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Environmental risk factors for liver cancer and nonalcoholic fatty liver disease

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Abstract

Purpose of review: The objective of this review was to summarize recent epidemiologic research examining the associations between environmental exposures and liver cancer and nonalcoholic fatty liver disease (NAFLD).

Recent findings: There were 28 liver cancer studies showing positive associations for exposures to aflatoxin, air pollution, polycyclic aromatic hydrocarbons, asbestos, chimney sweeping occupation, and paints; an inverse association for ultraviolet radiation; and null/inconsistent results for organic solvents, pesticides, perfluorooctanoic acid, nuclear radiation, iron foundry occupation, and brick kiln pollution. There were n=5 NAFLD studies showing positive associations for heavy metals, methyl tertiary-butyl ether, and selenium; and no association with trihalomethanes.

Summary: Evidence suggests that particular environmental exposures may be associated with liver cancer and NAFLD. Future liver cancer studies should examine specific histological subtypes and assess historical environmental exposures. Future NAFLD research should examine incident, biopsy-confirmed cases and the potential role of obesity and/or diabetes in studies of environmental factors and NAFLD.

Keywords

liver cancer; nonalcoholic fatty liver disease; environmental exposures; epidemiology; risk factors

Introduction

Liver cancer incidence and mortality has increased in many regions around the world [1–4]. Liver cancer was the seventh leading cause of cancer and the third leading cause of cancer-related death in 2018 [5]. Liver cancer incidence in 2018 was 13.9 per 100,000 among males and 4.9 per 100,000 among females [5]. Rising incidence is accompanied by low five-year

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Compliance with Ethical Standards

Conflict of Interest

Trang VoPham declares no potential conflict of interest.

Human and Animal Rights and Informed Consent

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relative survival rates (ranging from 5–30% from 2000–2014) as many cases are diagnosed at a late stage [6]. The most commonly occurring histological subtype of primary liver cancer is hepatocellular carcinoma (HCC), accounting for over 85% of cases [7]. Risk factors vary by geography and include chronic hepatitis B virus (HBV) infection and aflatoxin in parts of Asia, sub-Saharan Africa, and Guatemala; chronic HCV, heavy alcohol consumption, obesity, diabetes, and smoking are risk factors in parts of North America and Europe [8–10]. In the US, upwards of 40.5% of HCC cases are unexplained by known risk factors including chronic HBV, chronic HCV, alcohol consumption, obesity, and diabetes [11].

In addition to the rise in liver cancer incidence is the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) among adults, adolescents, and children [12–14]. NAFLD, a risk factor for HCC [15], is the most common cause of chronic liver disease in the world affecting approximately 24% of the global population [16]. NAFLD is defined as the presence of ≥5% of hepatic steatosis without competing liver disease etiologies (e.g., HCV), use of medications that induce steatosis (e.g., tamoxifen), other chronic liver diseases (e.g., hemochromatosis), and heavy alcohol consumption [17]. NAFLD is projected to be the next global epidemic as the leading cause of liver-related morbidity and mortality in 20 years [18]. NAFLD can progress to nonalcoholic steatohepatitis (NASH), cirrhosis, and HCC. The major risk factors for NAFLD include obesity, type II diabetes, and dyslipidemia [16]. However, upwards of 30% of NAFLD cases occur among the non-obese (i.e., lean NAFLD; who may have altered metabolic profiles that can lead to diabetes [19]), and up to 52% of cases occur among non-diabetics [20–22].

The liver is susceptible to xenobiotic-induced injury due to its central role in xenobiotic metabolism and its portal location within circulation [23, 24]. Toxic metabolites generated during metabolism are the predominant cause of liver damage, potentially leading to chronic intrahepatic exposures to chemicals that may affect gene expression related to their metabolism [24, 25]. Previous studies have demonstrated that particular environmental exposures, including aflatoxin, vinyl chloride, arsenic, and polycyclic aromatic hydrocarbons (PAHs), are hepatocarcinogenic in humans and animals [24]. Most cases of HCC develop within a background of oxidative stress and inflammation [26, 27]; many of these environmental factors (e.g., PAHs, asbestos) are hypothesized to contribute to liver cancer development through these mechanisms. However, as epidemiologic studies for several of these exposures (apart from aflatoxin) have largely been occupational, the results have been difficult to interpret due to issues such as small sample sizes [24].

To date, research into environmental risk factors for NAFLD has largely been conducted in animal compared to epidemiologic studies [28–30]. As the liver is the central organ controlling lipid homeostasis, exposures to endocrine-disrupting compounds (particularly during early life), such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphenyls (PCBs), benzo[*a*]pyrene, bisphenol A (BPA), and phthalates, have been implicated in the development of fatty liver disease through mechanisms including binding to nuclear hormone receptors and epigenetic alterations [28–30]. Many of these compounds, including BPA and phthalates, have also been shown to promote obesity, which is a risk factor for NAFLD [30]. Further, toxicant-associated fatty liver disease (TAFLD) is a recognized liver

pathology attributed to industrial chemical exposures such as pesticides, PCBs, and dioxin-like compounds (e.g., TCDD) [31, 32]. In addition, individuals with TAFLD may have a low body mass index (BMI) and no insulin resistance, suggesting a pathway unrelated to obesity and diabetes underlying fatty liver disease development in some cases [33].

The environmental epidemiology of liver cancer and NAFLD remain important research areas given existing geographic variation in liver cancer incidence [5, 24] and NAFLD prevalence [34–36], increasing incidence/prevalence [2, 13], HCC and NAFLD cases occurring among individuals without major risk factors [11, 20–22], and demonstrated biological plausibility in the hepatotoxic effects of particular environmental exposures [24, 28–32]. The objective of this narrative review was to summarize recent epidemiologic research examining the associations between environmental exposures and liver cancer and NAFLD.

Methods

Two separate searches of the MEDLINE database (accessed via PubMed) for liver cancer and NAFLD were performed for studies from January 2013 to April 2018. Limits for humans, English language, and original research were applied to the searches. The following terms were searched as exploded MeSH terms and in all fields (e.g., title and abstract): ‘environmental exposures AND liver neoplasms’ and ‘environmental exposures AND non-alcoholic fatty liver disease’. A total of n=359 liver cancer studies and n=31 NAFLD studies were screened by title and abstract for relevance, resulting in n=35 liver cancer studies and n=6 NAFLD studies reviewed for inclusion criteria. Full-text papers were evaluated according to the following *a priori*-determined eligibility criteria for inclusion into the review: an outcome of interest was primary liver cancer or NAFLD (excluding mortality studies due to potential lack of histological confirmation and study results addressing prognosis, e.g., differential survival influenced by socioeconomic factors, rather than cancer development); an exposure of interest was environmental (defined as physical, chemical, biological, social, or economic factors excluding dietary assessments [37]); and appropriate methodological design (.e., studies were excluded if they lacked methodological details to determine the study design, exposure assessment, or statistical analysis) and sufficient reporting of results (i.e., studies were excluded if there were no reported effect estimates). All cited references in each evaluated paper were also examined for inclusion into the review. There were n=28 (n=3 from citation chaining) liver cancer studies and n=5 (n=1 from citation chaining) NAFLD studies included in the review.

Results

Environmental exposures and liver cancer

Summary—There were n=28 liver cancer studies examining the following environmental exposures in Table 1: aflatoxin (4 studies), air pollution (3), polycyclic aromatic hydrocarbons (3), asbestos (3), organic solvents (3), pesticides (6), perfluorooctanoic acid (2), iron foundry occupation (1), radiation (2), brick kiln pollution (1), and parental occupational exposures to chemicals (1) (one study examined multiple exposures) [38–65]. Most studies were conducted in China and Taiwan (n=10) and the US (n=7). There were

n=13 epidemiologic studies conducted among occupationally exposed individuals [38, 40, 42, 43, 45, 46, 53, 57, 60–62, 64, 65]. Environmental exposure assessments included biomonitoring, occupational titles, job-exposure matrices (JEMs), self-report, and geospatial-based methods linking residential locations with exposure models using geographic information systems (GIS). Most studies examined liver cancer combining multiple histologies (e.g., HCC and intrahepatic bile duct cancer).

Aflatoxin—Aflatoxin, produced by fungi forming on food such as corn and rice in moist conditions, is a hepatocarcinogen acting through DNA damage mechanisms [7]. Although aflatoxin is an established risk factor for HCC [66], several studies in China and Taiwan conducted novel investigations into potential gene-environment interactions (GxE) [47, 63], the role of aflatoxin in the etiology of cirrhotic vs. non-cirrhotic HCC [41], and airborne aflatoxin exposure (compared to dietary exposure) [46]. Two retrospective case-control studies showed evidence of GxE interactions between AFB1-albumin and DNA adducts and variants for DNA repair genes (*XRCC1*, *XRCC3*, *XRCC7*, *XRCC4*, *XPC*, *XPD*) on HCC risk [47, 63]. A prospective nested case-control study among chronic HBV carriers showed that higher AFB1-albumin adducts were associated with an increased risk for cirrhotic HCC (adjusted OR 5.47, 95% CI 2.20–13.63) and non-cirrhotic HCC (adjusted OR 5.39, 95% CI 1.11–26.18) [41]. Aflatoxin was also associated with an increased risk for cirrhosis (adjusted OR 2.45, 95% CI 1.51–3.98) and cirrhotic HCC compared to cirrhotic controls (adjusted OR 3.04, 95% CI 1.11–8.30) [41]. Most HCC cases occur among cirrhotics [67]. These results demonstrate that aflatoxin may contribute to the development of cirrhosis, progression of cirrhosis to liver cancer, and the development of liver cancer without inducing cirrhosis. In a retrospective case-control study of sugar and papermaking factory workers, self-reported occupational exposure to airborne aflatoxin was associated with increased HCC risk (adjusted OR 5.24, 95% CI 2.77–9.88) [46].

Air pollution—Air pollution includes a mixture of substances (e.g., PAHs, particulate matter [PM]) from natural and anthropogenic sources and is classified as an International Agency for Research on Cancer (IARC) Group 1 human carcinogen (mainly based on lung cancer evidence) [68]. In particular, PM <2.5 microns in diameter ($PM_{2.5}$) has been shown to induce oxidative damage, inflammation, and genotoxicity in the liver [69]. Two prospective cohort studies in Taiwan and Europe showed generally positive associations between geospatial-based residential PM and nitrogen oxides (NO_x) exposures and liver cancer risk [49, 51]. $PM_{2.5}$ exposure was associated with increased HCC risk on the Taiwan Penghu Islands (adjusted HR 1.22, 95% CI 1.02–1.47 per IQR 0.73 $\mu g/m^3$ increase), although no association was observed on the Main Island [49]. In the European Study of Cohorts for Air Pollution Effects (ESCAPE) study, there were positive but non-statistically significant associations between exposures (such as to NO_x and $PM_{2.5}$) and liver cancer risk (adjusted HRs ranging from 1.04–1.44) [51]. In a retrospective case-control study in China, self-reported indoor air pollution (adjusted OR 2.46, 95% CI 1.47–4.14), environmental tobacco smoke (ETS) at home (adjusted OR 2.16, 95% CI 1.25–3.72), and ETS at work (adjusted OR 1.90, 95% CI 1.08–3.35) were associated with increased HCC risk [48].

Polycyclic aromatic hydrocarbons (PAHs)—PAHs are chemicals forming from incomplete combustion of materials such as coal, gasoline, tobacco, and grilled meats [70]. Benzo[*a*]pyrene (B[*a*]P) and occupational exposure of chimney sweepers (such as to soot, which contains toxic agents including PAHs) are IARC Group 1 human carcinogens [71, 72]. A retrospective case-control study in China showed higher levels of B[*a*]P in blood was associated with increased HCC risk (adjusted OR 7.44, 95% CI 5.29–10.45) [54]. Another retrospective study in China demonstrated higher levels of serum BPDE-albumin adducts and *GSTP* (detoxification gene) hypermethylation among HCC cases compared to controls and evidence of their interaction on HCC risk [55]. However, as blood was measured at enrollment, it is unclear if these epigenetic alterations are a driver or result of hepatocarcinogenesis [73, 74]. In a retrospective cohort study in Sweden, chimney sweeping occupation was associated with increased liver cancer risk (SIR 2.48, 95% CI 1.47–3.91) compared to the general Swedish male population [43].

Asbestos—Asbestos, an IARC Group 1 human carcinogen acting through mechanisms inducing genotoxicity, inflammation, and oxidative stress, includes naturally occurring mineral silicate fibers that were widely used in industrial and commercial applications including roofing and insulation [75]. Although asbestos has been banned in many countries, occupational exposure may still occur such as through shipbreaking [61]. Three retrospective studies examined occupational asbestos exposure in France and Taiwan [38, 61, 62]. Compared to the general population in France, there was an increased risk for liver cancer among asbestos-exposed workers for males (SIR 1.85, 95% CI 1.09–2.92), but not for females among whom there was n=1 case [38]. Liver cancer incidence was higher among shipbreaking workers in Taiwan compared to a population-based cohort matched on age, sex, and place of residence (adjusted HR 1.50, 95% CI 1.16–1.94) [61]. Similar positive associations were observed among highly exposed flame cutters and among those with high Total Exposure Potential scores [61]. In a study restricted to a smaller study population of male shipbreaking workers in Taiwan [62], liver cancer incidence was not elevated among shipbreaking workers, although this analysis had fewer cases compared to the more recent study [61] and the comparison group was the general population in Taiwan [62].

Organic solvents—Trichloroethylene (TCE), a volatile organic compound primarily used for cleaning and degreasing metal parts, is an IARC Group 1 human carcinogen primarily based on evidence for kidney cancer, with some positive associations observed for liver cancer [76]. Two prospective studies in Europe examined occupational exposure to TCE and/or perchloroethylene (PER) [42, 57]. There was higher incidence of liver cancer among workers exposed to TCE compared to the general population in Denmark, Finland, and Sweden (SIR 1.93, 95% CI 1.19–2.95) (similar results were observed among males but not females), although urinary trichloroacetic acid (TCE metabolite), measured in a subset of participants, were not associated with liver cancer risk [42]. Occupational TCE was not associated with liver cancer risk in the Nordic Occupational Cancer Cohort, although there was a suggestive positive association between occupational PER exposure and liver cancer risk (HR 1.13, 95% CI 0.92–1.38) [57]. A cancer cluster investigation in the US showed that residence near a US Environmental Protection Agency Superfund study area with suspected TCE contamination was not associated with increased liver cancer incidence, although there

was a limited number of cases and exposure was based on residential addresses at diagnosis [52].

Pesticides—Pesticides are chemicals used to treat pests such as insects, hypothesized to impact hepatocarcinogenesis through mechanisms of oxidative stress, genotoxicity, and immunotoxicity [77]. Dichlorodiphenyltrichloroethane (DDT), an organochlorine insecticide, has been associated with increased HCC risk in several studies (IARC Group 2A) [77, 78]. In a prospective analysis of the Korean Veterans Health Study, occupational Agent Orange exposure (an herbicide contaminated with TCDD used for military tactical use during the Vietnam War) was associated with increased liver cancer risk (adjusted HR 1.16, 95% CI 1.01–1.34) [64]. Associations were stronger when examining those who served in the Vietnam War for >6 months and among those who served in a military unit with a defined tactical area of responsibility [64]. Similar results were observed in a cross-sectional study in the same study population, although liver cancer was based on self-report [65]. In the US-based Agricultural Health Study prospective cohort, higher intensity-weighted lifetime days of occupational metolachlor exposure (an herbicide) was associated with increased liver cancer risk (adjusted RR 3.18, 95% CI 1.10–9.22) [53]. In a retrospective case-control study in the US, geospatial-based residential exposure to pesticides (from organochlorines, organophosphates, and carbamates) was not associated with HCC risk [59], although a suggestive positive association was observed for organochlorine pesticides in analyses limited to study participants residing in agriculturally intensive areas. In a retrospective case-control study in China, self-reported pesticide exposure (adjusted OR 1.99, 95% CI 1.10–3.60) was associated with increased HCC risk [48]. In a retrospective analysis of the Canadian Census Health and Environment Cohort, there was an inverse association with liver cancer risk among male agricultural workers (adjusted HR 0.51, 95% CI 0.38–0.68) and no association among female agricultural workers compared to all other employed individuals; results may have been influenced by the healthy worker effect and/or residual confounding from smoking and alcohol consumption [40].

Perfluorooctanoic acid (PFOA)—PFOA is produced from industrial and consumer products such as Teflon [79]. Animal studies have shown that the liver is an established target for PFOA-induced toxicity; potential mechanisms for carcinogenesis include peroxisome proliferator-activated receptor-α activation and cytotoxicity [80]. In a retrospective study as part of the US-based C8 Health Project, residence in a water district contaminated by a DuPont Teflon-manufacturing plant and predicted serum PFOA levels were not associated with liver cancer risk [56]. In another retrospective study as part of the C8 Health Project and DuPont Worker Cohort, predicted serum PFOA levels were not associated with liver cancer risk [39]. Null associations may be due to low exposure prevalence, a small number of cases, inclusion of HCC and other histologies, usage of other cancer controls, and/or residual confounding [39, 56].

Iron foundry occupation—Although occupational exposures in iron foundries, including from quartz, PAHs, benzene, and asbestos, are considered carcinogenic to humans (IARC

Group 1) [72], a prospective cohort study in Sweden based on a small number of cases showed no association with liver cancer risk compared to the general population [60].

Radiation—An excess in liver cancer incidence has been observed in atomic bomb survivors [81]. In a prospective analysis of nuclear workers in Russia, external gamma (ionizing) radiation measured using individual film badges was not associated with liver cancer risk, although there was a positive association between internal plutonium dose and liver cancer risk based on a small sample size [45]. In contrast, an ecological study in the US showed that ultraviolet (UV) radiation (UV-B wavelengths are involved in cutaneous vitamin D production) was associated with decreased HCC risk (adjusted IRR 0.83, 95% CI 0.77–0.90 per IQR 32.4 mW/m^2 increase) [58].

Brick kiln pollution—Industrial waste from brick kiln-related activities led to groundwater contamination from compounds such as vinyl chloride (established risk factor for liver angiosarcoma and HCC [72]), chlorinated ethenes, and ethanes [50]. In a retrospective cohort study in Italy, there was no observed excess in liver cancer incidence associated with residence in the contaminated East quadrant, a crude proxy for exposure, compared to the general population [50].

Parental occupational exposures to chemicals—A retrospective case-control study of children <15 years old in the US examined self-reported and JEM-based parental occupational exposures from chemicals, such as plastics and paints, in relation to risk for hepatoblastoma, a rare pediatric liver tumor [44]. Likely paternal exposure to paints was associated with increased risk for hepatoblastoma (adjusted OR 1.71, 95% CI 1.04–2.81), although no association was observed for maternal exposures [44].

Environmental exposures and NAFLD—There were n=5 NAFLD studies examining the following environmental exposures in Table 2: heavy metals (2 studies), trihalomethanes (1), methyl tert-butyl ether (1), and selenium (1) [33, 82–85]. All studies were cross-sectional and conducted in China, Taiwan, and the US. One study was conducted among occupationally exposed individuals [84]. Environmental exposure assessments included biomonitoring, personal sampling, and a residential location-based measure. NAFLD was defined using biochemical measures (e.g., alanine aminotransferase or ALT) and/or imaging.

Heavy metals—Environmental contamination from heavy metals is primarily sourced from industrial and agricultural activities, potentially promoting NAFLD development through mechanisms related to inflammation and insulin resistance [33, 83, 86]. In Taiwan, residential township-based heavy metals exposure (from arsenic, cadmium, chromium, copper, lead, mercury, nickel, and zinc – several of which are IARC Group 1 human carcinogens [75]) was associated with NAFLD among males (adjusted OR 1.83, 95% CI 1.16–2.90) but not females [33]. Although those with heavy alcohol consumption were not excluded, the authors noted that subjects with a history of alcohol consumption were light drinkers [33]. Statistically significant positive associations were observed for copper, chromium, nickel, and zinc (adjusted ORs ranging from 1.01–1.06), and for heavy metals (combined) among lean individuals with BMI <24 kg/m^2 [33]. Sex-based differences were also observed in the US-based National Health and Nutrition Examination Survey

(NHANES), where urinary cadmium levels were associated with NAFLD among males (adjusted OR 1.30, 95% CI 1.01–1.68) but not females [83]. Positive associations were also observed for hepatic necroinflammation (elevated liver enzymes) and NASH (progressive form of NAFLD), providing potential evidence for metals-induced hepatotoxicity being associated with a spectrum of liver disease outcome measures [83].

Trihalomethanes (THMs)—THMs are by-products formed from chlorination of drinking water, likely contributing to hepatotoxicity through oxidative stress [82]. Using NHANES, total THM levels in blood were not associated with NAFLD, although a positive association was observed for dibromochloromethane (adjusted OR 1.35, 95% CI 1.02–1.79) [82].

Methyl tertiary-butyl ether (MTBE)—MTBE is a component of gasoline that induces oxidative stress in animal studies [84]. Among petrol station attendants in China, there was a suggestive positive association between occupational MTBE exposure from personal monitoring and NAFLD (adjusted OR 1.52, 95% CI 0.93–1.61) [84].

Selenium—Selenium, a naturally occurring trace element that is also formed from industrial activities in electronics and glass, has been associated with increased insulin resistance and triglycerides in animal studies [85]. Plasma selenium levels were associated with NAFLD in China (adjusted OR 1.54, 95% CI 1.13–2.18) [85].

Discussion

In this narrative review of recent epidemiologic literature on environmental risk factors for liver cancer and NAFLD, there were n=28 liver cancer studies examining the effects of aflatoxin, air pollution, PAHs, asbestos, organic solvents, pesticides, PFOA, iron foundry occupation, radiation, brick kiln pollution, and parental occupational exposures to chemicals [38–65] and n=5 NAFLD studies examining the effects of heavy metals, THMs, MTBE, and selenium [33, 82–85].

Studies on the environmental epidemiology of liver cancer in recent years have expanded to provide new perspectives on established risk factors (i.e., aflatoxin) through conducting GxE research. Several studies demonstrated evidence of GxE interactions between serum aflatoxin and genetic polymorphisms in DNA repair genes (e.g., *XRCC4*) [47, 63], highlighting potential biological mechanisms through which aflatoxin may impact the development of HCC and identifying individuals who may be more susceptible to aflatoxin-induced liver cancer. Future GxE research should consistently conduct and report formal tests for interaction [87]. In addition, one prospective study investigated the impact of aflatoxin on cirrhosis and cirrhotic and non-cirrhotic HCC, which would be informative to explore in a study population that is not entirely comprised of chronic HBV carriers [41].

Environmental-focused liver cancer studies have also expanded to investigate factors classified as IARC Group 1 human carcinogens that have been less extensively studied in liver cancer (e.g., air pollution). For example, several prospective epidemiologic studies suggested a positive association between residential air pollution, particularly $PM_{2.5}$, and liver cancer risk [49, 51]. Geospatial-based methods in linking geocoded residential

addresses to exposure models using GIS have enabled the objective estimation of ambient environmental exposures within these large population-based studies [49, 51]. Positive associations in the ESCAPE study were not statistically significant [51]; inconsistent findings may be associated with examining HCC and other histologies [51] and temporal mismatches where exposures were estimated after liver cancer cases were diagnosed [49, 51]. Nonetheless, these air pollution findings are bolstered by how smoking is a risk factor for liver cancer [88] and several constituents in air pollution (e.g., PAHs, heavy metals such as cadmium) are also present in tobacco smoke [89]. Another study showed positive associations between self-reported indoor air pollution and ETS and HCC risk [48]. Further, B[*a*]P (a PAH) and occupational exposure among chimney sweepers to soot (which contains compounds such as PAHs and asbestos) were associated with increased liver cancer risk [43, 54, 55], with one study revealing evidence of an interaction between serum B[*a*]P and epigenetic alterations in *GSTP* hypermethylation [55]. Future research should examine historical exposures relevant to hepatocarcinogenesis to address a potential latency period (e.g., up to 20 years before diagnosis) and consider potential confounding by factors such as diabetes (associated with both $PM_{2.5}$ and HCC [90, 91]). HBV and HCV may not be strong confounders in study populations with low prevalence of these infections and as they may not be related to the fine-scale spatial distribution of air pollution (although they may be associated with general urban-rural patterns) [51].

Several retrospective studies demonstrated positive associations between occupational asbestos exposure and liver cancer risk, although they did not adjust for liver cancer risk factors and/or were limited in sample size [38, 61]. An ecological study showed an inverse association between UV radiation and HCC risk, which is consistent with previous epidemiologic research showing that serum vitamin D is associated with decreased HCC risk [92]. Additional research is needed using higher resolution exposure measures and accounting for individual-level HCC risk factors [58]. Although several recent studies examining pesticides were mixed [40, 48, 59], three studies (two were prospective) showed geospatial-based occupational Agent Orange exposure [64, 65] and occupational metolachlor exposure [53] increased liver cancer risk. This is consistent with evidence implicating organochlorine compounds with the development of HCC [77]; the insecticide DDT and TCDD, as a contaminant in Agent Orange, are organochlorines. Self-reported paternal occupational exposure to paints was associated with increased risk for hepatoblastoma, although results may be impacted by recall bias [44]. These findings should be further investigated.

Several studies showed null or inconsistent associations with organic solvents (TCE and PER) [42, 52, 57], pesticides [40, 48, 59], PFOA [39, 56], radiation [45], iron foundry occupation [60], and brick kiln pollution [50]. Several of these studies were occupational, characterized by a small number of cases, inconsistent case definitions, potential residual confounding from known liver cancer risk factors such as alcohol consumption and smoking, crude exposure assessments, and/or the healthy worker effect [40, 42, 45, 57, 60]. Non-occupational studies were also limited by sample size [39, 50, 52]. Differences in case confirmation as well as examination of different histological subtypes of liver cancer (including HCC and intrahepatic bile duct cancer) may have contributed to null/inconsistent results, as risk factor associations have varied by histology [93]. Limitations in exposure

assessment may have also influenced results, such as using coarse-scale geographic variables within which exposures may vary, residential location at diagnosis, and self-report [48, 50, 52, 56, 59].

Compared to the literature on liver cancer, the environmental epidemiology of NAFLD is a nascent field, reflected in the relatively modest number of studies included in this review. Several studies showed positive associations between exposures to selenium [85], heavy metals such as cadmium, copper, chromium, nickel, and zinc [33, 83] measured in urine or based on residential location and NAFLD. Sex-based differences in heavy metals adversely affecting males but not females may be due to the anti-inflammatory properties of estrogen [33]. Interestingly, heavy metals exposure was positively associated with NAFLD among individuals with BMI <24 kg/m^2, suggesting that adipose tissue may sequester toxins [33, 94]. In addition, there was a suggestive positive association for occupational exposure to MTBE and NAFLD [84] and no association with THMs [82].

However, the NAFLD studies included in this review were cross-sectional examining NAFLD prevalence, precluding the determination of a temporal relationship between exposure and outcome and making it difficult to interpret the findings. In addition, NAFLD was determined based on biochemical tests and/or imaging subject to outcome misclassification compared to the gold standard of liver biopsy. Prospective studies ascertaining biopsy-confirmed NAFLD with long-term follow-up to evaluate incidence are needed. In addition, as these environmental exposures are suspected to affect NAFLD development through mechanisms related to increased triglycerides, insulin resistance, oxidative stress, and/or inflammation, future research should explore if obesity and/or diabetes may mediate these potential associations, as well as identify risk factors among the non-obese to investigate the etiology of lean NAFLD.

Conclusions

Recent epidemiologic studies demonstrated that particular environmental factors may be associated with liver cancer risk, including air pollution; PAHs such as B[*a*]P; asbestos; chimney sweeping occupation; ultraviolet radiation; and paternal occupational exposure to paints. There was evidence of GxE interactions between aflatoxin, an established liver cancer risk factor, and genetic polymorphisms in DNA repair genes. Exposures to organic solvents such as TCE; pesticides; PFOA; nuclear ionizing radiation; iron foundry occupation; and brick kiln pollution showed null or inconsistent associations with liver cancer. Several studies showed generally positive associations between heavy metals (e.g., cadmium), selenium, MTBE, and NAFLD; no association was observed for THMs. Additional studies are needed to confirm these findings. Future liver cancer research should examine specific histological subtypes (e.g., HCC) and examine historical environmental exposures to address a potential latency period. Future NAFLD research should examine biopsy-confirmed, incident NAFLD cases, mediation by major NAFLD risk factors such as obesity and diabetes, and associations among lean NAFLD cases.

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•• Of major importance

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Table 1.

Epidemiologic studies examining environmental risk factors for liver cancer (2013–2018)

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
Aflatoxin								
Long et al. (2013) [47]	China	Retrospective case-control, GxE	2004–2010	Hospital-based; n=2,045 healthy controls matched on age, sex, ethnicity, HBV, HCV	Aflatoxin	Serum AFB1-DNA adducts	HCC (n=1,499) confirmed via histology	Higher AFB1-DNA adduct levels (≥2.01 μmol/mol DNA) compared to lower levels (<1.00 μmol/mol DNA) was associated with increased risk for HCC (OR 6.43, 95% CI 5.28–7.83) adjusting for age, sex, ethnicity, HBV, HCV, dietary aflatoxin Main effect for *XRCC4* gene is associated with HCC risk Evidence of GxE interaction was observed for *XRCC4* gene (multiplicative scale) (p int. not reported)
Yao et al. (2014) [63]	China	Retrospective case-control, GxE	2004–2012	Hospital-based; n=1,996 healthy controls matched on age, sex, ethnicity, HBV, HCV	Aflatoxin	Serum AFB1albumin adducts	HCC (n=1,486) confirmed via histology	Higher AFB1-albumin levels (>2.98 ln fmol/mg) compared to lower levels (2.18 ln fmol/mg) were associated with increased risk for HCC (OR 6.52, 95% CI 5.46–7.79) adjusting for age, sex, ethnicity, HBV, HCV Main effects for *XRCC1, XRCC3, XRCC7, XRCC4, XPC,* and *XPD* genes are associated with HCC risk GxE interactions were observed for each gene (multiplicative scale) (p int. <0.01)
Chu et al. (2017) [41]	Taiwan	Prospective nested casecontrol	1991–2004	Chronic HBV carriers; n=577 controls matched on age, sex, residence, date of blood collection	Aflatoxin	Serum AFB1-albumin adducts	HCC (n=262) confirmed via cancer registry and medical records (histology, imaging, or serum AFP ≥400 ng/mL)	Higher AFB1-albumin levels (≥21.5 fmol/mg) compared to undetectable levels were associated with increased risk for cirrhotic HCC (OR 5.47, 95% CI 2.20–13.63) and non-cirrhotic HCC (OR 5.39, 95% CI 1.11–26.18) adjusting for age, sex, alcohol consumption, serum ALT
Lai et al. (2014) [46]	China	Retrospective case-control	1994–2013	Sugar and papermaking factory workers; n=150 healthy controls who worked for same company	Aflatoxin	Self-reported airway exposure	HCC (n=68) confirmed via medical records	Occupational airborne aflatoxin dust exposure compared to no exposure was associated with increased risk for HCC (OR 5.24, 95% CI 2.77–9.88) adjusting for sex, alcohol consumption, smoking, HBV, family history of HCC
Air pollution								

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
Pan et al. (2016) [49]	Taiwan	Prospective cohort	1991–2009	Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study (n=22,062)	$PM_{2.5}$	Geocoded address linked to GIS-based exposure model developed using kriging methods	HCC (n=464) confirmed via histology, imaging, AFP, and cancer registry	$PM_{2.5}$ exposure was associated with increased risk for HCC on the Taiwan Penghu Islands (HR 1.22, 95% CI 1.02–1.47 per IQR 0.73 μg/m^3 increase) adjusting for age, sex, alcohol consumption, smoking, ALT, HBV, HCV
Pedersen et al. (2017) [51]	Austria, Denmark, Italy	Prospective cohort	1985–2012	Four cohorts in European Study of Cohorts for Air Pollution Effects (ESCAPE) study (n=174,770)	Available for all cohorts: NO_2 and NO_x; available for Denmark and Austria only: $PM_{10,}$ PM2.5, PM2.5–10, PM absorbance (soot), traffic density	Baseline geocoded residential address linked to GIS-based exposure models developed using land use regression	Liver cancer (n=279) confirmed via cancer registry	Higher exposures to NO_2 (HR 1.10, 95% CI 0.93–1.30 per 10 μg/m^3), NO_x (HR 1.12, 95% CI 0.96–1.30 per 20 μg/m^3), $PM_{2.5}$ (HR 1.34, 95% CI 0.76–2.35 per 5 μg/m^3), $PM_{2.5}$ absorbance (HR 1.21, 95% CI 0.68–2.15 per 10^{-5} μg/m^3), PM_{10} (HR 1.44, 95% CI 0.83–2.52 per 10 μg/m^3), $PM_{2.5}10$ (HR 1.34, 95% CI 0.65–2.78 per 5 μg/m^3), traffic density (HR 1.04, 95% CI 0.89–1.20 per 5,000 vehicles/day) were associated with non-statistically significant positive associations with liver cancer risk adjusting for age, sex, year, smoking, alcohol consumption, occupational exposures, employment status, education, area-specific SES
Niu et al. (2016) [48]	China	Retrospective case-control	2011–2014	Residents of Xiamen; n=346 healthy controls frequency-matched on age, sex	Indoor air pollution, pesticides, environmental tobacco smoke (ETS)	Self-reported exposure	HCC (n=314) confirmed via histology	Pesticide exposure (OR 1.99, 95% CI 1.10–3.60), indoor air pollution (OR 2.46, 95% CI 1.47–4.14), ETS at home (OR 2.16, 95% CI 1.25–3.72), and ETS at work (OR 1.90, 95% CI 1.08–3.35) were associated with increased risk for HCC adjusting for education, HBV, liver disease history, alcohol consumption, fruit consumption, tea consumption
Polycyclic aromatic hydrocarbons								
Su et al. (2014) [54]	China	Retrospective case-control	2007–2009	Hospital-based; n=961 healthy controls matched on age, sex, ethnicity	B[*a*]P	BPDE-DNA adducts in blood	HCC (n=345) confirmed via histology	Higher BPDE-DNA adduct levels (>0.71 fmol/μg) compared to lower levels (<0.31 fmol/μg) were associated with increased risk for HCC (OR 7.44, 95% CI 5.29–10.45) adjusting for age, sex, education, HBV, alcohol consumption, smoking, contaminated water drinking
								Higher BPDE-albumin adduct levels were observed among cases (median 1.79 fmol/mg, no IQR reported) compared to controls (median 1.51 fmol/mg) (p<0.01) Higher *GSTP* hypermethylation was observed among cases (53.3%) compared to controls (17.2%) (p<0.01)

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
Tian et al. (2016) [55]	China	Retrospective case-control	Not reported	Hospital-based; n=99 healthy volunteers	B[*a*]P	Serum BPDE-albumin adducts	HCC (n=90) confirmed via clinical diagnosis or imaging	Evidence of interaction was observed between BPDE-albumin adducts and *GSTP* gene methylation (multiplicative scale) adjusting for age, sex, BMI, alcohol consumption, smoking, liver cirrhosis, HBV, HCV
Hogstedt et al. (2013) [43]	Sweden	Retrospective cohort	1958–2006	Male chimney sweep trade union members (n=6,320)	Chimney sweeping occupation	Occupational title from Swedish Municipal Workers' Union	Liver cancer (n=18) confirmed via cancer registry	Chimney sweepers compared to the general Swedish male population had an increased risk for liver cancer (SIR 2.48, 95% CI 1.47–3.91)
Asbestos								
Boulanger et al. (2015) [38]	France	Retrospective cohort	1978–2009	Asbestos-exposed workers (n=2,024)	Asbestos	JEM	Liver cancer (n=18 males; n=1 female) confirmed via cancer registry	Asbestos-exposed workers compared to the general population in Calvados, France had an increased risk for liver cancer among males (SIR 1.85, 95% CI 1.09–2.92) but not females (SIR 2.55, 95% CI 0.03–14.2)
Wu et al. (2015) [61]	Taiwan	Retrospective cohort	1985–2008	Shipbreaking Workers Union; n=4,427 shipbreaking workers and population-based cohort (n=22,135) matched on age, sex, place of residence	Asbestos	Occupational title and Total Exposure Potential (TEP) Score estimated by panel of occupational experts	Liver cancer (n=349) confirmed via cancer registry	Shipbreaking workers compared to the population-based matched cohort had an increased risk for liver cancer (HR 1.50, 95% CI 1.16–1.94) adjusting for premium ratable wage per month
Wu et al. (2014) [62]	Taiwan	Retrospective cohort	1985–2008	Shipbreaking Workers Union (n= 4,155 males)	Asbestos	Occupational title and TEP Score estimated by panel of occupational experts	Liver cancer (n=72) confirmed via cancer registry	Liver cancer incidence was not elevated among shipbreaking workers compared to the general population in Taiwan (5-year latency period: SIR 1.05, 95% CI 0.82–1.33)
Organic solvents								
Hansen et al. (2013) [42]	Denmark, Finland, Sweden	Prospective cohort	1958–2008	Workers exposed to TCE (n=5,553)	TCE	Occupational title and urinary TCE metabolite (UTCA)	Liver cancer (n=15 males; n=5 females) confirmed via cancer registry	Workers exposed to TCE compared to the general population in Denmark, Finland, and Sweden had an increased risk for liver cancer (SIR 1.93, 95% CI 1.19–2.95) Higher U-TCA levels (>50 mg/L) compared to lower levels (<5 mg/L) were not associated with liver cancer risk (HR 0.63, 95% CI 0.22–1.68) adjusting for age, sex, country, calendar time
								Higher TCE exposure (highest tertile median 0.77 unit-years) compared to the occupationally unexposed was not associated with liver cancer risk (HR 1.00, 95% CI 0.90–1.11)

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
Vlaanderen et al. (2013) [57]	Denmark, Finland, Iceland, Norway, Sweden	Prospective nested casecontrol	1960–2005	Nordic Occupational Cancer Cohort (n>45 million); n=119,480 controls matched on age, sex, country	TCE and PER	JEM	Liver cancer (n=23,896) confirmed via cancer registry	PER exposure (highest tertile median 0.77 unit-years) compared to the occupationally unexposed was suggestively associated with liver cancer risk (HR 1.13, 95% CI 0.92–1.38)
Press et al. (2016) [52]	US	Cancer cluster	1988–2011	Greater Bay Area Cancer Registry catchment area in California	TCE	Residence in Middlefield-Ellis-Whisman (MEW) Superfund study area defined using Census tracts at diagnosis	Liver cancer (n≤17) confirmed via cancer registry	Liver cancer incidence was not elevated among residents in the MEW study area compared to the general population in Monterey, San Benito, Santa Clara, and Santa Cruz counties (1988–1995: SIR 0.8, 95% CI 0.1–2.8; 1996–2005: SIR 0.9, 95% CI 0.3–2.1; 2006–2011: SIR 0.6, 95% CI 0.1–1.6)
Pesticides								
Yi et al. (2014) [64]	Korea	Prospective cohort	1992–2003	Korean Veterans Health Study (n=180,251 males)	Agent Orange	Exposure Opportunity Index model (E4) using GIS-based proximity of military unit to area sprayed with Agent Orange	Liver cancer (n=1,956) confirmed via cancer registry	High Agent Orange exposure ($\log_{10}$ E4 ≥5) compared to no exposure ($\log_{10}$ E4 <0.1) was associated with increased risk for liver cancer (HR 1.16, 95% CI 1.01–1.34) adjusting for age at cohort entry, military rank
Yi et al. (2013) [65]	Korea	Cross-sectional	2004	Korean Veterans Health Study (n=114,562)	Agent Orange	Self-report and E4 using GIS-based proximity of military unit to area sprayed with Agent Orange	Liver cancer (n=2,242) from self-report	Self-reported high Agent Orange exposure (levels not reported) compared to low exposure was associated with increased risk for liver cancer (OR 1.74, 95% CI 1.54–1.96) adjusting for age, BMI, military rank, smoking, alcohol consumption, physical activity, education, household income, herbicide use
Silver et al. (2015) [53]	US	Prospective cohort	1993–2011	Agricultural Health Study (n=49,616)	Metolachlor	Lifetime days and intensity-weighted lifetime days (from self-report)	Liver cancer (n=40) confirmed via cancer registry	Higher lifetime days (>108.5 days; RR 3.99, 95% CI 1.43–11.1) and higher intensity-weighted lifetime days (>4,103 units; RR 3.18, 95% CI 1.10–9.22) of metolachlor use compared to unexposed individuals was associated with increased risk for liver cancer adjusting for age, smoking, alcohol consumption, applicator status, family history of cancer, state of residence, pesticides correlated with metolachlor (e.g., atrazine)
VoPham et al. (2015) [59]	US	Retrospective case-control	2000–2009	SEER-Medicare; n=14,991 controls frequency-matched on age, sex, race, duration of California residence, year	Pesticides (organochlorines, organophosphates, carbamates)	Residential ZIP Code linked with GIS-based exposure model	HCC (n=3,034) confirmed via cancer registry	Higher pesticide exposure (≥1.85 kg/km^2) compared to lower exposure (≤0.07 kg/km^2) was not associated with HCC risk (OR 0.95, 95% CI 0.82–1.09) adjusting for age, sex, race, duration of California residence, year, liver disease, diabetes, rare genetic disorders, SES

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
Kachuri et al. (2017) [40]	Canada	Retrospective cohort	1991–2010	Canadian Census Health and Environment Cohort (CanCHEC) (n=2,051,315)	Agricultural occupation	Self-reported occupation	Liver cancer (n=45 males; n=15 females) confirmed via cancer registry	There was an inverse association with liver cancer risk among male agricultural workers (HR 0.51, 95% CI 0.38–0.68) and no association among female agricultural workers (HR 0.90, 95% CI 0.51–1.57) compared to other employed individuals adjusting for age at cohort entry, province of residence, education
Perfluorooctanoic acid								
Vieira et al. (2013) [56]	US	Retrospective case-control	1996–2005	C8 Health Project (n=25,107 cancer cases) residents living near DuPont Teflonmanufacturing plant; other-cancer controls excluding kidney, pancreatic, testicular, and liver	PFOA	Residential water district and for Ohio residents only: predicted serum PFOA levels estimated using pharmacokinetic model and geocoded residential addresses at diagnosis linked with GIS-based exposure model	Liver cancer (n=179) confirmed via cancer registry	Residence in a contaminated water district (OR 1.1, 95% CI 0.7–1.6) and predicted serum PFOA levels (high 30.8–109.0 μg/L compared to unexposed: OR 1.0, 95% CI 0.3–3.1) was not associated with liver cancer risk adjusting for age, sex, race, diagnosis year, insurance provider, smoking
Barry et al. (2013) [39]	US	Retrospective cohort	1952–2011	Residents of MidOhio Valley as part of C8 Health Project and DuPont Worker Cohort (n=32,254)	PFOA	Predicted serum PFOA levels described above [56]; JEM was used for DuPont workers	Liver cancer (n=9) confirmed via cancer registry and medical records	PFOA exposure was not associated with liver cancer risk (HR 0.73, 95% CI 0.43–1.23) adjusting for age, sex, smoking, alcohol consumption, education, birth year
Iron foundry occupation								
Westberg et al. (2013) [60]	Sweden	Prospective cohort	1958–2004	Iron foundry workers (n=3,045 males)	Iron foundry occupation	Occupational title	Liver cancer (n=12) confirmed via cancer registry	Liver cancer incidence was not elevated among iron foundry workers compared to the general population in Sweden (SIR 1.59, 95% CI 0.82–2.78)
Radiation								
Labutina et al. (2013) [45]	Russia	Prospective cohort	1948–2004	Mayak nuclear workers (n=22,373)	Radiation: nuclear	External gamma radiation from individual film badges and internal plutonium dose from urine samples and biokinetic models	Liver cancer (n=46) confirmed via cancer registry and medical records	External gamma radiation dose was not associated with liver cancer risk (results not shown) Higher cumulative internal plutonium liver dose (≥4 Gy) compared to a lower lose (0 Gy) was associated with increased risk for liver cancer (RR 283.8, 95% CI 99.4–867.4) adjusting for age, sex, alcohol consumption
VoPham et al. (2017) [58]	US	Ecological	2000–2014	SEER	Radiation: ultraviolet (UV)	Residential county at diagnosis linked with GIS-based exposure model	HCC (n=56,245) confirmed via cancer registry	Higher ambient UV exposure was associated with decreased HCC risk (IRR 0.83, 95% CI 0.77–0.90 per IQR 32.4 mW/m^2) adjusting for age at diagnosis, sex, race, year of diagnosis, SEER registry, and area-level alcohol consumption, smoking,

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
								obesity, diabetes, median household income, unemployment, urbanicity, $PM_{2.5}$
Brick kiln pollution								
Pasetto et al. (2013) [50]	Italy	Retrospective cohort	1994–2007	Residents in East quadrant, Ferrara, Italy (n=2,578)	Brick kiln pollution (e.g., vinyl chloride, chlorinated ethenes, ethanes)	Residence in polluted area	Liver cancer (n=8) confirmed via cancer registry	Liver cancer incidence was not elevated among residents of the East quadrant compared to the general population in Ferrara, Italy (SIR 1.35, 90% CI 0.672.43)
Parental occupational exposures to chemicals								
Janitz et al. (2017) [44]	US	Retrospective case-control	2000–2008	HOPE study; n=387 birth certificate controls frequency-matched on sex, region of birth, birth weight	Parental occupational exposures (e.g., plastics, paints, diesel)	Self-reported parental occupational exposures and JEM	Hepatoblastoma (n=383) prior to 15 years of age confirmed via histology	Likely paternal exposure to paints compared to unlikely exposure was associated with increased risk for hepatoblastoma (OR 1.71, 95% CI 1.04–2.81) adjusting for year of birth, sex, region of birth, birth weight, household income

Abbreviations: AFB1, aflatoxin B1; AFP, alpha-febottomrotein; ALT, alanine aminotransferase; B[*a*]P, benzo[*a*]pyrene; BMI, body mass index; BPDE, benzo[*a*]pyrene diolepoxide; CI, confidence interval; GIS, geographic information system; GxE, gene-environment interaction; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; int, interaction; IRR, incidence rate ratio; JEM, job-exposure matrix; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OR, odds ratio; PER, perchloroethylene; PFOA, perfluorooctanoic acid; PM_{10}, particulate matter <10 microns; $PM_{2.5}$, particulate matter <2.5 microns; $PM_{2.5–10}$, particulate matter 2.5–10 microns; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results; SES, socioeconomic status; SIR, standardized incidence ratio; TCE, trichloroethylene; U-TCA, urinary trichloroacetate.

Table 2.

Epidemiologic studies examining environmental risk factors for NAFLD (2013–2018)

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
Heavy metals								
Lin et al. (2017) [33]	Taiwan	Crosssectional	2014	Hospital-based; n=1,137 individuals receiving transabdominal sonography	Heavy metals: arsenic, cadmium, chromium, copper, lead, mercury, nickel, zinc	Residential township linked with survey of soil heavy metal concentrations	NAFLD (n=301) using transabdominal sonography; exclusions for drug history of total parenteral nutrition, long-term use of estrogen, tamoxifen, amiodarone, sodium valproate, methotrexate or corticosteroids	Heavy metals exposures was associated with NAFLD among males (OR 1.83, 95% CI 1.16–2.90) but not females (OR 1.06, 95% CI 0.57–1.96) adjusting for age, BMI, metabolic syndrome, smoking, alcohol consumption, SES
Hyder et al. (2013) [83]	US	Crosssectional	1988–1994	National Health and Nutrition Examination Survey (NHANES)	Heavy metals: cadmium	Creatinine-corrected urinary cadmium	NAFLD (n=1,175 males and n=1,147 females) using gallbladder ultrasound videotapes and ALT or AST levels; exclusions for heavy alcohol consumption or zydovudine or didanosine use	Higher urinary cadmium levels (≥0.65 μg/g for males and ≥0.83 μg/g for females) compared to lower levels were associated with NAFLD among males (OR 1.30, 95% CI 1.01–1.68) but not females (OR 1.11, 95% CI 0.88–1.41) adjusting for age, race/ethnicity, education, smoking, pack years, sedentary lifestyle, BMI, alcohol consumption, total cholesterol
Trihalomethanes								
Burch et al. (2015) [82]	US	Crosssectional	1999–2006	NHANES	THM	Blood THM	NAFLD (n=353) using elevated ALT levels (>40 IU/L for males; >30 IU/L for females); exclusions for heavy alcohol consumption, HBV, HCV, self-reported liver cancer, or high transferrin saturation levels	Higher total THM levels (highest tertile mean 62.0 ± 88.9 pg/mL) compared to lower levels (mean 7.4 ± 2.5 pg/mL) were not associated with NAFLD (OR 1.23, 95% CI 0.87–1.72) adjusting for age, race, smoking, BMI, alcohol consumption,

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment	Outcome	Main findings
								selfreported high BP, diastolic BP, total cholesterol, albumin
Methyl tert-butyl ether								
Yang et al. (2016) [84]	China	Crosssectional	2014	Petrol station attendants (n=71)	MTBE	Personal exposure monitoring using charcoal-based organic vapor monitor	NAFLD (n=11) using abdominal ultrasonography; exclusions for heavy alcohol consumption, HBV, HCV, autoimmune hepatitis, primary biliary cirrhosis, or other chronic liver disease	Higher MTBE exposure (≥300 μg/m^3) compared to lower exposure (≤100 μg/m^3) was suggestively associated with NAFLD (OR 1.52, 95% CI 0.93–1.61) adjusting for age, sex, physical activity, BMI, SBP, DBP, ALT, WBC, TC, TG, LDL, HDL
Selenium								
Yang et al. (2016) [85]	China	Crosssectional	2011–2012	Shanghai subsample of Risk Evaluation of Cancers in Chinese Diabetic Individuals: a Longitudinal study (REACTION) (n=8,550)	Selenium	Plasma selenium	NAFLD (n=3,732) using ultrasonography; exclusions for heavy alcohol consumption or history of liver disease	Higher selenium levels (>247.4 μg/L) compared to lower levels (<181.6 ug/L) were associated with NAFLD (OR 1.54, 95% CI 1.13–2.18) adjusting for age, sex, BMI, smoking, alcohol consumption, physical activity, waist circumference, SBP, DBP, fasting plasma glucose, post-loading plasma glucose, HOMA-IR, lipid profiles and estimated glomerular filtration rate, ALT, AST, GGT, CRP

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; MTBE, methyl tert-butyl ether; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; SBP, systolic blood pressure; SES, socioeconomic status; TC, total cholesterol; TG, triglyceride; THM, trihalomethane; WBC, white blood cell.