (2) being an active FDNY firefighter or emergency medical worker (EMS) on 9/11; (3) having taken at least one post-9/11 health questionnaire within the study data collection period (2017 to 2019); and (4) being aged 40 years or older at the time of their most recent questionnaire. Neuropathic symptoms were measured using the Diabetic Neuropathy Symptom (DNS) score (which assessed only lower extremity paresthesia). Neuropathic symptoms were also assessed by self-report of paresthesia of the lower and upper extremities that was present within the previous two weeks of completing the FDNY self-administered health monitoring questionnaire. No other information was provided regarding the onset of paresthesia, including whether symptoms manifested prior to 9/11.

The study population was stratified into two mutually exclusive groups; the “indicated” group comprising persons with conditions known to be associated with paresthesia (n = 2,059), and the “non-indicated” group including all others (n = 7,180). Indicated conditions included diabetes, a history of confirmed cancer (not including *in situ* cancers or non-melanoma skin cancers), or a history of confirmed autoimmune disease. The level of 9/11 exposure was categorized by time of arrival on the WTC site as either being high (arrived on the morning of 9/11), moderate (arrived in the afternoon of 9/11 or on 9/12/2001), or low (arrived between 9/13/2001 and 9/24/2001). The prevalence of self-reported peripheral neuropathy and symptoms were calculated among indicated and non-indicated groups. Multivariable logistic regression was used to examine the association between 9/11 exposure and neuropathic symptoms within the non-indicated group, controlling for age, sex, race, work assignment (firefighter versus EMS), smoking, and excessive alcohol use. Comparisons were also made with an external referent group using weighted data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) adjusting for age,

31 *See supra*, note 2.

32 A proxy variable (measurement) is an easily measured variable that is used in place of a variable that cannot be directly measured or is difficult to measure. *See* Nilsson et al. [2023].

race, and sex. The NHANES sample comprised survey participants 40 years and older who completed responses to questions about numbness, loss of feeling, painful sensation, or tingling in the hands or feet — other than from the hands or feet falling asleep — in the past three months from the date of survey. NHANES participants who reported a diagnosis of diabetes (*n* = 519) or who reported borderline or unknown diabetes (*n* = 62) were excluded. The final NHANES sample comprised 2,718 non-diabetic participants.

The overall FDNY cohort (*n* = 9,239) was mostly male (97.6%), non-Hispanic white (89.7%), with a work assignment of firefighter (88.2%). Most (69.3%) were moderately exposed. In the FDNY non-indicated group, 97.8% were male and 90.3% were firefighters. The prevalence of scoring positive on the DNS was 30.6% and 23.8% for the indicated and non-indicated groups, respectively. In contrast, the prevalence in the non-diabetic NHANES sample was 13%. Self-reported physician-diagnosis of peripheral neuropathy was approximately 2% in the indicated group and 1% in the non-indicated group. In the non-indicated group, the odds of a positive DNS score or self-reported paresthesia increased with moderate and high 9/11 exposures compared with the low exposure group. *See* **Table 4**.

Estimates were statistically significant for all paresthesia combined, and for paresthesia of the upper extremity. Estimates were not statistically significant for isolated paresthesia of the lower extremity when assessed using the FDNY questionnaire but were when using DNS. Compared with NHANES, the odds of reporting symptoms of peripheral neuropathy among the FDNY responders were significantly increased (odds ratio [OR] = 2.06; 95% confidence interval [CI]: 1.65, 2.57). The exposure-response trend across categories appeared monotonically positive using the NHANES referent. Paresthesia of the upper and lower extremities were combined in this analysis.

Overall, Colbeth et al. [2019] found increased reporting of peripheral neuropathy symptoms among responders compared with an external reference group. The study also reported evidence of a modest association between 9/11 exposure and self-reported symptoms of upper extremity paresthesia, but findings for lower extremity paresthesia were equivocal. Notable study strengths are the large study size and data available from periodic health surveillance. However, in addition to limitations frequently associated with observational studies (e.g., the potential for residual confounding, selection bias, and exposure misclassification), there are other important limitations.

First, the study is cross-sectional; therefore, causal inference is limited by the lack of information on the temporality of cause and effect. Without longitudinal data, there is no information on the persistence of the health outcome or an ability to determine whether the association is related to 9/11 exposure or other aspects of career firefighting (or another risk factor) that occurred before or after September 11, 2001.

Second, the study relied on self-reported information that is prone to error, especially when using a proxy (paresthesia) for a health condition of interest (peripheral neuropathy) that is broadly defined, considerably common, and difficult to diagnose. The Science Team noted that the prevalence of self-reported symptoms in this study was much greater than the prevalence of self-reported, physician-diagnosed peripheral neuropathy. Without a diagnosis of peripheral neuropathy, it is unclear whether the outcome used in analysis represents an idiopathic peripheral neuropathy that might be caused by 9/11 exposure or is attributable to some other cause. Third, there is a potential for strong selection bias when using the NHANES sample as the reference group, given important differences in the populations. FDNY responders are routinely monitored for WTC-related health conditions while participating in the WTC Health Program. Increased surveillance among responders compared with the NHANES reference group could bias risk estimates. Fourth, although paresthesia of the upper extremity was significantly associated with 9/11-exposure, the upper extremity paresthesia may be related to peripheral neuropathy arising from repetitive trauma, which may already be covered under a WTC-related health condition on the List. Fifth, the findings for paresthesia in the lower extremity were equivocal. High 9/11 exposures were significantly associated with lower extremity paresthesia assessed using the FDNY questionnaire but were not when using DNS. The authors did not explain the possible reasons for this difference in lower extremity paresthesia findings. Due to the preceding factors, the Science Team was unable to consider Colbeth et al. [2019] a high-quality study and as a result it has not been further evaluated.

b. Thawani et al. [2019]

Thawani et al. [2019] enrolled 3,411 consenting patients from the WTC Environmental Health Center (EHC) between 2008–2018 who responded to questions regarding paresthesia. Subjects were those exposed on 9/11 and reporting medical or mental health conditions that were identified as potentially due to exposure to the WTC event, excluding those reporting paresthesia prior to 9/11, diabetes mellitus, or a history of cancer. To estimate incidence rates of lower extremity paresthesia (subjects with isolated upper extremity paresthesia were presumably excluded), time-to-event survival analyses were conducted using an inferred date of onset. Among those reporting paresthesia at baseline, the date of onset was derived from the patient's recall of the time of onset post-September 11, 2001. Among those without reported paresthesia at the baseline visit, but who reported paresthesia at the first return visit, onset was estimated as the mid-point between those two visits. Right-censoring of patients without self-reported paresthesia was based on the date of last visit.[33]

33 The term "censoring" is used in statistics to describe a condition in which the value of an observation or measurement is only partially known. Thawani et al. [2019] right-censored (i.e., authors stopped following the study participants) in two instances for subjects without paresthesia: (1) after the baseline visit if the subject did not attend a return visit; and (2) on the dates of the last return visit. *See* Lesko et al. [2018].

Exposure was defined as a dichotomous variable based on self-report of a "cleaning job" involving WTC-dusts or if the person was heavily "covered with dust" on September 11, 2001. Exposure-response associations were examined using multivariable Cox proportional hazards regression with time-on-study[34] as the time scale. Models were adjusted for age, race, ethnicity, depression, anxiety, post-traumatic stress disorder (PTSD), and elevated body mass index (BMI).

The cohort (n = 3,411) included slightly more females (50.7%) and was mostly non-Hispanic white (47.9%). The median age was 53 years. There were 605 patients (17.7%) reporting "often" or "almost continuous" symptoms of paresthesia of the lower extremities at baseline (i.e., at their initial visit). Of the 2,806 remaining baseline subjects, 1,004 (35.7%) described occasional paresthesia at baseline or a return visit. There was a modest positive association between paresthesia and having worked in a job that required cleaning of WTC dust (HR = 1.37, p = 0.003). The association strengthened when removing those reporting occasional paresthesia (HR = 1.52, p < 0.0001). Nonparametric cumulative hazard functions comparing patients who worked in a cleaning job to other patients showed a significant difference between the two groups (p < 0.0001, log-rank test), with shorter time to onset among exposed patients. The risk persisted over the course of the study (17 years). *See* **Table 5**.

The authors also reported that paresthesia resolved or decreased in a subset of subjects between the baseline (initial) and return visits (the count of such participants was not reported). Among 1,373 participants who had a return visit, 159 newly reported paresthesia. The authors did not report how many participants had paresthesia at both visits, so the prevalence among those with a return visit is unclear.

The strengths of the study are its size and longitudinal design examining self-reported paresthesia in the 9/11 population over time. Overall, the results suggested persistent exposure-related risk of self-reported paresthesia in a select group of the 9/11 population. However, there were several important limitations.

First, only 36% of subjects had at least one follow-up visit; therefore, date of onset was mostly inferred from patient recall at baseline visit of symptoms onset between 2001 and 2008 (or longer). Without frequent measures during this period, inference on temporal characteristics merit caution given limitations of recall. Second, time-on-study began with exposure on 9/11 and all subjects who entered the study were assumed "risk-free" at entry and all those at risk (i.e., exposed) were available for study. Neither assumption appears valid. For example, although the authors excluded persons reporting paresthesia prior to 9/11, this decision resulted in the exclusion of only 3% of the eligible population, suggesting under-ascertainment of previous case status given how common paresthesia is in the general population. Furthermore, the cohort comprised a highly selected

34 "Time-on-study" generally refers to the duration a participant is followed from the start of a study until an event or study conclusion occurs.

group that was enrolled well after 9/11. This group demonstrated relatively high prevalence of self-reported paresthesia (17%), a set of symptoms found in many health conditions, including several causes of peripheral neuropathy potentially covered by conditions currently on the List (e.g., CTS). In addition, paresthesia is not exclusive to peripheral neuropathy (e.g., paresthesia arising from depression likely has a central nervous system origin) [Benavides et al. 2020]. Therefore, the validity of its use as a proxy for peripheral neuropathy is limited. Third, persons in the "exposed" group may differ from those in the unexposed group in ways not addressed by covariate control. Therefore, residual, or unmeasured confounding cannot be ruled out. Fourth, the use of time-on-study as the time scale may result in an overestimation of risk when age is a strong determinant of the health condition, even in analyses controlling for age [Thiebaut and Bénichou 2004]. Based on the analysis presented, age is an important risk factor for paresthesia, suggesting a strong potential for bias. Finally, some cases of lower extremity paresthesia may have arisen from low back injury and related lumbar spine radiculopathy, which is excluded from peripheral neuropathy for purposes of this evaluation. Due to the preceding factors, the Science Team was unable to consider Thawani et al. [2019] a high-quality study and as a result it has not been further evaluated.

c. **Marmor et al. [2020]**

Marmor et al. [2020] examined the association between paresthesia of the lower extremities and 9/11 exposure in a case-control study of community members (described as "local workers, local residents, students and passersby") who were potentially exposed to WTC dust and fumes on and after 9/11. This study is a continuation of work previously evaluated by the Science Team [Marmor et al. 2017] which was cited in **Petition 015**. *See* Section VIII.B.1.c. Cases were self-referred consenting adult patients aged 18 to 75 years who enrolled in the WTC EHC between 2005 and 2018, reported paresthesia of the lower extremities at their most recent visit, and indicated a symptom frequency of "often" or "almost continuous." Two control groups were selected. The first group comprised "clinic" controls who were recruited from WTC EHC patients who did not report paresthesia at any study visit, or at screening or at study enrollment. The second control group was described as "community" controls and comprised persons without 9/11 exposure who were either (1) friends or relatives of cases or clinic controls; (2) participants in other research studies being conducted at the Bellevue Hospital Center; or (3) participants in a secure registry of persons willing to participate in research studies that is maintained by another medical center.

Individuals (cases, clinic, and community controls) were excluded if they met any of the following criteria: (1) paresthesia before 9/11; (2) received cancer chemotherapy at any time; (3) known vitamin B12 deficiency; (4) diabetes mellitus; (5) ever use of antiretroviral

medications; and (6) health conditions that would preclude elective skin punch biopsies (e.g., bleeding disorders, use of anticoagulants, or history of keloid scarring). In addition, cases with isolated upper extremity paresthesia were excluded to minimize inclusion of CTS cases. All subjects completed self-administered questionnaires and underwent neurologic examinations with trained neurologists. Neurologists appear not to have been blinded to case status. The PCL-17 was used to quantify the degree of PTSD. Controls were frequency matched to cases on sex and age. Categorical variables were evaluated by chi-squared or Fisher exact tests. Odds-ratios (ORs) were calculated using the Mantel-Haenszel technique.

Following initial screening, exclusions for histories of paresthesia before 9/11, diabetes, and cancer treatment, and accounting for non-contacts, refusals, and further exclusions, final recruitment comprised only 41 cases, 38 clinic controls, and 20 community controls (the authors reported that their goal was to recruit 40 cases, 40 clinic controls, and 20 community controls). There were no significant differences between groups by age, sex, race or ethnicity, BMI, or alcohol use. Household income was significantly less among cases as compared with controls ($p = 0.04$).

With respect to 9/11 exposures, about 27% of self-reported paresthesia cases reported high dust exposure compared with 3% of clinic controls (OR = 2.3; 95% CI: 07, 7.8). Self-reported paresthesia cases also had non-significantly increased odds of ever working in a job requiring cleaning of WTC dust compared to clinic controls (OR = 2.4; 95% CI: 0.7, 8.3; $p = 0.23$). Not unexpectedly, several standardized neurological questionnaires indicated higher (i.e., worse) neurologic symptom scores among paresthesia cases compared with both control groups. The physician-administered neurological examinations found that 39% of paresthesia cases had findings consistent with distal symmetric polyneuropathy versus 8% of clinic controls and none of community controls. Based on an evaluation of symptoms and examination findings, the neurologists rated 58% of cases as definite and 34% as possible for having clinically evident distal symmetric polyneuropathy, versus 3% and 21% respectively, among clinic controls. None of the community controls were found to have definite or possible clinically evident distal symmetric polyneuropathy. On average, PCL-17 scores were significantly higher among paresthesia cases compared with either control group ($p < 0.0001$). Blood tests for factors commonly associated with health conditions associated with peripheral neuropathy did not reveal any differences across groups.

Nerve conduction studies and epidermal nerve and sweat gland nerve fiber densities were evaluated in paresthesia cases only. None of the cases had slowed conduction velocity of the sensory nerves; however, 29% had abnormal sural to radial sensory nerve amplitude ratios (abnormal sural to radial sensory nerve amplitude ratios are suggestive of axonal polyneuropathy). The composite measure of epidermal or sweat gland small nerve fiber density was abnormally

low in 57% of cases compared with an expected abnormal prevalence of 4% to 5% from age- and gender-similar historical controls (no other information was provided on these historical controls). There was no examination of the association between 9/11 exposure and clinically evident distal symmetric polyneuropathy or abnormal sural to radial sensory nerve amplitude ratios.

In summary, Marmor et al. [2020] found that WTC EHC patients with self-reported paresthesia (i.e., the case group) were more likely to have abnormal neurologic examination suggestive of peripheral neuropathy compared to the control groups who denied having paresthesia. The case group also had significantly higher PCL-17 scores compared to the control groups. Skin biopsy examinations, which were performed only in the case group, to assess epidermal nerve and sweat gland nerve fiber density, suggested findings consistent with a diagnosis of small and large fiber neuropathy. There was no evidence of differences in blood test factors between the case and control groups indicating no clear associations with non-WTC-related disease, metabolic, or toxic etiologies of peripheral neuropathy. There was some evidence greater 9/11 exposure among those with self-reported paresthesia (i.e., cases); however, estimates were largely imprecise (confidence intervals included the null) given low statistical power from a small study size.

The study did not directly examine the association between clinically diagnosed peripheral neuropathy and 9/11 exposure. Instead, such an association was examined only for paresthesia. Paresthesia, although a symptom of peripheral neuropathy, can be a component of several other health conditions; therefore, causal inference in this study is limited. The information provided was insufficient to characterize risk of peripheral neuropathy in the 9/11-exposed population.

There are other important limitations as well. First, the case-control design used is prone to several sources of bias inherent to retrospective sampling with case status known. As in a conventional cross-sectional design, this study provided no information on the longitudinal course of paresthesia in this population. Other than self-reporting of paresthesia onset on or after 9/11, temporal factors are not considered in assessing risk. Lacking this information, alternative causes, such as exposures occurring prior to or after 9/11, cannot be ruled out. Second, excluding the community controls, the study population is drawn from patients within the WTC EHC who have 9/11 exposures. The selection into a rather unique hospital-based case-control study population introduces the potential for biased estimates [Schwartzbaum et al. 2003]. Third, study participation was remarkably low and differentially distributed among cases (~14% among contacts) and clinic controls (~26% among contacts), which also introduces the potential for bias. Without additional information, the magnitude and direction of bias is not clear. Finally, participants with paresthesia arising from back injury or repetitive trauma were not excluded. Due to the preceding factors, the Science Team was unable to consider

Marmor et al. [2020] a high-quality study and as a result it has not been further evaluated.

C. Identified High-Quality Studies

None of the six peer-reviewed, published, epidemiologic studies of 9/11-exposed populations examining peripheral neuropathy or paresthesia identified in the current or previous literature searches were found to have sufficient validity indicators to be considered high-quality studies eligible for further review.[35]

IX. SYNTHESIS OF EVIDENCE FOR CATEGORIZATION

In accordance with the *Policy and Procedures* [NIOSH 2024], the Science Team evaluates and synthesizes evidence from the studies identified following the literature review and from the medical basis provided by the current and previous petitions. Synthesis refers to the process by which the Science Team evaluates the evidence presented in scientific studies, individually and together, to characterize the evidence of a causal association between 9/11 exposures and the health condition of interest[36] and to assign findings regarding causal association to one of five categories as described below in Section IX.A.4. This evaluation includes a consideration of the Bradford Hill criteria, limitations, and representativeness of the findings.

A. Introduction

1. Bradford Hill Framework for Weight-of-the-Evidence Determinations

The *Policy and Procedures* [NIOSH 2024] utilizes the Bradford Hill criteria to determine the degree to which the weight of evidence presented by high-quality peer-reviewed, published, epidemiologic studies supports a causal association between 9/11 exposures and the health condition.

The Bradford Hill criteria include: (1) **strength of the association** between 9/11 exposures and the health condition under consideration and precision of the risk estimate; (2) **consistency of associations** across multiple studies; (3) **specificity** that an association is more likely to be causal if one cause (9/11 exposures) and one effect (peripheral neuropathy) is observed; (4) **temporality** of the cause and effect, i.e., 9/11 exposure precedes the health condition (peripheral neuropathy); (5) **biological gradient** or dose-response relationship where changes in 9/11 exposures are associated with corresponding changes in the magnitude of the outcome (peripheral neuropathy); (6) **biological plausibility** — the extent to which 9/11 studies align with known facts about the biology of the health condition being evaluated (peripheral neuropathy); (7) **coherence** between a causal association and known disease etiology; and (8) **analogy** with an established similar causal relationship [Hill 1965].

Four Bradford Hill criteria — strength of the association, consistency of associations, temporality, and biological gradient — are directly applicable to the evaluation of evidence from high-quality studies identified in the scientific literature review. Each of these four criteria is given significant weight in

35 *See Policy and Procedures*, Section III.C. [NIOSH 2024].
36 *See Policy and Procedures*, Section IV.A. [NIOSH 2024].

synthesizing evidence from high-quality studies found after a review of the scientific literature. In contrast, the Bradford Hill criterion of specificity is given no weight due to the multiple causes that can lead to peripheral neuropathy.

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 the criteria of biological plausibility, coherence, and analogy. To address any concerns regarding incomplete information in the identified studies, the Science Team exercises scientific and medical judgment to refer to additional information from biological, 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.

2. Study Limitations

In synthesizing evidence from high-quality studies, the Science Team considers limitations that may affect the validity of study findings. 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 the association, consistency of associations, temporality, and biological gradient. For example, large effects (i.e., strength of the association) are generally less vulnerable to study biases. Likewise, cross-sectional studies, by design, generally offer little information on temporality compared with longitudinal studies.

3. Study Representativeness

In synthesizing evidence from high-quality studies, the Science Team considers the representativeness of the 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 responder or survivor populations is represented. If the 9/11-exposed 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 of associations such that similar findings observed in multiple populations are generally weighted more heavily than findings observed in a single population.

Due to the interrelatedness of certain Bradford Hill criteria, such as strength of the association, consistency of associations, temporality, and biological

gradient, and consideration of study limitations and representativeness, those respective aspects may be grouped together for synthesizing evidence from the totality of high-quality studies.

4. Categorization of Evidence

After evaluation of the totality of the evidence from high-quality studies, the Science Team categorizes the totality of the evidence into one of the following five categories: (1) Category I — the evidence supports *substantial likelihood* of a causal association; (2) Category II — the evidence supports the *high likelihood* of a causal association; (3) Category III — the evidence supports a *limited likelihood* of a causal association; (4) Category IV — the *evidence does not support* a causal association; or (5) Category V — the evidence is *inadequate* to determine the likelihood of a causal association [NIOSH 2024].

This categorization of the evidence is used by the Administrator to determine if there is sufficient evidence of a causal association to conclude that 9/11 exposures are *substantially likely* to be causally associated with the health condition. If categorization of the evidence demonstrates a high, but not substantial, likelihood of causal association between 9/11 exposures and the health condition (Category II), the Administrator may 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 on such information, coupled with evidence from the evaluation of high-quality studies of the health condition in 9/11-exposed populations, the Science Team will determine whether the totality of the evidence supports a causal association as either Category I (substantial likelihood) or Category II (high likelihood).

B. Summary of Evaluation and Evidence Synthesis

Since the peer-reviewed, published, epidemiologic studies examining the risk of peripheral neuropathy in the 9/11-exposed population identified in the literature search were determined to not have sufficient validity indicators to be considered high-quality studies, there was no evidence available to further evaluate or synthesize.

X. CONCLUSION

The literature search conducted by the Science Team did not identify any high-quality peer-reviewed, published, epidemiologic studies of peripheral neuropathy in 9/11-exposed populations. Therefore, pursuant to the WTC Health Program's *Policy and Procedures* [NIOSH 2024], there was no evidence available for synthesis by the Science Team. The Science Team concluded that the available scientific evidence for a causal association between 9/11 exposure and peripheral neuropathy was inadequate to determine the likelihood of causal association (Category V).[37]

XI. REFERENCES

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37 *See Policy and Procedures*, Section V.E. [NIOSH 2024].

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APPENDIX - TABLES

Table 1a. Information Provided by Current Petitioners and Medical Basis Determination.

Petition Number	Information Provided by Each Petition	Medical Basis[1] (Yes/No)
Petition 032	1. Marmor M, Shao Y, Bhatt DH, et al. [2017]. Paresthesias among community members exposed to the World Trade Center disaster. J Occup Environ Med *59*(4):389–396, https://pmc.ncbi.nlm.nih.gov/articles/PMC5374747/	No
	2. Stecker MM, Yu H, Barlev R, et al. [2016]. Neurologic evaluations of patients exposed to the World Trade Center disaster. J Occup Environ Med *58*(11):1150–1154, https://doi.org/10.1097/JOM.0000000000000889	No
	3. Wilkenfeld M, Fazzari M, Segelnick J, Stecker M [2016]. Neuropathic symptoms in World Trade Center disaster survivors and responders. J Occup Environ Med *58*(1):83–86, https://doi.org/10.1097/JOM.0000000000000619	No
	4. Marmor M, Thawani S, Cotrina ML, et al. [2020]. Case-control study of paresthesia among World Trade Center-exposed community members. J Occup Environ Med *62*(4):307–316, https://doi.org/10.1097/JOM.0000000000001828	Yes
Petition 033	1. Stecker M, Segelnick J, Wilkenfeld M [2014]. Analysis of short-term effects of World Trade Center dust on rat sciatic nerve. J Occup Environ Med *56*(10):1024–1028, https://doi.org/10.1097/JOM.0000000000000296	No
	2. Wilkenfeld M, Fazzari M, Segelnick J, Stecker M [2016]. Neuropathic symptoms in World Trade Center disaster survivors and responders. J Occup Environ Med *58*(1):83–86, https://doi.org/10.1097/JOM.0000000000000619	No
	3. Lioy PJ, Weisel C P, Millette JR, et al. [2002]. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after collapse of the WTC 11 September 2001. Environ Health Perspect *110*(7):703–714, https://pmc.ncbi.nlm.nih.gov/articles/PMC1240917/	No
	4. Chia LG, Chu FL [1984]. Neurological studies on polychlorinated biphenyl (PCB)-poisoned patients. Am J Ind Med *5*(1-2):117–126, https://pubmed.ncbi.nlm.nih.gov/6422742/	Yes

Petition Number	Information Provided by Each Petition	Medical Basis[1] (Yes/No)
Petition 033	5. Thomke F, Jung D, Besser R, et al. [1999]. Increased risk of sensory neuropathy in workers with chloracne after exposure to 2,3,7,8-polychlorinated dioxins and furans. Acta Neurol Scand *100*(1):1–5, https://doi.org/10.1111/j.1600-0404.1999.tb00716.x	Yes
	6. Staff NP, Windebank AJ [2014]. Peripheral neuropathy due to vitamin deficiency, toxins, and medications. Continuum *20*(5):1293–1306, https://doi.org/10.1212/01.CON.0000455880.06675.5a	Yes
	7. Stecker MM, Yu H, Barlev R, et al. [2016]. Neurologic evaluations of patients exposed to the World Trade Center disaster. J Occup Environ Med *58*(11):1150–1154, https://doi.org/10.1097/JOM.0000000000000889	No
	8. Marmor M, Shao Y, Bhatt DH, et al. [2017]. Paresthesias among community members exposed to the World Trade Center disaster. J Occup Environ Med *59*(4):389–396, https://pmc.ncbi.nlm.nih.gov/articles/PMC5374747/	No
	9. Colbeth HL, Zeig-Owens R, Webber MP, et al. [2019]. Post-9/11 peripheral neuropathy symptoms among World Trade Center-exposed firefighters and emergency medical service workers. Int J Environ Res Public Health *16*(10):1727, https://doi.org/10.3390/ijerph16101727	Yes
	10. Marmor M, Thawani S, Cotrina ML, et al. [2020]. Case-control study of paresthesia among World Trade Center-exposed community members. J Occup Environ Med *62*(4):307–316, https://doi.org/10.1097/JOM.0000000000001828	Yes
Petition 068	1. Colbeth HL, Zeig-Owens R, Webber MP, et al. [2019]. Post-9/11 peripheral neuropathy symptoms among World Trade Center-exposed firefighters and emergency medical service workers. Int J Environ Res Public Health *16*(10):1727, https://doi.org/10.3390/ijerph16101727	Yes

1 Medical basis must be scientific in nature and provide a positive association between the September 11, 2001, terrorist attacks and the condition to be added through peer-reviewed, published literature that has not been previously evaluated by the Program. For more information, please see *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions* at https://www.cdc.gov/wtc/policies.html.

Table 1b. — Studies that Provided Sufficient Medical Basis Information and Whether They Met High-Quality Study Criteria, by Petition.

	Petition 032	Petition 033	Petition 068	Met High Quality Study Criteria
Chia and Chu [1984]		☑		
Thomke et al. [1999]		☑		
Staff and Windebank [2014]		☑		
Colbeth et al. [2019]		☑	☑	
Marmor et al. [2020]	☑	☑		

Table 2. Identified studies evaluated by the Science Team from Previous Petitions.

Author	Design	Follow-up	Outcome	Population	Person-years	Characteristics
Stecker et al. [2016]	Cross-sectional	NA	WTC-exposed patients were more likely to have EMG findings consistent with axonal polyneuropathy; some differences were observed in NCS: shorter sural sensory amplitudes, longer sural sensory durations, slower peroneal motor velocity, shorter tibial motor amplitudes, and slower tibial motor velocity.	Responders & Survivors	NA	16 patients (10 responders and 6 survivors) with WTC exposures and 174 non-exposed controls referred for an outpatient EMG.
Wilkenfeld et al. [2016]	Cross-sectional	NA	Persons with WTC exposures were more likely to have clinical neuropathy, defined as an MNSI score of 4 or greater. Neuropathic symptoms were more severe in persons with greater exposure.	Responders & Survivors	NA	Convenience sample, 139 persons with WTC exposures and 116 non-exposed controls; self-reported outcomes not clinically verified; no information on date of symptom onset.
Marmor et al. [2017]	Cross-sectional	NA	Paresthesia were associated with severity of exposure to the WTC dust cloud and working in a job requiring cleaning of WTC dust. There were significantly elevated ORs for paresthesia associated with respiratory symptoms and reduced lung function. Elevated anxiety, depression and PTSD scores also were significantly associated with paresthesia.	WTC EHC	NA	3,141 participants, 1,793 (57%) reported paresthesia; no exclusion of participants with pre-9/11 paresthesia; no clinical confirmation that paresthesia were caused by peripheral neuropathy.

Abbreviations: EMG, electromyogram; MNSI, Michigan Neuropathy Screening Instrument; NA, not applicable; NCS, nerve conduction studies; ORs, odds ratios; WTC, World Trade Center; WTC EHC, World Trade Center Environmental Health Center.

Table 3. Identified studies evaluated by the Science Team from Current Petitions.

Author	Design	Follow-up	Outcome	Population	Person-years	Characteristics
Colbeth et al. [2019]	Cross-sectional	NA	This study found odds of a positive DNS score or self-reported paresthesia (upper and lower paresthesia combined) were significantly increased with 9/11 moderate and high exposures compared with the low exposure group. Multivariable logistic models with an NHANES comparison group found that all three levels of WTC-exposure were significantly associated with DNS (validated four-item questionnaire used for identifying neuropathic symptoms) positive outcomes, after controlling for potential confounders, and the odds increased monotonically with increasing WTC exposure.	FDNY	NA	7,180 responders without conditions known to be linked to paresthesia (i.e., diabetes, cancer or autoimmune disease); 2.2% female; mean age on 9/11 was 39.
Thawani et al. [2019]	Cohort	17 years	This study reported modestly higher risks in time to onset of paresthesia (i.e., incidence) among those working in a job that required cleaning of WTC dust in the workplace, and among those heavily exposed to WTC dust on September 11, 2001, after adjusting for age, race-ethnicity, depression, anxiety, PTSD, and elevated BMI.	WTC EHC	NR	3,411 patients; 50.7% female; median age was 53 (IQR = 44–61) years; incidence rates were estimated using time-to-event survival analyses in which dates of paresthesia onset were inferred.

Author	Design	Follow-up	Outcome	Population	Person-years	Characteristics
Marmor et al. [2020]	Case-Control	NA	Prevalence of self-reported paresthesia in the lower extremities among WTC EHC patients was associated with abnormal findings in clinical and laboratory tests. Patients with self-reported paresthesia (i.e., the “case group”) were more likely to have an abnormal neurologic examination suggestive of peripheral neuropathy compared to the control groups who denied having paresthesia. Cases were also significantly more likely to have reported heavy dust exposure compared to the clinic controls.	WTC EHC	NA	41 cases of paresthesia of the lower extremities (case group), 38 clinic controls, and 20 community controls. Both control groups were free of paresthesia. Cases and controls were frequency matched on sex and age.

Abbreviations: BMI, body mass index; DNS, Diabetic Neuropathy Symptom; FDNY, Fire Department of the City of New York; IQR, interquartile range; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; NR, not reported; PTSD, post-traumatic stress disorder; WTC EHC, World Trade Center Environmental Health Center.

Table 4. Odds ratios (ORs) from multivariable logistic regression of self-reported peripheral neuropathy symptoms and 9/11 exposure categories with low exposure referent.[1] Adapted from Colbeth et al. [2019].

9/11 Exposure OR (95% CI)	DNS positive OR (95% CI)	Paresthesia OR (95% CI)[2]		
		Legs/Feet	Arms/Hands	All
High	1.35 (1.10, 1.65)	1.36 (1.10, 1.87)	1.47 (1.04, 2.08)	2.47 (1.35, 4.53)
Moderate	1.17 (0.99, 1.38)	1.30 (1.00, 1.70)	1.33 (0.99, 1.78)	2.18 (1.27, 3.75)

1 Only those in the non-indicated group were included in these analyses. The non-indicated group included only those without conditions known to be linked to paresthesia.
2 Defined as often or almost continuously reported prickling, pins and needles, burning, aching pain or tenderness in the area shown in the two weeks preceding questionnaire administration.

Abbreviations: CI, confidence interval; DNS, Diabetic Neuropathy Symptom score; OR, odds ratio.

Table 5. Multivariable Cox proportional hazards regression models of time to paresthesia. Adapted from Thawani et al. [2019].

Variable		HR (95% CI)	
		Full data set	Reduced data set[1]
Cleaning Job	Yes vs. No	1.37 (1.11, 1.69)	1.52 (1.24, 1.87)
Covered in Dust	Much vs. Little	1.09 (0.94, 1.27)	1.19 (1.03, 1.38)

1 Excluding study participants reporting occasional paresthesia.

Abbreviations: CI, confidence interval; HR, hazard ratio.