DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 88

[NIOSH Docket 094]

World Trade Center Health Program; Petitions 016 and 017—Parkinson's Disease and Parkinsonism, Including Manganese-Induced Parkinsonism; Finding of Insufficient Evidence

AGENCY: Centers for Disease Control and Prevention, HHS.

ACTION: Denial of petitions for addition of health conditions.

SUMMARY: On February 22, 2017, the Administrator of the World Trade Center (WTC) Health Program received a petition (Petition 016) to add Parkinson's disease and parkinsonism, including manganese-induced parkinsonism, to the List of WTC-Related Health Conditions (List). On May 10, 2017, the Administrator received a second petition (Petition 017) to add the same health conditions to the List. Upon reviewing the scientific and medical literature, including information provided by the two petitioners, the Administrator has determined that the available evidence does not have the potential to provide a basis for a decision on whether to add Parkinson's disease and/or parkinsonism, including manganese-induced parkinsonism, to the List. The Administrator also finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a

proposed rule, or to publish a determination not to publish a proposed rule.

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

FOR FURTHER INFORMATION CONTACT: Rachel Weiss, Program Analyst, 1090 Tusculum Avenue, MS: C-46, Cincinnati, OH 45226; telephone (855) 818-1629 (this is a toll-free number); email *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),

added Title XXXIII to the Public Health Service (PHS) Act,[1] establishing the WTC Health Program within the Department of Health and Human Services (HHS). The WTC Health Program provides medical monitoring and treatment benefits 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), and 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 (survivors).

All references to the Administrator of the WTC Health Program (Administrator) in this notice 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 (2017). Within 90 days after receipt of a 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 42 CFR 88.16(a)(2): (1) Request a recommendation of the STAC; (2) publish a proposed rule in the *Federal Register* to add such

[1] 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.

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. In accordance with 42 CFR 88.16(a)(4), the Administrator may consider more than one petition simultaneously when the petitions propose the addition of the same health condition(s) and the required *Federal Register* notices may respond to more than one petition.

In addition to the regulatory provisions, the WTC Health Program has developed policies to guide the review of submissions and petitions,[2] as well as the analysis of evidence supporting the potential addition of a non-cancer health condition to the List.[3] In accordance with the aforementioned non-cancer health condition addition policy, the Administrator directs the WTC Health 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. The literature review includes a search for peer-reviewed, published, epidemiologic studies (including direct observational studies in the case of health conditions such as injuries) about the health condition among 9/11-exposed populations. The Program evaluates the scientific

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[2] *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, *http://www.cdc.gov/wtc/pdfs/WTCHPPPPetitionHandlingProcedures14May2014.pdf*.

[3] *See* WTC Health Program [2017], *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*, February 14, *https://www.cdc.gov/wtc/pdfs/WTCHP_PP_Adding_NonCancers_14_February_2017.pdf*.

quality limitations 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 studies provide support that the health condition is substantially likely[4] 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[5] 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.

B. Petition 016 and Petition 017

[4] 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.

[5] 9/11 agents are chemical, physical, biological, or other agents or hazards reported in a published, peer-reviewed exposure assessment study of responders or survivors who were present in the New York City disaster area, at the Pentagon site, or at the Shanksville, Pennsylvania site, as those locations are defined in 42 CFR 88.1.

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.[6] Studies linking 9/11 agents to the petitioned health condition may also provide sufficient medical basis for a valid petition.

On February 22, 2017, the Administrator received a petition (Petition 016) from a WTC responder who worked at Ground Zero, requesting the addition of "young onset Parkinson Disease"[7] and "Parkinsonia Syndrome" to the List. The petition included eight peer-reviewed, published studies and reviews of studies of parkinsonism associated with manganese exposure in non-9/11-exposed populations and laboratory animals, and mechanistic studies of manganese-induced parkinsonism, discussed below.[8] The Program noted the various terms used to describe the health condition in the petition and the references included with the petition. 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

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[6] *See supra* note 2.
[7] The diagnosis of young-onset Parkinson's disease is the same as typical Parkinson's disease, except for the age of the patient.
[8] *See* Petition 016, WTC Health Program: Petitions Received, *http://www.cdc.gov/wtc/received.html*.

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.[9] The term "Parkinsonia Syndrome," used by the petitioner, was likely intended to refer to "Parkinsonian syndrome," a less-commonly used term for atypical parkinsonism.

The first of the eight peer-reviewed, published studies provided in Petition 016, reference 1, "Manganese-Induced Parkinsonism Is Not Idiopathic Parkinson's Disease: Environmental and Genetic Evidence" by Guilarte *et al*. [2015],[10] is a review of various peer-reviewed and published epidemiologic and animal studies highlighting the difference between manganese-induced parkinsonism and Parkinson's disease. Reference 2, "Manganese-Induced Parkinsonism and Parkinson's Disease: Shared and Distinguishable Features" by Kwakye *et al*. [2015],[11] is also a review of peer-reviewed and published epidemiologic, animal, and mechanistic studies comparing characteristics of manganese-induced parkinsonism and Parkinson's disease. Reference 3, "Inducible Nitric Oxide Synthase Gene Methylation and

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[9] *See* Kwakye GF, Paoliello MMB, Mukhopadhyay S, *et al*. [2015], *Manganese-Induced Parkinsonism and Parkinson's Disease: Shared and Distinguishable Features*, Int J Environ Res Public Health 12(7):7519-7540).
[10] Guilarte TR, Gonzales KK [2015], *Manganese-Induced Parkinsonism is Not Idiopathic Parkinson's Disease: Environmental and Genetic Evidence*, Toxicol Sci 146(2):204-212.
[11] *Supra* note 9.

Parkinsonism in Manganese-Exposed Welders" by Searles *et al*. [2015],[12] is an epidemiologic study examining gene methylation of inducible nitric oxide synthase, an enzyme involved in inflammation, among manganese-exposed welders. Reference 4, "α-Synuclein Protects Against Manganese Neurotoxic Insult During the Early Stages of Exposure in a Dopaminergic Cell Model of Parkinson's Disease" by Harischandra *et al*. [2015],[13] is an ex vivo laboratory study in rat cell lines exploring the effects of α-synuclein, a protein found in the brain, on manganese-induced dopaminergic neurotoxicity. Reference 5, "SLC30A10 is a Cell Surface-Localized Manganese Efflux Transporter, and Parkinsonism-Causing Mutations Block its Intracellular Trafficking and Efflux Activity" by Leyva-Illades *et al*. [2014],[14] is a mechanistic and functional cell culture study looking at the role of interactions between genetic and environmental factors in the development of parkinsonism. Reference 6, "Correlation Between the Biochemical Pathways Altered by Mutated Parkinson-Related Genes and Chronic Exposure to Manganese" by Roth [2014],[15] is a review of peer-reviewed, published studies describing genes involved in the development of parkinsonism and illustrating how the proposed mechanism of each gene may relate to the onset and severity of

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[12] Searles Nielsen S, Checkoway H, Criswell SR, *et al*. [2015], *Inducible Nitric Oxide Synthase Gene Methylation and Parkinsonism in Manganese-Exposed Welders*, Parkinsonism. Relat Disord 21(4):355-60.
[13] Harischandra DS, Jin H, Anantharam V, *et al*. [2015], *α-Synuclein Protects Against Manganese Neurotoxic Insult During the Early Stages of Exposure in a Dopaminergic Cell Model of Parkinson's Disease*, Toxicol Sci 143(2):454-468.
[14] Leyva-Illades D, Chen P, Zogzas CE, *et al*. [2014], *SLC30A10 Is a Cell Surface-Localized Manganese Efflux Transporter, and Parkinsonism-Causing Mutations Block Its Intracellular Trafficking and Efflux Activity*, J Neurosci 34(42):14079-14095.
[15] Roth, JA [2014], *Correlation Between the Biochemical Pathways Altered by Mutated Parkinson-Related Genes and Chronic Exposure to Manganese*, Neurotoxicology Sep;44:314-325.

manganese toxicity. Reference 7, "Manganese-Induced Atypical Parkinsonism is Associated with Altered Basal Ganglia Activity and Changes in Tissue Levels of Monoamines in the Rat" by Bouabid *et al*. [2014],[16] is a study on changes to motor and non-motor functions and behavior, similar to those observed in parkinsonism, in manganese-exposed rats. Finally, reference 8, "Neurofunctional Dopaminergic Impairment in Elderly After Lifetime Exposure to Manganese" by Lucchini *et al*. [2014],[17] is an epidemiologic study of the effects of manganese exposure due to emissions from nearby ferroalloy plants on the neurocognitive and motor functions of elderly study participants.

The eight references offered as medical basis for Petition 016 suggested a potential association between exposure to the 9/11 agent manganese and manganese-induced parkinsonism and Parkinson's disease and established a sufficient medical basis to consider the submission a valid petition for manganese-induced parkinsonism. Although the petitioner requested the addition of "young onset Parkinson Disease" and "Parkinsonia Syndrome," the medical basis provided by the petitioner primarily included studies concerning manganese-induced parkinsonism; therefore, the Administrator determined that the petitioner requested the addition of both Parkinson's disease and parkinsonism, including manganese-induced parkinsonism.

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[16] Bouabid S, Delaville C, De Deurwaerdère P, *et al*. [2014], *Manganese-Induced Atypical Parkinsonism Is Associated With Altered Basal Ganglia Activity and Changes in Tissue Levels of Monoamines in the Rat*, PLoS ONE 9(6):e98952.
[17] Lucchini RG, Guazzetti S, Zoni S, *et al*. [2014], *Neurofunctional Dopaminergic Impairment in Elderly After Lifetime Exposure to Manganese*, Neurotoxicology 0:309-17.

On May 10, 2017, the Administrator received a petition from a WTC survivor (Petition 017), requesting the addition of "Parkinson's Disease" to the List. The petition referenced five peer-reviewed, published, epidemiologic studies of heavy metal exposure, including manganese, and Parkinson's disease or parkinsonism in non-9/11-exposed populations.[18]

The first of the five peer-reviewed, published, epidemiologic studies provided in Petition 017, reference 1, "Increased Risk of Parkinsonism Associated With Welding Exposure" by Racette *et al*. [2012],[19] examined the prevalence and clinical characteristics of parkinsonism among workers exposed to welding fumes. Reference 2, "Inducible Nitric Oxide Synthase Gene Methylation and Parkinsonism in Manganese-Exposed Welders" by Searles *et al*. [2015],[20] was also cited as reference 3 in Petition 016, as discussed above. Reference 3, "Multiple Risk Factors for Parkinson's Disease" by Gorell *et al*. [2004],[21] evaluated the contribution of various occupational, lifestyle, and genetic risk factors, including manganese exposure, to the development of Parkinson's disease. Reference 4, "Occupational Exposure to Manganese, Copper, Lead, Iron, Mercury and Zinc and the Risk of Parkinson's Disease" by Gorell *et al*. [1999],[22] assessed the association between a variety of heavy metals and Parkinson's

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[18] *See* Petition 017, WTC Health Program: Petitions Received, *http://www.cdc.gov/wtc/received.html*.
[19] Racette BA, *et al*. [2012], *Increased Risk of Parkinsonism Associated With Welding Exposure*, Neurotoxicology 33(5):1356-1361.
[20] *Supra* note 12.
[21] Gorell JM, *et al*. [2004], *Multiple Risk Factors for Parkinson's Disease*, J Neurol Sci 217(2):169-174.
[22] Gorell JM, *et al*. [1999], *Occupational Exposure to Manganese, Copper, Lead, Iron, Mercury and Zinc and the Risk of Parkinson's Disease*, Neurotoxicology 20(2-3):239-247.

disease. Finally, reference 5, "Whole-Body Lifetime Occupational Lead Exposure and Risk of Parkinson's Disease" by Coon *et al.* [2006],[23] evaluated the role of chronic lead exposure among individuals with Parkinson's disease.

These five studies suggested a potential association between exposure to known 9/11 agents and Parkinson's disease and parkinsonism, including manganese-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 both Parkinson's disease and manganese-induced parkinsonism, the Administrator determined that the petitioner requested the addition of both Parkinson's disease and manganese-induced parkinsonism.

Since the Administrator determined that the scope of both Petition 016 and Petition 017 include requests for the addition of Parkinson's disease and parkinsonism, including manganese-induced parkinsonism, the Administrator decided to exercise his discretion, as permitted by 42 CFR 88.16(a)(4), to combine consideration of the petitions and issue a single *Federal Register* notice.

C. Review of Scientific and Medical Information and Administrator Determination

[23] Coon S, Stark A, Peterson E, *et al.* [2006], *Whole-Body Lifetime Occupational Lead Exposure and Risk of Parkinson's Disease*, Environ Health Perspect Dec;114(12):1872-6.

In response to Petition 016 and Petition 017, and pursuant to the Program policy on the addition of non-cancer health conditions to the List,[24] the Program conducted reviews of the scientific literature on Parkinson's disease and parkinsonism, including manganese-induced parkinsonism.[25]

Neither the references provided in the petitions nor the literature search conducted by the Program identified any peer-reviewed, published, epidemiologic studies of either Parkinson's disease or parkinsonism, including manganese-induced parkinsonism, in 9/11-exposed populations. Since no peer-reviewed, published, epidemiologic studies of Parkinson's disease or parkinsonism, including manganese-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.

D. Administrator's Final Decision on Whether to Propose the Addition of Parkinson's Disease and/or Manganese-Induced Parkinsonism to the List

Because no peer-reviewed, published, epidemiologic studies of Parkinson's disease or parkinsonism, including manganese-induced parkinsonism, in 9/11 populations were identified, the Administrator has determined that insufficient evidence is

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[24] *Supra* note 3.
[25] Databases searched include: Embase, NIOSHTIC-2, ProQuest Health & Safety, PsycINFO, PubMed, Scopus, Toxicology Abstracts, and TOXLINE.

available to take further action at this time, including either proposing the addition of Parkinson's disease or parkinsonism, including manganese-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 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 016 and Petition 017 requests to add Parkinson's disease and/or parkinsonism, including manganese-induced parkinsonism, to the List of WTC-Related Health Conditions are denied.

E. 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. Anne Schuchat, M.D., Acting Director, CDC, and Acting Administrator, ATSDR, approved this document for publication on July 6, 2017.

John Howard,

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

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