



## **Policy and Procedures for Adding Non-Cancer Health Conditions to the List of WTC-Related Health Conditions**

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**Note for May 1, 2019 Update:** This version incorporates non-substantive changes to update the definition of “9/11 agents” and describe the Inventory of 9/11 agents as established in the “Development of the Inventory of 9/11 Agents,” published July 17, 2018.

**Note for September 11, 2019 Update:** This version incorporates non-substantive changes to describe the process by which the Science Team evaluates the quality of scientific evidence, adds descriptions of the select Bradford Hill criteria used by the Science Team to evaluate causality, and provides an additional bibliographic reference.

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### **I. Authority**

The *Policy and Procedures for Adding Non-Cancer Health Conditions to the List of WTC-Related Health Conditions* is based on the James Zadroga 9/11 Health and Compensation Act of 2010 (“Act”)<sup>1</sup> and the World Trade Center (WTC) Health Program regulations.<sup>2</sup>

### **II. Initiation of the Process for Adding a Health Condition**

A health condition may only be added to the List of WTC-Related Health Conditions (List) by rulemaking.<sup>3</sup> The Act provides two pathways to initiate the process of deciding

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<sup>1</sup> Pub. L. 111-347, as amended by Pub. L. 114-113, codified at 42 U.S.C. §§ 300mm to 300mm-61.

<sup>2</sup> 42 C.F.R. Part 88.

<sup>3</sup> See generally 42 U.S.C. § 300mm-22(a)(6); 42 C.F.R. § 88.16; the revised List is promulgated at 42 C.F.R. § 88.15.

whether to propose adding a health condition to the List—at the discretion of the Administrator and by a petition request.

**A. Administrator’s Discretion**

The Administrator of the WTC Health Program may initiate the process of promulgating a proposed rule to add a health condition to the List at the Administrator’s discretion.<sup>4</sup>

**B. Petition Request**

Upon receipt of a valid petition<sup>5</sup> requesting that a health condition be added to the List, the Administrator of the WTC Health Program must initiate the process of evaluating whether to add a health condition to the List and take one of the four actions described in Section IV of the Policy and Procedures within 90 days of receipt of the valid petition.<sup>6</sup>

**III. Science Team Evaluation Process**

**A. Petition Review and Identification of Health Condition for Evaluation**

Once it has been determined that the Administrator has received a valid petition, the WTC Health Program’s Associate Director for Science (ADS) and the ADS’ Science Team will review the information provided by the petitioner, including the medical basis provided in the petition, to determine the specific health condition that will be the subject of the scientific evidence evaluation.

**Note:** When necessary, the Administrator will ensure that discipline-specific, subject matter experts within the WTC Health Program, NIOSH and/or other Federal science agencies are available for consultation about the definitions of health conditions, analysis of scientific evidence, and the assessment of petitions to add health conditions.

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<sup>4</sup> 42 U.S.C. § 300mm-22(a)(6)(A).

<sup>5</sup> When the Administrator receives a written submission from an interested party to add a health condition to the List, the Administrator follows the steps outlined in “Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions” (available at <http://www.cdc.gov/wtc/policies.html>) and determines whether the submission meets the requirements for a valid petition specified in 42 C.F.R. § 88.16(a)(1).

<sup>6</sup> 42 U.S.C. § 300mm-22(a)(6); 42 C.F.R. § 88.16(a)(2).

## **B. Evaluation of Science Evidence<sup>7</sup>**

### **1. Science Evidence from Studies of 9/11-Exposed Populations**

#### **a. Identification of Studies**

The WTC Health Program ADS' Science Team will first conduct a scientific literature review to identify all peer-reviewed,<sup>8</sup> published,<sup>9</sup> epidemiologic studies<sup>10</sup> of the health condition among 9/11-exposed populations.

#### **b. Evaluation of Scientific Evidence**

##### **(1) Science Quality Evaluation of Each Study**

The Science Team will summarize each peer-reviewed, published, epidemiologic study and evaluate the scientific quality of each study, including, but not necessarily limited to, the following validity<sup>11</sup> indicators:

- (a) Possible confounders are identified and adequately corrected for;
- (b) Recruitment bias is adequately addressed;
- (c) All aspects of exposure are completely considered;

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<sup>7</sup> The steps described in this section are applicable whether the Science Team's evaluation is initiated in response to a valid petition or at the Administrator's discretion.

<sup>8</sup> The Administrator has determined that articles and reports published in CDC's *Morbidity and Mortality Weekly Report* (MMWR) are also eligible for review for their potential to provide a basis for deciding whether to propose adding a condition to the List. MMWR publications undergo a review process that has been independently evaluated and found to be similar or equivalent to peer review.

<sup>9</sup> Published studies also include those published online ahead of print.

<sup>10</sup> Epidemiologic studies include "descriptive epidemiologic studies" which describe the "what, who, where, when and why/how of a situation," as well as analytic epidemiologic studies which involve the use of a comparison group. See Centers for Disease Control and Prevention, HHS, *Principles of Epidemiology in Public Health Practice* (3rd ed. 2012), at 1-46. The WTC Health Program reviews these epidemiologic studies to determine if they identify any causal associations between exposures and health outcomes with the potential to provide a basis for deciding whether to propose adding a condition to the List.

<sup>11</sup> Validity is defined as the lack of bias and confounding. Bias is an error committed by the investigator in the design or conduct of a study that leads to a false association between the exposure and the study outcome. See Aschengrau A and Seage GR [2018], *Essentials of Epidemiology in Public Health*, 4th Edition, (Burlington, MA: Jones & Bartlett), 528.

- (d) Blinding of exposure allocation from assessors and other exposure assessment methods lead to reliable classification;
- (e) Inadequacies of the control population(s) are addressed;
- (f) Results are not selectively reported; and
- (g) Any conflicts of interest are identified and reported.

## **(2) Application of Bradford Hill Criteria**

The Science Team will compile the scientific findings from the available peer-reviewed, published, epidemiologic studies<sup>12</sup> and apply the following select Bradford Hill criteria<sup>13</sup> to the compiled findings, if the studies are of sufficient quality to allow such an analysis:

- (a) Strength of the association between a 9/11 exposure and the health condition under consideration<sup>14</sup> and precision of the risk estimate;<sup>15</sup>
- (b) Consistency of the association across multiple studies;<sup>16</sup>

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<sup>12</sup> Injury studies are instead evaluated for onsite occurrence, presence of known causative factors, and quality. See generally Baker SP, O'Neill, Ginsburg MJ, and Guohua L, [1992], *The Injury Fact Book* 2<sup>nd</sup> ed. New York: Oxford University Press (regarding causation); see also National Academies Press [1985], *Injury in America: A Continuing public health problem*. The injury studies provide information about injuries recorded in contemporaneous medical records and studies which when combined with known hazards and known connections between those hazards and injury may demonstrate concordance of an injury and 9/11 exposures, allowing the Administrator to evaluate whether there is support for a causal association between those exposures and the injury.

<sup>13</sup> See Aschengrau and Seage, *supra* note 11.

<sup>14</sup> It is generally thought that strong associations are more likely to be causal than weak associations; however, a weak association does not rule out a causal relationship. See Aschengrau and Seage, *supra* note 11.

<sup>15</sup> Precision of the risk estimate describes the uncertainty inherent in estimating the strength of association (the effect size) between exposure and health effect from observational data. It is expressed as a confidence interval illustrating a range of values that contains the true effect size. A narrow confidence interval indicates a more precise measure of the effect size and a wider interval indicates greater uncertainty. While precision is not a Bradford Hill criterion, the Science Team takes it into consideration to evaluate the existence of random error in a study. See Aschengrau and Seage, *supra* note 11.

<sup>16</sup> Consistent findings are demonstrated when they have been repeatedly reported by multiple studies. See Aschengrau and Seage, *supra* note 11.

**Note:** If only a single study is available for evaluation, the consistency of association cannot be evaluated. Therefore, in such a case, more emphasis will be placed on evaluating the strength of the association and the precision of the risk estimate.

- (c) Biological gradient, or exposure-response, relationships between 9/11 exposures and the health condition under consideration;<sup>17</sup> and
- (d) Plausibility of the studies and coherence of the study findings with known facts about the biology of the health condition under consideration.<sup>18</sup>

### **(3) Representativeness Evaluation**

The Science Team will evaluate whether the results of the studies represent both 9/11 responder and survivor populations or, if only a subgroup of 9/11-exposed populations is represented, whether the results can reasonably be extrapolated to the complete 9/11-exposed population of responders and survivors.

### **(c) Scientific Evidence Evaluation Summary**

The WTC Health Program ADS will summarize the Science Team's evaluation of the scientific evidence and advise the Administrator whether the health condition is substantially likely to be causally associated with 9/11 exposures in 9/11-exposed populations.<sup>19</sup>

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<sup>17</sup> Studies establish an exposure-response relationship by demonstrating that increases in exposure (i.e., exposures of greater intensity and/or longer duration) are associated with a greater incidence of disease. A thorough evaluation of exposure-response requires analysis of multiple levels of exposure such that the investigator can demonstrate that the risk increases with increasing levels of exposure. See Aschengrau and Seage, *supra* note 11.

<sup>18</sup> Study findings demonstrate a basis in scientific theory that supports the relationship between the exposure and the health effect, and do not conflict with known facts about the biology of the health condition. See Aschengrau and Seage, *supra* note 11.

<sup>19</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, *i.e.*, meets Bradford Hill criteria after considering the science quality evaluation and representativeness.

**(1) Evidence Supports Causal Association**

If, after reviewing the peer-reviewed, published, epidemiologic evidence of the health condition in 9/11-exposed populations as a whole, the evaluation of the scientific evidence supports that the health condition is substantially likely to be causally associated with 9/11 exposures, then the Administrator will propose adding the health condition to the List, as described in Section IV.B.

**(2) Evidence Supports High Likelihood of Causal Association**

If, after reviewing the peer-reviewed, published, epidemiologic evidence of the health condition in 9/11-exposed populations as a whole, the evaluation of the scientific evidence leads to the conclusion that the health condition is not substantially likely, but nevertheless demonstrates a high likelihood of being causally associated with 9/11 exposures, then the Administrator may direct the Science Team to consider additional highly relevant scientific evidence from sources using non-9/11-exposed populations (see Section III.B.2.) or the Administrator may take an action specified in Section IV.A. or D.

**(3) Limited or Inadequate Evidence of Causal Association**

If, after reviewing the peer-reviewed, published, epidemiologic evidence of the health condition in 9/11-exposed populations as a whole, the evaluation of the scientific evidence leads to the conclusion that there is some or inconclusive evidence of causal association between the 9/11 exposures and the health condition, but not sufficient evidence to establish a high likelihood, then the Administrator may take an action specified in Section IV.D.

**(4) Evidence Does Not Support Causal Association**

If, after reviewing the peer-reviewed, published, epidemiologic evidence of the health condition in 9/11-exposed populations as a whole, the evaluation of the scientific evidence leads to the conclusion that the health condition is not causally associated with 9/11 exposures,

then the Administrator may take the action specified in Section IV.C.

## 2. Science Evidence from Sources Using Non-9/11-Exposed Populations

Where the available peer-reviewed, published epidemiologic studies of the health condition in 9/11-exposed populations demonstrate a high, but not substantial, likelihood of causal association between the 9/11 exposure and the health condition, the Administrator may direct the Science Team to evaluate additional scientific evidence regarding exposures to known 9/11 agents<sup>20</sup> in additional sources using non-9/11-exposed populations.

### a. Identification of Scientific Evidence

If the Administrator determines that the findings of the evaluation of peer-reviewed, published, epidemiologic studies in 9/11-exposed populations warrants further evaluation using additional scientific sources, the Administrator will direct the Science Team to consider highly relevant scientific evidence from sources using non-9/11-exposed populations. The Science Team will then identify and evaluate additional peer-reviewed, scientific evidence obtained from an authoritative scientific source published by the U.S. government, such as:

- *Toxicological Profiles* published by the Agency for Toxic Substances and Disease Registry (ATSDR);<sup>21</sup>
- *Monographs* published by the National Toxicology Program (NTP);<sup>22</sup> and
- *Human Health Risk Assessments* published by the Environmental Protection Agency (EPA).<sup>23</sup>

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<sup>20</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 C.F.R. § 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. WTC Health Program, “Development of the Inventory of 9/11 Agents,” published July 17, 2018, available at: [https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development\\_of\\_the\\_Inventory\\_of\\_9-11\\_Agents\\_20180717.pdf](https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf).

<sup>21</sup> For available ATSDR Toxicological Profiles, see <http://www.atsdr.cdc.gov/toxprofiles/index.asp>.

<sup>22</sup> For available NTP Monographs, see <http://ntp.niehs.nih.gov/pubhealth/hat/noms/index.html>.

<sup>23</sup> For EPA Human Health Risk Assessment Products and Publications, see <https://cfpub.epa.gov/ncea/risk/hhra/advSearch.cfm>.

**b. Review of Scientific Evidence**

- (1) The review of the evidence from the additional scientific sources will include, but not be limited to, an evaluation of the following:
  - (a) Whether the evidence provides a scientific basis for a determination that exposures to 9/11 agents are substantially likely to cause the health condition;
  - (b) Whether the evidence fills an important gap in establishing a causal association between exposures to 9/11 agents and the health condition; and/or
  - (c) Whether the evidence mitigates the quality limitations found in peer-reviewed, published, epidemiologic studies of the health condition among 9/11-exposed populations.
  
- (2) The review of scientific evidence from additional sources will include an evaluation of the similarity of the exposure conditions to 9/11 exposure conditions including, but not limited to, the following:
  - (a) The amount of exposure;
  - (b) Route of exposure;
  - (c) Physical form of the exposure to the 9/11 agent, *e.g.*, particulate, gas, fume, vapor, or solute;
  - (d) Duration and consistency of the exposure; and
  - (e) Whether the adverse health outcome arises from acute, sub-chronic, or chronic exposure.
  
- (3) Review of Source Quality

The Science Team will evaluate the scientific quality of the evidence used by additional sources which may impact the ability to determine if a causal relationship between the exposure to a 9/11 agent and the health condition is

substantially likely. For example, if the scientific evidence is inconclusive or outdated, the Science Team will consider such limitations in its evaluation.

**c. Summary of Evaluations**

The WTC Health Program ADS will summarize the evaluations of the scientific evidence sources using non-9/11-exposed populations, in addition to the evidence from peer-reviewed, published, epidemiologic studies in 9/11-exposed populations, and provide advice to the Administrator regarding whether the health condition is substantially likely to be causally associated with 9/11 exposures among 9/11-exposed populations. Upon receipt of the ADS' advice, the Administrator will take action regarding the health condition, as described in Section IV.A., B., or D. as appropriate.

**IV. Administrator Actions**

At the conclusion of the evaluation, the Administrator will take one of the following actions:<sup>24</sup>

**A. Request a Recommendation of the STAC**

The Administrator may request a recommendation from the STAC if the Administrator believes the expertise of the STAC would be helpful in making a determination on whether to propose the addition of a health condition to the List.<sup>25</sup> For example, the STAC may be convened to help clarify an interpretation of conflicting or inconclusive published scientific evidence. If the Administrator exercises the Administrator's discretion to request a recommendation from the STAC, the Administrator will also take the STAC's recommendation into consideration in determining which of the actions to take regarding the health condition.<sup>26</sup>

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<sup>24</sup> Where the evaluation by the Science Team is in response to a valid petition, one of these actions must be taken within 90 days of receipt of the petition. *See* 42 U.S.C. § 300mm-22(a)(6)(B); 42 C.F.R. § 88.16(a)(2). The statutory deadlines do not apply where the evaluation is conducted at the discretion of the Administrator.

<sup>25</sup> 42 U.S.C. § 300mm-22(a)(6)(B)(i); 42 C.F.R. § 88.16(a)(2)(i).

<sup>26</sup> The Administrator may alternatively exercise the Administrator's discretion to request a recommendation from the STAC under 42 U.S.C. § 300mm-22(a)(6)(B)(i) or (C) at any time during the evaluation process, including before or during the Science Team's evaluation.

**B. Publish a Notice of Proposed Rulemaking to Add the Health Condition**

If the evidence supports that it is substantially likely that the health condition is causally associated with 9/11 exposures, then the Administrator will publish in the *Federal Register* a notice of proposed rulemaking (NPRM) to add the health condition to the List of WTC-Related Health Conditions.<sup>27</sup>

**C. Publish a Notice of Determination Not to Propose a Rule to Add a Condition**

If the evidence supports that the health condition is not causally associated with 9/11 exposures, then the Administrator will publish in the *Federal Register* a determination not to propose a rule and the basis for such determination.<sup>28</sup>

**D. Publish a Notice of Insufficient Evidence**

If the evidence is insufficient to take either of the actions in Sections IV.B. or C., then the Administrator will publish that determination in the *Federal Register*.<sup>29</sup>

**V. WTC Health Program Scientific/Technical Advisory Committee (STAC)**

**A. Convening the STAC**

The Administrator may send a letter to the STAC Chair requesting a recommendation from the STAC on whether to add a health condition, including the scientific and medical basis for the recommendation.<sup>30</sup>

**B. STAC Meeting Procedures**

The Designated Federal Official will work with the STAC to schedule meetings and assemble information needed to develop recommendations on whether 9/11 exposures are causally associated with the health condition.

**C. Time Limits**

**1. STAC Recommendation**

The STAC will submit its recommendations on whether to add the health condition to the Administrator no later than 90 days after the date of the

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<sup>27</sup> 42 U.S.C. § 300mm-22(a)(6)(B)(ii); 42 C.F.R. § 88.16(a)(2)(ii).

<sup>28</sup> 42 U.S.C. § 300mm-22(a)(6)(B)(iii); 42 C.F.R. § 88.16(a)(2)(iii).

<sup>29</sup> 42 U.S.C. § 300mm-22(a)(6)(B)(iv); 42 C.F.R. § 88.16(a)(2)(iv).

<sup>30</sup> 42 U.S.C. § 300mm-22(a)(6)(B)(i) and (C).

Administrator's request or by such date (not to exceed 180 days from the date of the request) as specified by the Administrator.<sup>31</sup>

## **2. Administrator Actions after Receipt of a STAC Recommendation**

Where the Administrator is reviewing a potential addition of a health condition to the List, whether at the Administrator's own discretion or in response to a petition, and has requested a recommendation from the STAC, the Administrator will evaluate the STAC's recommendation(s) and take one of the following actions within 90 days after receipt:

- a. Publish an NPRM to propose the addition of a health condition (see Section VI.B.); or
- b. Publish a notice in the *Federal Register* of the determination not to propose a rule and the basis for such a determination (see Section IV.C.).

## **VI. Rulemaking and Peer Review**

### **A. NPRM**

If the Administrator decides to propose adding the health condition to the List, the Administrator will publish an NPRM in the *Federal Register*. The Administrator will solicit written public comments on the NPRM.<sup>32</sup>

### **B. Independent Peer Review**

As required by the James Zadroga 9/11 Health and Compensation Reauthorization Act, the Administrator will conduct an independent peer review of the WTC Health Program's evaluation of the scientific and technical evidence supporting the addition of the health condition prior to issuing a final rule.<sup>33</sup>

#### **1. Selection of Peer Reviewers**

- a. At least every two years, the Administrator will develop a pool of potential peer reviewers with medical and/or scientific expertise by requesting recommendations from the WTC Health Program STAC regarding the identification of potential independent peer

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<sup>31</sup> 42 U.S.C. § 300mm-22(a)(6)(C); 42 C.F.R. § 88.16(b)(1).

<sup>32</sup> 42 U.S.C. § 300mm-22(a)(6)(D); 42 C.F.R. § 88.16(b).

<sup>33</sup> 42 U.S.C. § 300mm-22(a)(6)(F); 42 C.F.R. § 88.16(b)(2).

reviewers,<sup>34</sup> and by publishing a *Federal Register* notice soliciting nominees for potential peer reviewers for the Program.

- b. The Administrator will select three subject matter experts for each health condition being proposed for addition to the List of WTC-Related Health Conditions<sup>35</sup> from a standing pool of peer reviewers. If the Administrator cannot identify three peer reviewers from among the standing pool of nominated reviewers, other peer reviewers may be selected at the Administrator's discretion. In selecting peer reviewers to review the Program's evaluation of evidence regarding a specific health condition, the Administrator will balance the following factors:
  - (1) Medical and/or scientific expertise needed to evaluate the evidence relied on to propose adding the health condition including the authorship of publication(s) concerning the respective health condition;
  - (2) Independence from the National Institute for Occupational Safety and Health (NIOSH) and the Centers for Disease Control and Prevention; and
  - (3) Previous service as a peer reviewer (rotation of peer reviewers).
- c. The Administrator will apply Federal science agency conflict or bias prevention methods to:
  - (1) Limit potential conflicts of interest;
  - (2) Ensure that bias is minimized in the peer review process;
  - (3) Achieve a high level of credibility; and
  - (4) Balance extremes in scientific perspectives.

## **2. Charge to Peer Reviewers**

- a. Peer reviewers will be asked to review the assessment of the evidence for adding the health condition to the List within the context of this policy. Within 30 days of when the NPRM is

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<sup>34</sup> 42 U.S.C. § 300mm-22(a)(6)(G)(ii).

<sup>35</sup> 42 C.F.R. § 88.15.

published in the *Federal Register*, reviewers will be expected to provide a brief written report answering the following questions:<sup>36</sup>

- (1) Are you aware of any other studies which should be considered? If so, please identify them.
- (2) Have the requirements of this *Policy and Procedures* been fulfilled? If not, please explain which elements are missing or deficient.
- (3) Is the interpretation of the available evidence appropriate, and does it support the conclusion to add the health condition, as described in the proposed regulatory text, to the List? If not, please explain why.

- b. The peer reviews will be compiled and posted to the NIOSH rulemaking docket at the end of 30 days. Peer reviewers will be identified without individual attribution of their comments.

#### **C. Public Comments**

All public comments and peer reviews will be considered and responded to, as appropriate, in the final rule preamble. The public comment period will remain open no less than 45 days after publication of the NPRM in the *Federal Register* to allow the public an additional 15 days to comment after peer reviewers' comments are posted. The public comments will be posted to the rulemaking docket.

#### **D. Final Rule**

After reviewing the public comments and peer reviews, the Administrator will determine whether the rationale discussed in the NPRM is changed by the information supplied by commenters. If the evidence continues to support the addition of the health condition:

1. A final rule will be developed and published in the *Federal Register*;
2. The condition will be added to the List on the final rule's effective date; and

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<sup>36</sup> The questions given to the peer reviewers may be modified by the Administrator, as necessary, for the specific health condition being considered.

3. Implementation procedures will be developed, which may include:
  - a. Exposure qualifications;
  - b. Time intervals for diagnosis and/or symptom onset; and
  - c. Other procedures as appropriate to the particular health condition.

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