9.11 World Trade Center Health Program

Evaluation of Scientific Evidence Supporting the Addition of Hepatic Steatosis 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, the WTC Health Program's Science Team (Science Team) reviewed **Petitions 029**, **034**, **035**, and **062** requesting the addition of Hepatic Steatosis to the List of WTC-Related Health Conditions (the List). The Science Team evaluated the scientific evidence of a causal association between 9/11 exposure and hepatic steatosis 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 2001 and 2025 identified two high-quality studies reporting on the risk of hepatic steatosis in 9/11-exposed populations. The Science Team evaluated the information from these two studies, individually and together, to characterize the totality of the scientific evidence of a causal association between 9/11 exposures and hepatic steatosis. The Science Team concludes that there is *inadequate evidence* to determine the likelihood of a causal association between 9/11 exposures and hepatic steatosis (Category V).[1]

II. BACKGROUND

Pursuant to the James Zadroga 9/11 Health and Compensation Act of 2010,[2] 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.[3,4] To petition the Program, petitioners must submit, in writing, their name, contact information, and signature of the interested party requesting the addition of the 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 condition.[5] 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 2026]. Submissions that meet all requirements are considered valid petitions.

A. Petition 029

On November 12, 2020, the Administrator received a submission requesting the addition of several conditions, including "hepatotoxic injury — fatty liver disease," to the List. Upon review, the submission was found to be valid and assigned an ordinal number, **Petition 029**.

B. Petition 034

On August 4, 2021, the Administrator received a submission requesting the

1 *See Policy and Procedures*, Section V. E. [NIOSH 2024].
2 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, Pub. L. 119-75; codified at 42 U.S.C. §§ 300mm – 300mm-64.
3 42 U.S.C. § 300mm-22(a)(6)(B).
4 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).
5 *See* 42 C.F.R. § 88.16(a)(1).

addition of "hepatic steatosis (also known as fatty liver disease or non-alcoholic liver disease)" to the List. Upon review, the submission was found to be valid and assigned an ordinal number, **Petition 034**.

C. Petition 035

On November 15, 2021, the Administrator received a submission requesting the addition of "hepatic steatosis/cirrhosis" to the List. Upon review, the submission was found to be valid and assigned an ordinal number, **Petition 035**.

D. Petition 062

On May 14, 2025, the Administrator received a submission requesting the addition of "hepatic steatosis (fatty liver disease)" to the List. Upon review, the submission was found to be valid and assigned an ordinal number, **Petition 062**.

Because hepatic steatosis is a form of fatty liver disease and is a precursor to fatty cirrhosis, these four petitions are considered jointly in this scientific evaluation for the health condition "hepatic steatosis," as permitted by the Program regulations.[6] There are no petitions for hepatic steatosis that preceded **Petition 029** on November 12, 2020. 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 hepatic steatosis.

III. PURPOSE

The purpose of this evaluation is to assess the scientific evidence from peer-reviewed, published, epidemiologic studies of hepatic steatosis in the 9/11-exposed population,[7] to determine whether sufficient evidence of a causal association between 9/11-related exposures, including exposure to 9/11 agents,[8] and hepatic steatosis exists to support adding this condition to the List. This evaluation is being provided to the Administrator of the WTC Health Program to inform the Administrator's determination regarding Petitions **029**, **034**, **035**, and **062** 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 previously established by the Program in accordance with Program regulations and the *Policy and Procedures for Handling Submissions and Petitions*

6 *See* 42 C.F.R. § 88.16(a)(4).

7 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* (the *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]. Development of the Inventory of 9/11 Agents. Cincinnati, OH: National Institute for Occupational Safety and Health, https://www.cdc.gov/wtc/pdfs/research/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf.

8 9/11 agents are chemical, physical, biological, or other agents or 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 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].

[NIOSH 2026]. The Program examined the references provided with the submissions to determine whether they included a medical basis for the association between the September 11, 2001, terrorist attacks and the condition to be added. *See* **Table 1**.

A. Petition 029

Petition 029 provided the study of hepatic steatosis in 9/11 exposed populations by Chen et al. [2020]. This study provided sufficient medical basis for the petition.

B. Petition 034

Petition 034 included two studies regarding hepatic steatosis in the 9/11-exposed population [Chen et al. 2020; Jirapatnakul et al. 2021]. These studies provided sufficient medical basis for the petition.

C. Petition 035

Petition 035 included Jirapatnakul et al. [2021] which is a study regarding hepatic steatosis in the 9/11-exposed population and therefore is sufficient medical basis.

D. Petition 062

Petition 062 also included the study by Jirapatnakul et al. [2021] which is sufficient medical basis.

V. EVALUATED HEALTH CONDITION

In accordance with the *Policy and Procedures* [NIOSH 2024], the Science Team reviewed the information provided by the petitioners, including the medical basis information, and determined that the health condition of interest for this evaluation is hepatic steatosis, also known as fatty liver, not elsewhere classified (ICD-10 76.0). Hepatic steatosis is caused by an excess accumulation of fat in hepatocytes (i.e., the name of most of the cells of the liver).

Hepatic steatosis may progress to steatohepatitis, liver fibrosis, cirrhosis (i.e., a degenerative disease of the liver that results in scarring and liver failure), and hepatocellular cancer (i.e., liver cancer). The three most frequent causes of steatosis and steatohepatitis are: (1) alcohol, causing alcoholic steatohepatitis (ASH); (2) obesity or metabolic syndrome, causing nonalcoholic steatohepatitis or metabolic dysfunction-associated steatohepatitis (MASH); and (3) environmental toxicants, causing toxicant-associated steatohepatitis (TASH) [Joshi-Barve et al. 2015]. Environmental toxicants include solvents and other halogenated, volatile organic mixtures, persistent organic pollutants, pesticides, and some nitro-organic compounds [Wahlang et al. 2013a].

The three types of steatohepatitis (i.e., ASH, MASH, TASH) share many common pathogenic mechanisms and histologic features, but they also show subtle variations [Joshi-Barve et al. 2015; Singal and Mathurin 2021]. All three types of steatohepatitis can progress to histologically identical, more severe liver disease (i.e., advanced fibrosis, cirrhosis, and liver cancer). Disease progression is a result of both direct effects on the liver as well as indirect alterations in other organs or tissues such as gastrointestinal tissue, adipose tissue, and the immune system.

Metabolic dysfunction-associated steatotic liver disease (MASLD), which is the new name

for "nonalcoholic fatty liver disease" (NAFLD) since 2023, is defined as the presence of hepatic fat accumulation and is diagnosed when metabolic abnormalities (e.g., overweight or obesity, type 2 diabetes mellitus, or two or more attributes of metabolic syndrome)[9] are present and after the exclusion of other causes of hepatic steatosis, such as excessive alcohol consumption and exposure to environmental toxicants. MASLD comprises a broad clinical spectrum that ranges from liver-fat accumulation to MASH, advanced fibrosis, cirrhosis, and finally liver cancer [Targher et al. 2025].

The term "toxicant-associated fatty liver disease" (TAFLD) has been proposed to designate the fatty liver diseases associated with toxicant exposure. Like its MASLD counterpart, TAFLD describes the spectrum of toxicant-associated fatty liver diseases (e.g., steatosis, steatohepatitis, fibrosis, cirrhosis, liver cancer) [Wahlang et al. 2013a]. Alcohol-associated liver disease (ALD) is the term used to describe the clinical spectrum that arises from excessive alcohol consumption. ALD begins with the development of steatosis and can progress to ASH, fibrosis, cirrhosis, and liver cancer. In ALD, MASLD, and TAFLD, a liver biopsy may show only one feature of liver disease (e.g., steatosis, hepatitis, fibrosis, or cirrhosis) or a combination of those features. Collectively, ALD, MASLD, and TAFLD are referred to as hepatic steatosis for this evaluation.

VI. RISK FACTORS FOR EVALUATED HEALTH CONDITION

A. General Risk Factors

Fatty liver disease related to, or resulting from, exposure to environmental toxicants (i.e., TAFLD) may be associated with many classes of industrial chemicals, including solvents and other halogenated hydrocarbons, volatile organic mixtures, persistent organic pollutants, pesticides, and some nitro-organic compounds [Wahlang et al. 2013a]. Aside from the exposure level, a person's susceptibility to TAFLD is affected by polymorphisms in the genes of xenobiotic metabolism,[10] concurrent use of alcohol or prescription medications, nutritional factors, and obesity [Wahlang et al. 2013a].

If a history of toxicant exposure or excessive alcohol consumption is not obtained from a patient, ALD and TAFLD generally cannot be distinguished from MASLD. As explained in Section V., ALD can arise from excessive alcohol consumption, and individuals with overweight or obesity, type 2 diabetes mellitus, or attributes of metabolic syndrome are at risk for MASLD.

B. 9/11 Risk Factors

Responders to and survivors of the September 11, 2001, terrorist attacks

9 Attributes of metabolic syndrome include: (1) abdominal obesity, defined as waist circumference > 102 cm for Caucasian men and > 88 cm in Caucasian women or > 90 cm for Asian men and > /80 cm for Asian women; (2) blood pressure > 130/85 mmHg or receiving treatment for hypertension; (3) elevated plasma triglycerides or under treatment for hypertriglyceridemia; (4) reduced plasma HDL-cholesterol or under treatment for low HDL-cholesterol; and/or (5) pre-diabetes mellitus (e.g., HbA1c 5.7 to 6.4%). See Eslam et al. [2020]. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. *73*(1):202–209, https://doi.org/10.1016/j.jhep.2020.03.039.

10 The term "xenobiotic metabolism" refers to the body's process of chemically modifying foreign compounds (i.e., xenobiotic) like drugs, pollutants, and toxins, primarily in the liver, to make them water-soluble for excretion by the kidney. *See* van Vugt-Lussenburg BMA, et al. [2022]. "*Commandeuring*" xenobiotic metabolism: Advances in understanding xenobiotic metabolism. Chem Res Toxicol. *35*(4):1184–1201, https://doi.org/10.1021/acs.chemrestox.2c00067.

experienced a variety of exposures to environmental toxicants. The collapse of the WTC towers resulted in a massive and dense cloud of suspended toxic dust, gases, and smoke that engulfed the highly populated areas of southern Manhattan and Brooklyn [Lioy and Georgopoulos 2006]. The bulk (about 80–90%) 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 3 months [Landrigan et al. 2004]. Exposures continued in the days and months that followed 9/11; first mostly from burning jet fuel and building fires, followed by the resuspension of dusts during the many months of cleanup and recovery. Hepatic steatosis is linked to exposures to toxicants identified as 9/11 agents in the *Inventory* [NIOSH 2018]. The 9/11 agents linked to hepatic steatosis include trichloroethylene, tetrachloroethylene, trichloroethane, carbon tetrachloride, polychlorinated biphenyls, arsenic, thallium, phosphorus, dioxin, lead, and chloroform [Wahlang et al. 2013a].

VII. SCIENCE 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;[11] (2) review identified studies to determine which studies are high-quality studies for further evaluation;[12] (3) evaluate and integrate the evidence of a causal association between 9/11 exposures and the health condition being evaluated;[13] 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.[14] The Science Team then advises the Administrator of its findings.[15]

VIII. REVIEW OF THE LITERATURE

A. Literature Search

The literature search identifies high-quality, peer-reviewed, published, epidemiologic studies that provide evidence on the proposed causal association between 9/11 exposures and the health condition under consideration — hepatic steatosis. To identify potentially relevant studies, the Science Team searched abstracts and titles from peer-reviewed English language literature. In addition to search terms used to identify epidemiologic studies of the 9/11-exposed population, keywords used to uncover potentially informative studies included: fatty liver disease, hepatic steatosis, fatty liver, steatohepatitis, MASLD (metabolic dysfunction-associated steatotic liver disease), MAFLD (metabolic dysfunction-associated fatty liver disease), NAFLD (nonalcoholic fatty liver disease), NAFL (nonalcoholic fatty liver), MASH (metabolic dysfunction-associated steatohepatitis), NASH (nonalcoholic steatohepatitis), toxicant-associated steatohepatitis (TASH), toxicant-associated fatty liver disease

11 *See Policy and Procedures*, Section III.B. [NIOSH 2024].
12 *See Policy and Procedures*, Section III.C. [NIOSH 2024].
13 *See Policy and Procedures*, Section IV. [NIOSH 2024].
14 *See Policy and Procedures*, Section V. [NIOSH 2024].
15 *See Policy and Procedures*, Section VI. [NIOSH 2024].

(TAFLD), pseudo-alcoholic hepatitis, alcohol-like hepatitis, alcohol-associated liver disease (ALD), fatty liver hepatitis, steatonecrosis, diabetic hepatitis, liver fibrosis, and cirrhosis. 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).

Following the baseline search, additional weekly searches were conducted using the WTC Health Program Bibliographic Database, a database of relevant WTC-related research maintained by the Program and updated at least weekly using a standing search of the previously mentioned databases. The last follow-up search was conducted in January 2026. The literature search identified four studies of hepatic steatosis among 9/11-exposed population for full review as potential studies for evaluation [Cho et al. 2014; Chen et al. 2020; Jirapatnakul et al. 2021; Singh et al. 2025]. Two of the four studies [Chen et al. 2020; Jirapatnakul et al. 2021] were included in the medical basis provided by the petitioners. These two studies were determined to have sufficient validity indicators to be considered high-quality studies eligible for further evaluation in accordance with the *Program's Policy and Procedures* [NIOSH 2024].[16] These two high-quality studies are listed in **Table 2** and further described in Section VIII.C. of this evaluation. The other two studies identified in the literature search were determined not to demonstrate sufficient validity indicators to be considered high-quality studies eligible for further review [Cho et al. 2014; Singh et al. 2025]. These two studies were removed from further consideration but are discussed in Section VIII.B. below for completeness.

B. Studies Not Further Considered

Two of the four studies identified in the literature search did not meet the criteria for further evaluation as high-quality studies.

1. Cho et al. [2014]

The study by Cho et al. [2014] is a biomarker study that compared levels of specific serum biomarkers including YKL-40 and chitotriosidase in cases of NAFLD and controls without the disease, all among Fire Department of the City of New York (FDNY) 9/11 responders. It did not evaluate the association between 9/11 exposures and NAFLD.

2. Singh et al. [2025]

The study by Singh et al. [2025] evaluated liver fibrosis scores among FDNY and General Responder Cohort (GRC) 9/11 responders to determine if those liver fibrosis scores were associated with mortality (i.e., all-cause, liver disease-related, and non-liver disease-related mortality) and liver cancer incidence. The study did not evaluate the association between 9/11 exposures and any liver disease outcomes, such as hepatic steatosis.

16 *See Policy and Procedures*, Section III.C. [NIOSH 2024].

C. Identified High-Quality Studies

Two cross-sectional studies were identified in the review of the literature and were found to have sufficient indicators of validity to be high-quality studies in accordance with the *Policy and Procedures*.[17] *See* **Table 2**.

1. Chen et al. [2020]

Chen et al. [2020] conducted a cross-sectional study to determine the prevalence of moderate-to-severe hepatic steatosis and associated risk factors in WTC Health Program general responders undergoing screening for lung cancer and compare the prevalence of hepatic steatosis in WTC-exposed responders (referred to as WTC participants) with non-WTC-exposed participants (referred to as non-WTC participants) in the same screening program. The prevalence comparison portion included 159 WTC Health Program general responders who were 55 to 77 years of age, had a smoking history of ≥ 30 pack-years, and were either current smokers or quit smoking within the last 15 years. The non-WTC exposed comparison group included 170 community participants who were asymptomatic ever-smokers, aged 40 or older who participated in the same computed tomography (CT) screening program. There was no mention of the comparison group having 9/11 exposures. Liver attenuation, as measured by the Hounsfield Unit (HU), was assessed using low dose computerized tomography (LDCT) scans at the hepatic portal level in four sectors defined by the Couinaud system [Couinaud 1999]. The authors used the cutoff of < 40 HU, indicating moderate-to-severe hepatic steatosis, which was two standard deviations below the mean in another study [Chen et al. 2017]. LDCT scans were performed on the WTC participants between February 2016 and January 2017, whereas they were performed on the non-WTC participants between August 2011 and April 2016. The prevalence of moderate-to-severe hepatic steatosis was 16.2% among WTC participants compared to 5.3% among non-WTC participants. In logistic regression models, the odds ratio for moderate-to-severe hepatic steatosis was 3.4 (95% CI 1.7–6.7) in WTC participants compared with non-WTC participants. Moderate-to-severe hepatic steatosis was also associated with higher body mass index (BMI) (mean BMI = 33.2 for those with liver attenuation < 40 HU versus 29.0 for those with liver attenuation > 40 HU, p = 0.002), and former smoker status (p = 0.02).

Exposure was limited to status as a WTC participant or non-WTC participant. Magnetic resonance imaging (MRI) or pathologic confirmation of hepatic steatosis, the standard diagnostic methods, were lacking [Obika and Noguchi 2012]. The study evaluated covariates such as age, gender, smoking status, pack-years, race, body mass index, self-reported comorbidities of diabetes, hypertension, and chronic obstructive pulmonary disease (COPD); but important confounders such as alcohol consumption, occupational and environmental exposures, and steroid use were not measured. In addition, information on other potential confounders such as family history of NAFLD, and presence of autoimmune disease, obstructive sleep apnea (OSA), or hepatitis C infection was not available. The use of an external reference group

17 *See Policy and Procedures*, Section III.C. [NIOSH 2024].

selected using different entry criteria is prone to potential selection bias. There was little overlap in the time period when the CT scans were obtained for the WTC participants versus the non-WTC participants, suggesting the possibility of measurement bias. Although the cross-sectional design provided information on disease prevalence at the time of examination (i.e., the combination of disease incidence, persistence, and survival), it did not provide information on the timing of disease onset; therefore, information on the temporality of the cause and effect is lacking and causal inference is limited. Given these limitations and others, the Science Team agreed with the authors' assertion that the findings from this study should be considered preliminary.

2. **Jirapatnakul et al. [2021]**

Jirapatnakul et al. [2021] conducted a cross-sectional study within a cohort of general responders to evaluate the existence of a dose-response relationship between the intensity of exposure to the WTC site and the prevalence of hepatic steatosis. The study included 1,788 participants of the WTC GRC which is part of the WTC Health Program. All had laboratory test data performed within 12 months of their first LDCT scan after 9/11. Study participants were classified into five exposure groups based on their arrival date to the WTC site: (1) September 11, 2001, in the dust cloud; (2) September 11, 2001, not in the dust cloud; (3) September 12 or 13, 2001; (4) September 14 to the end of September 2001; and (5) October 2001 and beyond. Chest CT scans were performed using different scanner manufacturers, models, and protocols, and were used primarily to evaluate pulmonary outcomes, but were available as screening tests for liver disease. Hepatic steatosis was defined as liver attenuation on LDCT of <40 HU. Liver attenuation is inversely related to hepatic steatosis, meaning that the lower attenuation means higher amounts of hepatic steatosis. CT liver density (i.e., liver attenuation) was estimated using the validated Statistics-based Liver Density Estimation from Imaging (SLIDEI) algorithm. The prevalence of liver attenuation <40 HU was 17.0% for arrivals on September 11, 2001; 16.0% for arrivals on September 12, 2001, or September 13, 2001; 10.9% for arrivals on September 14–30, 2001; and 9.0% for arrivals on January 10, 2001, or later ($p = 0.0015$). In adjusted models, WTC arrival date appeared to be an independent predictor of decreased liver attenuation (i.e., hepatic steatosis prevalence) after controlling for sex, age, race, smoking status, alcohol use, BMI, diabetes, gastroesophageal reflux disease (GERD), and forced expiratory volume in 1 second (FEV1). When liver attenuation was assessed as a continuous variable, WTC-exposed responders who arrived on September 11, 2001, in the dust cloud ($p = 0.01$), on September 11, 2001, without dust cloud exposure ($p = 0.001$), and between September 12–13, 2001 ($p = 0.047$) had increased amounts of liver steatosis (i.e., reduced liver attenuation) compared with responders who arrived on or after October 1, 2001. No significant difference was found in liver attenuation between WTC responders who arrived on September 14–30, 2001, versus those who arrived in October 2001 and later. However, paradoxically, when comparing the two groups who arrived on September 11, 2001, those with little to no dust cloud exposure had lower liver attenuation (i.e., greater amounts of hepatic

steatosis) compared to those with extensive dust cloud exposure. The authors did not report if this difference was statistically significant.

The study has several strengths, including the large sample size. The authors conducted unadjusted and adjusted analyses for sex, age, race, smoking status, alcohol use, BMI, diabetes, GERD, and FEV_1. However, the presence of medical comorbidities such as diabetes mellitus, COPD, and GERD was self-reported. Information on alcohol use was unclear, given that the authors did not report when the alcohol use information was collected and did not define the alcohol use categories (i.e., the low, moderate, and high alcohol use categories were undefined). No information on occupational and environmental co-exposures, steroid use, family history of NAFLD or MASLD, autoimmune disease, OSA, or hepatitis C infection was obtained. In addition, there are concerns about the diagnosis of hepatic steatosis: the condition was not confirmed by MRI or biopsy, the standard diagnostic methods [Obika and Noguchi 2012]; the scanning protocols for the imaging exams varied, which could introduce variation in the liver density measurement; and CT scans were obtained years after 9/11 exposure (the first LDCT images were obtained between 2003 and 2018). Selection bias may also be an issue, since information was not provided on those not included in the study. In addition, information on the timing of the collection of outcome, exposure, and covariate data was not provided, limiting interpretation on causality. Overall, the study has many strengths, but chance, bias, and confounding cannot be ruled out with reasonable confidence.

IX. SYNTHESIS OF EVIDENCE FOR CATEGORIZATION

In accordance with the *Policy and Procedures* [NIOSH 2024], the Science Team evaluated and synthesized evidence from the "high-quality" studies identified following the Review of Literature. 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 and to assign findings regarding causal association to one of five categories as described below in Section IX.A.4.[18] 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 (hepatic steatosis) is observed; (4) **temporality** of

18 *See Policy and Procedures*, Section IV.A. [NIOSH 2024].

the cause and effect (i.e., the 9/11 exposure precedes the health condition (hepatic steatosis)); (5) **biological gradient** or dose-response relationship where changes in 9/11 exposures are associated with corresponding changes in the magnitude of the outcome (hepatic steatosis); (6) **biological plausibility** — the extent to which 9/11 studies align with known facts about the biology of the health condition being evaluated (hepatic steatosis); (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 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 hepatic steatosis.

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 the *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. Evaluation and Evidence Synthesis of High-Quality Studies

The evaluation and synthesis of the evidence from high-quality studies is provided in two parts: (1) consideration of the strength of the association, consistency of associations, temporality, and biological gradient in the identified high-quality studies, including assessment of study limitations and representativeness of study populations; and (2) consideration of biological plausibility, coherence, and analogy that combines information from the identified high-quality studies with additional information.

1. **Consideration of Strength of the Association, Consistency of Associations, Temporality, and Biological Gradient, Including an Assessment of Limitations and Representativeness**

   Two peer-reviewed, published, epidemiologic studies were identified and found to be high-quality studies eligible for further evaluation on a potential causal relationship between 9/11 exposure and hepatic steatosis [Chen et al. 2020; Jirapatnakul et al. 2021]. The statistical analyses in each study appeared appropriate for the available data.

   Chen et al. [2020] found that the prevalence of moderate-to-severe hepatic steatosis was more than 3-fold higher in the WTC participant group compared with non-WTC participants. However, exposure was limited to status as a WTC participant or non-WTC participant. Some important confounders, including alcohol consumption and occupational and non-WTC environmental exposures, were not measured. Given the use of an external reference group and differences in eligibility between groups, this study was vulnerable to potential selection bias. The effect measures were imprecise but were statistically significantly elevated. The authors considered the findings preliminary, and the Science Team concurs.

   More compelling evidence of an association between hepatic steatosis and 9/11 exposure stems from Jirapatnakul et al. [2021], who found significant differences in disease prevalence based on responders' arrival date at the WTC site. The prevalence of steatosis was highest among those who arrived first (i.e., on September 11, 2001) and decreased for responders with later arrival dates, suggesting a monotonic trend of increasing hepatic steatosis prevalence with earlier arrival date. The exposure-response effect of hepatic steatosis prevalence based on arrival date persisted following control of several potential confounders, although certain important risk factors were not considered (i.e., occupational or non-WTC environmental exposures) or were poorly defined (i.e., alcohol consumption). However, there was no gradient between the two responder groups who arrived on 9/11 (i.e., those with extensive dust cloud exposure versus those without extensive dust cloud exposure). In both of the groups that arrived on 9/11, the prevalence of hepatic steatosis was identical at 17%. Paradoxically, among the two responder groups that arrived on 9/11, when liver attenuation was assessed as a continuous variable, those without extensive dust cloud exposure had lower liver attenuation (i.e., greater amounts of hepatic steatosis) compared to those with extensive dust cloud exposure. It was not reported if this difference was statistically significant. Selection bias may also be an issue, since information was not provided on those not included in the study.

   Both studies were cross-sectional (i.e., exposure status and outcome are determined at the same time); therefore, there is limited information on the temporality of the cause and effect. On one hand, hepatic steatosis was ascertained many years after 9/11 exposure; therefore, it is less likely that disease onset preceded exposure. On the other hand, there is no accounting of the etiologically relevant period between exposure and disease onset; therefore, it is not clear whether results indicate persistent or delayed 9/11-related effects or stem from other causes encountered before or after

the attacks. For example, neither study included information on non-9/11 occupational and environmental exposures occurring prior to or after 9/11. Additionally, both studies used proxies[19] for the health condition of interest and the primary exposure, which could lead to exposure and outcome misclassification.

The Science Team evaluation also considered the representativeness of the body of evidence to assess whether the studies, taken together, represented both WTC responder and survivor populations or, if only a subgroup of 9/11-exposed population is represented. If the 9/11 population is only partially represented, then the Science Team considered whether the results can reasonably be extrapolated to the 9/11-exposed population. Participants in the Chen et al. [2020] and the Jirapatnakul et al. [2021] studies belong to the same cohort of workers and volunteers who participated in rescue/recovery efforts at the WTC site on or in the aftermath of September 11, 2001, until the Ground Zero site closed in July 2002. Only a small number of FDNY responders are included in this cohort, but Pentagon and Shanksville responders and survivors are not included in either of these studies. Study participants were mostly male, predominantly White, with a mean age of 42.5 years. The findings of these studies might not be generalizable to other 9/11-exposed groups.

2. Consideration of Biological Plausibility, Coherence, and Analogy

Exposures to toxic chemicals are known to cause liver damage in humans and in animal disease models. Some 9/11 agents have been identified as risk factors for hepatic steatosis and plausible mechanisms have been described [Wahlang et al. 2013a]. Some chemicals disrupt normal development and balance of lipid metabolism (obesogens) to cause steatosis [Chamorro-Garcia et al. 2013; Wahlang et al. 2013b]. This is a similar mechanism to the role high-fat diets likely play in NAFLD/MASLD. Likewise, some 9/11 chemical agents, such as polychlorinated biphenyls, arsenic, and perfluorooctanoic acid, may modify the hepatic response to diet-induced obesity and mediate the transition from steatosis to steatohepatitis [Tan et al. 2011; Tan et al. 2013; Wahlang et al. 2014].

Other mechanisms that have been described as mediating the association between toxicant exposure and TAFLD include alteration of the gut microbiome and its metabolic activity, oxidative stress and lipid peroxidation, endoplasmic reticulum stress, fibrosis that results from an imbalance between production and resorption of extracellular matrix, hepatic inflammation, and hepatocyte cell death (necrosis and necroptosis) [Joshi-Barve et al. 2015]. In addition, studies have shown that epigenetic factors are important for disease pathogenesis and progression of steatohepatitis, including TASH [Buendia and Neuveut 2015; Kirpich et al. 2012]. Therefore, the Science Team concludes that an association between exposure to 9/11 agents and hepatic steatosis can be plausibly explained biologically and mechanistically. Furthermore, a causal conclusion does not contradict present known facts of the pathogenesis of hepatic steatosis.

19 A proxy variable (measurement) is one that is used in place of a variable that cannot be directly measured.

C. Summary of Evaluation and Evidence Synthesis

The evaluation and synthesis of the evidence included an assessment of the strength of the association, consistency of association, specificity, temporality, biological gradient based on information in the two identified high-quality studies and an assessment of plausibility, coherence, and analogy based on information from the identified studies and supplemental information, as necessary. A summary of the Science Team's findings is presented in **Table 3**.

The Science Team evaluated the studies by Chen et al. [2020] and Jirapatnakul et al. [2021] using the Bradford Hill criteria described above to evaluate whether a causal association between 9/11 exposures and hepatic steatosis is supported. The information available in the studies is *insufficient* to support a claim for causation using these criteria. Only the study by Jirapatnakul et al. [2021] reported an exposure-response gradient with hepatic steatosis prevalence. However, Jirapatnakul et al. [2021] found no such gradient among those who arrived on 9/11 and had extensive dust cloud exposure versus those who arrived on 9/11 but did not have extensive dust cloud exposure. Even though both studies showed positive associations, the risk estimate in the study by Chen et al. [2020] lacked precision and is subject to potential selection bias. Both studies controlled for some, but not all, important confounders, and misclassification of exposure and outcome are possible.

Consequently, chance, bias, and confounding cannot be ruled out with reasonable confidence for either study. The known information on mechanisms of action supports an association between certain 9/11 agents and hepatic steatosis. However, given the limitations discussed above, the Science Team concluded that the available evidence is *inadequate* to determine the likelihood of a causal association between 9/11 exposure and hepatic steatosis (Category V).[20]

X. CONCLUSION

As discussed above, the Science Team concluded that the available evidence is *inadequate* to determine the likelihood of a causal association between 9/11 exposure and hepatic steatosis (Category V).

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

XI. REFERENCES

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APPENDIX — TABLES

Table 1. Information Provided by the Petitioners and Medical Basis Determination.

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 029	1. Webber MP, Moir W, Zeig-Owens R, et al. [2015]. Nested case–control study of selected systemic autoimmune diseases in World Trade Center rescue/recovery workers. Arthritis Rheumatol *67*(5):1369–1376, https://doi.org/10.1002/art.39059.	No
	2. Chen X, Ma T, Yip R, et al. [2020]. Elevated prevalence of moderate-to-severe hepatic steatosis in World Trade Center General Responder Cohort in a program of CT lung screening. Clin Imaging, *60*(2):237–243. https://doi.org/10.1016/j.clinimag.2019.12.009.	Yes
Petition 034	1. Jirapatnakul A, Yip R, Branch AD, et al. [2021]. Dose-response relationship between World Trade Center dust exposure and hepatic steatosis. Am J Ind Med *64*(10):837–844, https://doi.org/10.1002/ajim.23269.	Yes
	2. Reja D, Sameera S, Patel R, et al. [2020]. Prevalence of suspected toxic alcohol fatty liver disease (TAFLD) in World Trade Center first responders: findings from the World Trade Center Health Program. In: Annual Meeting of the American Association for the Study of Liver Disease, Virtual Meeting, November 13-16, 2020. Gastroenterology *158*(6):S-1430–S-1431, https://doi.org/10.1016/S0016-5085(20)34243-8.	No
	3. Chen X, Ma T, Yip R, et al. [2020]. Elevated prevalence of moderate-to-severe hepatic steatosis in World Trade Center General Responder Cohort in a program of CT lung screening. Clin Imaging, *60*(2):237–243. https://doi.org/10.1016/j.clinimag.2019.12.009.	Yes
Petition 035	1. Jirapatnakul A, Yip R, Branch AD, et al. [2021]. Dose-response relationship between World Trade Center dust exposure and hepatic steatosis. Am J Ind Med *64*(10):837–844, https://doi.org/10.1002/ajim.23269.	Yes

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 062	1. Jirapatnakul A, Yip R, Branch AD, et al. [2021]. Dose-response relationship between World Trade Center dust exposure and hepatic steatosis. Am J Ind Med *64*(10):837–844, https://doi.org/10.1002/ajim.23269.	Yes
	2. Mount Sinai Hospital [2024]. Researchers Reveal the Risk of Liver Damage in WTC General Responders. Liver Diseases 2024. https://reports.mountsinai.org/article/liver2024-wtc-and-liver-disease	No

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 published, peer-reviewed literature that has not been previously evaluated by the Program. For more information, please see NIOSH [2026]. *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 2. High-Quality Studies of 9/11-Exposed Populations.

Author	Design	Follow-up	Outcome	Population	Person-years	Characteristics
Chen et al. [2020]	Cross-sectional	NA	This study found that the prevalence of moderate-to-severe hepatic steatosis was more than 3-fold higher in the WTC-participant group compared with non-WTC participants. Exposure was limited to being a WTC-participant or not.	GRC	NA	159 WTC Health Program participants were 55 to 77 years of age, had a smoking history of ≥30 pack-years, and were either current smokers or quit within the last 15 years. 170 non-WTC participants were asymptomatic ever-smokers, aged 40 or older.
Jirapatnakul et al. [2021]	Cross-sectional	NA	This study reported a significant difference in liver steatosis prevalence by the WTC arrival date. The prevalence of steatosis was highest among those who arrived on 9/11 and decreased with later arrival dates among the WTC workers, showing a statistically significant trend after controlling for other covariates.	GRC	NA	1,788 study participants. All had laboratory test data performed within 12 months of the first low dose CT scan.

Abbreviations: CT, computed tomography; GRC, General Responder Cohort; NA, not applicable; WTC, World Trade Center

Table 3. Summary of Bradford Hill Criteria for Evaluation and Synthesis.

Aspect of Association ("Bradford Hill Criteria") [Hill 1965]	Evaluation Findings
Strength of the Association	Two high-quality studies were available for evaluation [Chen et al. 2020; Jirapatnakul et al. 2021]. Both studies reported statistically significant estimates of increased prevalence of hepatic steatosis in the 9/11 responder population. Chen et al. [2020] found that the prevalence of moderate-to-severe hepatic steatosis was more than 3-fold higher in the WTC-participant group compared with non-WTC participants, while the linear regression estimates reported by Jirapatnakul et al. [2021] for liver attenuation were lower among those with earlier arrival dates, suggesting an exposure-response of more hepatic steatosis among those with higher 9/11 exposures (liver attenuation is inversely related to hepatic steatosis, meaning that lower liver attenuation demonstrates higher amounts of hepatic steatosis).
Precision of the risk estimate	The confidence interval for the risk estimate in the Chen et al. [2020] study is wide but does not include the null value. Likewise, the multivariable regression estimates in the Jirapatnakul et al. [2021] study were above the statistical significance level of 0.05, except for the exposure category of those arriving on or after September 14, 2001.
Consistency of Associations	The findings are consistent among both studies, but the study by Chen et al. [2020] includes only a small sample of heavy smokers. Further studies, particularly among other 9/11 populations (e.g., survivors, responders from the Fire Department of the City of New York [FDNY]), are needed to confirm the findings reported by Jirapatnakul et al. [2021].
Temporality	Both studies were cross-sectional; therefore, information on temporality was limited. It is unclear in either study whether occupational and environmental exposures occurring prior to 9/11 or unmeasured exposures after 9/11 may have contributed to the observed health conditions.
Biological Gradient	The study by Jirapatnakul et al. [2021] suggests a trend of increasing hepatic steatosis prevalence with earlier arrival dates. However, no such gradient was found among those who arrived on 9/11 and had extensive dust cloud exposure versus those who arrived on 9/11 but did not have extensive dust cloud exposure [Jirapatnakul et al. 2021]. The study by Chen et al. [2020] did not report biological gradient findings.

Aspect of Association ("Bradford Hill Criteria") [Hill 1965]	Evaluation Findings
Plausibility, Coherence, and Analogy	An association between 9/11 agents such as trichloroethylene, tetrachloroethylene, trichloroethane, carbon tetrachloride, polychlorinated biphenyls, arsenic, thallium, phosphorus, dioxin, lead, and chloroform, and hepatic steatosis satisfies this criterion and agrees with the available evidence.
Representativeness	The two studies examined persons in the General Responder Cohort. There were no studies of hepatic steatosis in the survivor population nor from the FDNY, Pentagon, or Shanksville responder cohorts. The findings of the evaluated studies might not be generalizable to other 9/11-exposed groups.