



**BILLING CODE 4163-18-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Centers for Disease Control and Prevention**

**42 CFR Part 88**

**[NIOSH Docket 094]**

**World Trade Center Health Program; Petition 025—Parkinson’s Disease and Parkinsonism, Including Heavy Metal-Induced Parkinsonism; Finding of Insufficient Evidence**

**AGENCY:** Centers for Disease Control and Prevention, HHS.

**ACTION:** Denial of petition for addition of a health condition.

**SUMMARY:** On October 15, 2019, the Administrator of the World Trade Center (WTC) Health Program received a petition (Petition 025) to add “Parkinson’s disease” to the List of WTC-Related Health Conditions (List). Upon reviewing the scientific and medical literature, including information provided by the petitioner, the Administrator has determined that there is insufficient evidence available to support taking further action at this time regarding Parkinson’s disease and parkinsonism, including heavy metal-induced parkinsonism. The Administrator also finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a proposed rule, or to publish a determination not to publish a proposed rule.

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

**ADDRESSES:** Visit the WTC Health Program website at <https://www.cdc.gov/wtc/received.html> to review Petition 025.

**FOR FURTHER INFORMATION CONTACT:** Rachel Weiss, Program Analyst, 1090 Tusculum Avenue, MS: C-48, Cincinnati, OH 45226; telephone (855) 818-1629 (this is a toll-free number); email [NIOSHregs@cdc.gov](mailto:NIOSHregs@cdc.gov).

**SUPPLEMENTARY INFORMATION:**

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**A. WTC Health Program Statutory Authority**

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 (Pub. L. 111-347, as amended by Pub. L. 114-113 and Pub. L. 116-59), added Title XXXIII to the Public Health Service (PHS) Act,<sup>1</sup> establishing the WTC Health Program within the Department of Health and Human Services (HHS). The WTC Health Program provides medical monitoring and treatment benefits for health conditions on the List<sup>2</sup> to eligible firefighters and related personnel, law enforcement officers, and rescue, recovery, and cleanup workers who responded to the September 11, 2001, terrorist attacks in New York City, at the Pentagon, and in Shanksville, Pennsylvania (responders). The Program also

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<sup>1</sup> Title XXXIII of the PHS Act is codified at 42 U.S.C. 300mm to 300mm-61. Those portions of the James Zadroga 9/11 Health and Compensation Act of 2010 found in Titles II and III of Public Law 111-347 do not pertain to the WTC Health Program and are codified elsewhere.

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

provides benefits to eligible persons who were present in the dust or dust cloud on September 11, 2001, or who worked, resided, or attended school, childcare, or adult daycare in the New York City disaster area<sup>3</sup> (survivors).

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

Pursuant to section 3312(a)(6)(B) of the PHS Act, interested parties may petition the Administrator to add a health condition to the List in 42 CFR 88.15. Within 90 days after receipt of a valid petition to add a condition to the List, the Administrator must take one of the following four actions described in section 3312(a)(6)(B) of the PHS Act and § 88.16(a)(2) of the Program regulations: (1) Request a recommendation of the STAC; (2) publish a proposed rule in the *Federal Register* to add such health condition; (3) publish in the *Federal Register* the Administrator's determination not to publish such a proposed rule and the basis for such determination; or (4) publish in the *Federal Register* a determination that insufficient evidence exists to take action under (1) through (3) above.

More information about the WTC Health Program, including the List and the petition process, is available at [www.cdc.gov/wtc/](http://www.cdc.gov/wtc/).

## **B. Procedures for Evaluating a Petition**

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

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

<sup>4</sup> See WTC Health Program [2014], *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions*, May 14, 2014, <http://www.cdc.gov/wtc/pdfs/WTCHPPPpetitionHandlingProcedures14May2014.pdf>.

A valid petition must include sufficient medical basis for the association between the September 11, 2001, terrorist attacks and the health condition to be added. In accordance with WTC Health Program policy, reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11-exposed populations or to clinical case reports of health conditions in WTC responders or survivors may demonstrate the required medical basis.<sup>6</sup> Studies linking 9/11 agents or hazards<sup>7</sup> to the petitioned health condition may also provide sufficient medical basis for a valid petition.

After the Program has determined that a petition is valid, the Administrator must direct the Program to conduct a review of the scientific literature to determine if the available scientific information has the potential to provide a basis for a decision on whether to add the health condition to the List.<sup>8</sup> The literature review is a keyword search of relevant scientific databases intended to identify peer-reviewed, published, epidemiologic studies about the health condition among 9/11-exposed populations. The Program evaluates the scientific quality of each peer-reviewed, published, epidemiologic study of the health condition identified in the literature search; the Program then compiles the scientific results of each study to assess whether a causal relationship between 9/11 exposures and the health condition is supported and evaluates whether the results of the studies are representative of the 9/11-exposed population of responders and survivors. A health condition may be added to the List if peer-reviewed, published, epidemiologic

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<sup>5</sup> See WTC Health Program [2017], *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*, February 14, 2017, [https://www.cdc.gov/wtc/pdfs/policies/WTCHP\\_PP\\_Adding\\_NonCancers\\_14\\_February\\_2017-508.pdf](https://www.cdc.gov/wtc/pdfs/policies/WTCHP_PP_Adding_NonCancers_14_February_2017-508.pdf).

<sup>6</sup> See *supra* note 4.

<sup>7</sup> 9/11 agents are chemical, physical, biological, or other hazards reported in a published, peer-reviewed exposure assessment study of responders, recovery workers, or survivors who were present in the New York City disaster area, or at the Pentagon site, or the Shanksville, Pennsylvania site, as those locations are defined in 42 CFR 88.1, as well as those hazards not identified in a published, peer-reviewed exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. See WTC Health Program [2018], *Development of the Inventory of 9/11 Agents*, July 17, 2018, [https://www.cdc.gov/ResearchGateway/Content/pdfs/Development\\_of\\_the\\_Inventory\\_of\\_9-11\\_Agents\\_20180717.pdf](https://www.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf).

<sup>8</sup> See *supra* note 5.

studies provide support that the health condition is substantially likely<sup>9</sup> to be causally associated with 9/11 exposures. If the evaluation of evidence provided in peer-reviewed, published, epidemiologic studies of the health condition in 9/11 populations demonstrates a high, but not substantial, likelihood of a causal association between the 9/11 exposures and the health condition, then the Administrator may consider additional highly relevant scientific evidence regarding exposures to 9/11 agents from sources using non-9/11-exposed populations. If that additional assessment establishes that the health condition is substantially likely to be causally associated with 9/11 exposures among 9/11-exposed populations, the health condition may be added to the List.

More information about the WTC Health Program, including the List and the petition process, is available at [www.cdc.gov/wtc/](http://www.cdc.gov/wtc/).

### **C. Petition 025**

On October 15, 2019, the Administrator received a petition (Petition 025) requesting the addition of “Parkinson’s disease” to the List.<sup>10</sup> The Program has determined that the scope of the Petition 025 review should include not only “Parkinson’s disease” but also “parkinsonism, including heavy metal-induced parkinsonism,”<sup>11</sup> because the references provided in the petition address the association between copper, iron, and manganese and the health condition, as described below.

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<sup>9</sup> The “substantially likely” standard is met when the scientific evidence, taken as a whole, demonstrates a strong relationship between the 9/11 exposures and the health condition.

<sup>10</sup> See Petition 025, *WTC Health Program: Petitions Received*, <http://www.cdc.gov/wtc/received.html>.

<sup>11</sup> “The general term ‘Parkinsonism’ refers to a category of neurological diseases exhibiting disturbance in the dopamine systems of the basal ganglia, which leads to the symptoms characterizing the disease: Tremors, slowness of movement, and stiffness. Classic (idiopathic) Parkinson’s disease is the most common and treatable form of parkinsonism; non-idiopathic types are considered atypical and referred to by the more general term “‘parkinsonism.’ One type of atypical parkinsonism, manganese-induced parkinsonism, has been found to be caused by elevated and prolonged exposure to manganese.” *World Trade Center Health Program; Petitions 016 and 017—Parkinson’s Disease and Parkinsonism, Including Manganese-Induced Parkinsonism; Finding of Insufficient Evidence*, 82 FR 32312 at 32313, July 13, 2017.

The petition's validity was established by references to four web articles<sup>12</sup> which, in turn, referenced six peer-reviewed, published epidemiologic studies and literature reviews identifying a positive association between 9/11 agents and Parkinson's disease and/or parkinsonism (although none of the studies were conducted in the 9/11-exposed population). A quote provided in the petition is attributed to a seventh peer-reviewed, published epidemiologic study. Because the web articles reference scientific sources identifying a positive association between 9/11 agents and the petitioned condition, the petition provides the necessary medical basis to require the Administrator to conduct an evaluation of the petition. The referenced studies and literature reviews each individually establishing a medical basis are as follows:

- *Heavy Metals and the Etiology of Parkinson's Disease and Other Movement Disorders*, by Montgomery [1994],<sup>13</sup> is a peer-reviewed, published literature review discussing the role of heavy metals (iron and manganese) in Parkinson's disease and speculating on possible mechanisms of pathogenesis.
- *Metals, Oxidative Stress and Neurodegenerative Disorders*, by Jomova *et al.* [2010],<sup>14</sup> is a peer-reviewed, published review article discussing the role of iron, copper, and zinc in the oxidative stress-related etiology of Parkinson's disease (the theory that heavy metals cause oxidative stress, which in turn leads to the neurodegeneration that characterizes Parkinson's disease).

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<sup>12</sup> Adams C. [2018], *Parkinson's Disease Linked to Exposure to Heavy Metals*, <https://www.realnatural.org/parkinsons-disease-linked-to-exposure-to-heavy-metals/>; The Parkinson's Plan [2018], *Heavy Metals, Neurotoxins, and Parkinson's Disease*, <https://www.theparkinsonsplan.com/blog/heavy-metals-and-parkinsons-disease/>; Iowa State University News Service [2019], *Researchers Explore Link Between Metal Exposure and Parkinson's Symptoms*, <https://www.news.iastate.edu/news/2019/03/12/manganeseparkinsons>; Wilson L [2019], *Parkinson's Disease*, <https://drlwilson.com/Articles/PARKINSON.htm>.

<sup>13</sup> Montgomery EB [1994], *Heavy Metals and the Etiology of Parkinson's Disease and Other Movement Disorders*, *Toxicology* 97(1), [https://doi.org/10.1016/0300-483X\(94\)02962-T](https://doi.org/10.1016/0300-483X(94)02962-T).

<sup>14</sup> Jomova K, Vondrakova D, Lawson M, Valko M [2010], *Metals, Oxidative Stress and Neurodegenerative Disorders*, *Mol Cell Biochem* 345(1-2), 91-104.

- *Metal Emissions and Urban Incident Parkinson Disease: A Community Health Study of Medicare Beneficiaries by Using Geographic Information Systems*, by Willis *et al.* [2010],<sup>15</sup> is a peer-reviewed, published epidemiologic study demonstrating increased Parkinson's disease incidence in urban counties with high levels of environmental copper or manganese.
- *Association of Parkinson's Disease with Altered Serum Levels of Lead and Transition Metals among South Indian Subjects*, by Kumudini *et al.* [2014],<sup>16</sup> is a peer-reviewed, published epidemiologic (case-control) study demonstrating the positive association of Parkinson's disease with plasma levels of iron and copper in urban and rural populations in India. The authors speculate that increased iron levels induce oxidative stress which leads to Parkinson's disease.
- *A Revised Picture of the Cu (II)–  $\alpha$ -Synuclein Complex: The Role of N-Terminal Acetylation*, by Moriarty *et al.* [2014],<sup>17</sup> is a peer-reviewed, published *in vitro* study suggesting new avenues of investigation into copper-mediated neurodegeneration in Parkinson's disease pathology.
- *Inflammasomes: An Emerging Mechanism Translating Environmental Toxicant Exposure into Neuroinflammation in Parkinson's Disease*, by Anderson *et al.* [2018],<sup>18</sup> is a peer-reviewed, published literature review positing that exposure to heavy metals, which are known to cause cellular stress, may do so by triggering intracellular

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<sup>15</sup> Willis AW, Evanoff BA, Lian M, Galarza A, Wegrzyn A, Schootman M, Racette BA [2010], *Metal Emissions and Urban Incident Parkinson Disease: A Community Health Study of Medicare Beneficiaries by Using Geographic Information Systems*, *Am J Epidemiol* 172(12):1357-1363.

<sup>16</sup> Kumudini N, Uma A, Devi YP, Naushad SM, Mridula R, Borgohain R, Kutala VK [2014], *Association of Parkinson's Disease with Altered Serum Levels of Lead and Transition Metals among South Indian Subjects*, *Indian J Biochem Biophys* 51(2):121-126.

<sup>17</sup> Moriarty GM, Minetti CA, Remeta DP, Baum J [2014], *A Revised Picture of the Cu (II)–  $\alpha$ -Synuclein Complex: The Role of N-Terminal Acetylation*, *Biochemistry* 53(17), 2815-2817.

<sup>18</sup> Anderson FL, Coffey MM, Berwin BL, Havrda MC [2018], *Inflammasomes: An Emerging Mechanism Translating Environmental Toxicant Exposure into Neuroinflammation in Parkinson's Disease*, *Toxicol Sci* 166(1), 3-15.

inflammasomes (cytosolic assemblies of proteins) which in turn lead to neurodegeneration and Parkinson's disease.

- *Manganese Promotes the Aggregation and Prion-Like Cell-to-Cell Exosomal Transmission of  $\alpha$ -Synuclein*, by Harischandra *et al.* [2019],<sup>19</sup> is a peer-reviewed, published experimental study demonstrating in cell cultures and animal models that manganese exposure promotes the pathological propagation of  $\alpha$ -synuclein (a neuronal protein found in the brain) leading to Parkinson's disease through neuroinflammation and neurodegeneration.

These seven studies suggest a potential association between exposure to 9/11 agents (specifically copper, iron, and manganese) and Parkinson's disease and parkinsonism, including heavy metal-induced parkinsonism, and thus provided a sufficient medical basis to consider the submission a valid petition. Because the medical basis provided by the petitioner included studies concerning parkinsonism induced by copper, iron, and manganese, the Administrator determined that the petitioner requested the addition of both Parkinson's disease and parkinsonism, including heavy metal-induced parkinsonism.

#### **D. Review of Scientific and Medical Information and Administrator Determination**

In response to Petition 025, and pursuant to the Program policy on the addition of non-cancer health conditions to the List, the Program conducted a review of the scientific literature on Parkinson's disease and parkinsonism, including heavy metal-induced

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<sup>19</sup> Harischandra DS, Rokad D, Neal ML, Ghaisas S, Manne S, Sarkar S, Panicker N, Zenitsky G, Jin H, Lewis M, Huang X, Anantharam V, Kanthasamy A, Kanthasamy AG [2019], *Manganese Promotes the Aggregation and Prion-Like Cell-to-Cell Exosomal Transmission of  $\alpha$ -Synuclein*, *Sci Signal* 12(572).

parkinsonism, to identify peer-reviewed, published, epidemiologic studies of the health condition in the 9/11-exposed population.<sup>20</sup>

Neither the references provided in the petitions, including those described above, nor the literature search conducted by the Program identified any peer-reviewed, published, epidemiologic studies of either Parkinson's disease or parkinsonism, including heavy metal-induced parkinsonism, in 9/11-exposed populations. Pursuant to the WTC Health Program's policy on the evaluation of petitions,<sup>21</sup> since no peer-reviewed, published, epidemiologic studies of Parkinson's disease or parkinsonism, including heavy metal-induced parkinsonism, in 9/11 populations were identified, the Program was unable to conduct an evaluation of scientific evidence to determine the likelihood of a causal association between 9/11 exposures and the petitioned health conditions.

**E. Administrator's Final Decision on Whether to Propose the Addition of Parkinson's Disease and Parkinsonism, Including Heavy Metal-Induced Parkinsonism, to the List**

Pursuant to PHS Act, sec. 3312(a)(6)(B)(iv) and 42 CFR 88.16(a)(2)(iv), the Administrator has determined that insufficient evidence is available to take further action at this time, including proposing the addition of Parkinson's disease and parkinsonism, including heavy metal-induced parkinsonism, to the List (pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.16(a)(2)(ii)) or publishing a determination not to

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<sup>20</sup> Databases searched include: CINAHL, Embase, NIOSHTIC-2, ProQuest Health & Safety, PsycINFO, PubMed, Scopus, Toxicology Abstracts, TOXLINE, and the WTC Research Compendium Endnote Database. Keywords/phrases used to conduct the search include: World Trade Center; WTC; September 11; parkinsonian disorders; parkinson\*; manganism; supranuclear palsy, progressive; progressive supranuclear palsy; multiple system atrophy; multiple system atrophy; Lewy body disease; dementia with Lewy bodies; corticobasal degeneration; hypokinesia; bradykinesia; tremor; tremors; slow movement; stiffness; muscle rigidity; rigidity; masked face; micrographia; monotonous speech; loss of postural reflex; cock-walk gait; asymmetric dystonia; levodopa; basal ganglia; and basal ganglia nuclei. The literature search was conducted in English-language journals on December 27, 2019.

<sup>21</sup> See *supra* note 5.

publish a proposed rule in the *Federal Register* (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR 88.16(a)(2)(iii)). The Administrator has also determined that requesting a recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.16(a)(2)(i)) is unwarranted.

For the reasons discussed above, the Petition 025 request to add Parkinson's disease and parkinsonism, including heavy metal-induced parkinsonism, to the List of WTC-Related Health Conditions is denied.

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

The Secretary, HHS, or his designee, the Director, Centers for Disease Control and Prevention (CDC) and Administrator, Agency for Toxic Substances and Disease Registry (ATSDR), authorized the undersigned, the Administrator of the WTC Health Program, to sign and submit the document to the Office of the Federal Register for publication as an official document of the WTC Health Program. Robert Redfield M.D., Director, CDC, and Administrator, ATSDR, approved this document for publication on February 3, 2020.

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

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