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REVIEW

Chemical Risk Factors of Primary Liver Cancer: An Update

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Adam Barsouk[1]
Krishna Chaitanya Thandra[2]
Kalyan Saginala[3]
Prashanth Rawla[4]
Alexander Barsouk[5]

[1]Sidney Kimmel Cancer Center, Jefferson University, Philadelphia, PA 19107, USA; [2]Department of Pulmonary and Critical Care Medicine, Sentara Virginia Beach General Hospital, Virginia Beach, VA, USA; [3]Plains Regional Medical Group Internal Medicine, Clovis, NM 88101, USA; [4]Department of Medicine, Sovah Health, Martinsville, VA 24112, USA; [5]Hematologist-Oncologist, Allegheny Health Network, Pittsburgh, PA 15212, USA

Abstract: Primary liver cancer has the sixth highest incidence and fourth highest cancer mortality worldwide. Hepatitis B is the leading cause of liver cancer, though its incidence is decreasing with vaccination. Alcohol is the leading cause of liver transplant, cirrhosis, and cancer in the developed world, and is projected to surpass hepatitis B as the leading hepatic cancer etiology worldwide. Tobacco smoking has shown a positive association with liver cancer in a majority of studies, though not all. Aflatoxin, a mycotoxin produced by *Aspergillus*, is estimated to account for 3–20% of global liver cancer cases, 40% of which occur in sub-Saharan Africa. These statistics are confounded by the prevalence of hepatitis B, which may have a synergistic effect on hepatic carcinogenesis. Aflatoxin is ingested and likely inhaled from agricultural products, placing farmers, food processors, and textile workers in developing nations at risk. Vinyl-chloride is used in the production of PVC plastics and causes rare liver angiosarcoma, hepatocellular carcinoma, and other neoplasms. Arsenic and cadmium are naturally-occurring, hepatocarcinogenic metals with high occupational exposure in industries involving coal, metals, plastics, and batteries. Millions of laborers in waste-disposal and manufacturing are exposed to organic solvents and N-nitrosamines, which vary from carcinogenic (group 1) to possibly carcinogenic (group 2B) in their IARC designation. Insecticide DDT is possibly hepatocarcinogenic (group 2B), though continues to be used for malaria control in the developing world. While suggested by case reports, anabolic steroids and oral contraceptives have not been shown to increase liver cancer risk in large studies.

Keywords: chemical agents, hepatocellular carcinoma, occupational exposure, aflatoxin, pesticides

Introduction

Cancer of the liver is the sixth most commonly diagnosed cancer and the fourth most common cause of cancer death worldwide, according to the most recent GLOBOCAN estimates. There were an estimated 841,000 new cases of liver cancer in 2018, and the neoplasm was responsible for an estimated 782,000 mortalities.[1] In the United States, liver cancer is the fifth leading cause of cancer death, responsible for 30,160 deaths in 2020, which accounts for 5.0% of all cancer deaths. Liver cancer is over twice as likely in men.[2]

Primary liver cancer is mostly composed of hepatocellular carcinoma (HCC), which accounts for 75–85% of cases, and intrahepatic cholangiocarcinoma (neoplasm of the bile ducts), which accounts for 10–15% of cases. Around the world, chronic viral hepatitis, namely hepatitis B and C, is currently the leading cause of HCC. However, rising rates of global alcohol consumption and obesity are predicted to surpass viral hepatitis as the most common etiologies of HCC. Between

Correspondence: Prashanth Rawla
Department of Internal Medicine/ Hospitalist, SOVAH Health, 320 Hospital Dr, Martinsville, VA 24115, USA
Tel +1 336-701-2285
Email rawlap@gmail.com

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1990 and 2015, global liver cancer incidence has increased by 75%. Liver cancer incidence due to hepatitis B decreased during this period (when adjusted for population growth) thanks to vaccinations, while liver cancer due to hepatitis C and alcohol increased by 114% and 109%, respectively.[3]

In the United States, liver cancer incidence has more than tripled from 2.6/100,000 new cases in 1975 to 8.7/100,000 in 2017. Lifestyle changes such as growing rates of obesity and injectable-drug abuse (associated with HCV), as well as immigration of large populations from regions with high chronic HBV prevalence, has contributed to the growing US HCC incidence. Mortality has also increased, albeit less rapidly due to improved survival rates, from 2.8/100,000 to 6.7/100,000 in the same time frame. The 5-year survival rate of the disease was a dismal 19.6% in 2016, still an improvement from 3.1% in 1975. Limited early detection contributes to poor survival, as the 5-year survival rate for metastatic disease is only 2.5%.[2]

With low survival rates and increasing global incidence, particularly in developed and transitioning countries, it is imperative to understand and address the growing non-viral etiologies of liver cancer. Alcohol is the major chemical risk factor for primary liver cancer around the world, however other toxins such as aflatoxin, tobacco, and vinyl chloride account for significant disease burden in certain populations. Namely, developing-worlds agricultural laborers are at a particular risk of aflatoxin-related and pesticide-related liver cancer, while factory workers are at risk of occupational exposure to vinyl chloride, arsenic, cadmium, and several other identified hepatotoxins. While many occupations have been linked with increased risk of liver cancer, fewer than a dozen causative agents have been shown to have an association.[4] Commonly used medications such as oral contraceptives and anabolic androgenic steroids have also been reported in case studies to increase liver cancer risk, though large studies have not confirmed the results.

A better understanding of the role of chemical risk factors in HCC and other primary liver cancers, such as alcohol, vinyl-chloride, aflatoxin and insecticides, can inform prevention efforts such as education and public health reform and curb the growing disease burden of liver cancer worldwide.

Available meta-analyses, case-control and cohort studies for common chemical risk factors for hepatic cancers, identified by the International Agency for Research on Cancer (IARC) as group 1 or 2A/B carcinogens, are reviewed and synthesized below.

Lifestyle

Alcohol

Alcohol (ethanol) is the greatest contributor to liver cancer incidence in the developed world and is projected to soon surpass hepatitis B as the most common liver cancer etiology worldwide. Globally in 2015, alcohol contributed to an estimated 30% of cases, while hepatitis B contributed to 33%, though the proportion of hepatitis B-related cases is decreasing due to vaccination. As of 2015, alcohol was already the most common etiology for liver cancer in men.[3] Alcohol is recognized by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen. Alcohol is also the leading cause of cirrhosis and the leading contributor to liver transplants in the developed world.[5]

An alcohol consumption history of >30 g/daily for over 10 years for men and 20 g/day for women is considered significant for alcohol-induced liver disease.[6] Unlike heavy alcohol consumption, light to moderate consumption has not been shown to increase liver cancer risk.[7] For those with an unclear history and other liver-disease risk factors (such as obesity), the ALD/NAFLD Index (ANI) factors mean corpuscular volume (MCV), the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, the body mass index (BMI), and gender to identify patients with an alcohol-related component.[8]

Alcohol is metabolized to acetaldehyde in the liver primarily by alcohol dehydrogenase and secondarily by the cytochrome p450 microsomal enzyme oxidation system (MEOS). Acetaldehyde is metabolized by aldehyde dehydrogenase to acetate (and then acetyl-CoA), which is highly reactive and can disrupt protein and DNA structure. Acetaldehyde itself is a mutagen and carcinogen, implicated in liver cancer as well as esophageal and gastric cancers. The MEOS likewise generates reactive oxygen radicals that cause lipid peroxidation and depletion of glutathione (an important antioxidant agent whose depletion in alcoholism causes toxicity with concomitant acetaminophen consumption). Chronic alcoholism upregulates the MEOS, worsening oxidative stress from alcohol metabolism and hepatocyte damage. Damaged hepatocytes trigger an inflammatory response which further destroys hepatocytes and damages DNA integrity, increasing the risk of carcinogenesis. Other mechanisms of alcohol-

related liver damage include depletion of NAD+ leading to steatosis, as well as bacterial overgrowth and increased gut permeability, both of which promote inflammation.[9]

The anti-inflammatory agent aspirin has been shown to decrease the risk of HCC among those with chronic hepatitis and may play a role in mediating the risk of HCC from other etiologies such as alcohol.[10] Other promising approaches under investigation for mitigating alcohol-induced HCC risk include anti-inflammatory agents like IL-1 antagonists, probiotics, anti-fibrotic cannabinoids,[9] and NAD+ regenerating enzyme Nicotinamide Riboside.[11] Education and resources for alcohol limitation and rehabilitation could significantly decrease worldwide incidence in liver cancer.

Tobacco

Smoking tobacco is the leading cause of preventable cancer death in the world. Tobacco is designated as a group 1 carcinogen by the IARC for its significant impact on the risk of lung and urothelial cancers. One study of 14 US prospective cohort studies found that current smoking increased the risk of both HCC and intrahepatic cholangiocarcinoma. Those who had quit smoking >30 years ago did not have a statistically significant greater risk of either.[7] An earlier study from Japan found that of 12 cohort and 11 case-control studies, 9 cohort and 5 case-control studies reported associations between cigarette smoking and liver cancer risk, with 3 demonstrating dose-dependent associations.[12]

Combustion of tobacco and other additives during smoking produces carcinogens such as beta-naphthylamine and polycyclic aromatic hydrocarbons. These particles induce inflammation, and their metabolism, primarily in the liver, culminates in DNA-adduct formation and carcinogenesis-promoting mutations. Certain inherited genetic polymorphisms associated with abnormal function of detoxification enzymes have been shown to increase the susceptibility to carcinogenesis among those who smoke.[13] Tobacco cessation resources and medications, such as bupropion and varenicline, significantly increase successful cessation rates and are important public health interventions to limit global cancer incidence.

Occupational Hazards

Aflatoxin

Aflatoxin is produced by fungi of the *Aspergillus* species, which are known to grow on foods stored in warm, damp conditions, most commonly corn and peanuts. Of the aflatoxins, aflatoxin B1 (AFB1) is known to be the most potent hepatocarcinogen.[14] AFM1 and AFG1 are also recognized carcinogens, albeit weaker. AFM1 in particular has been identified in human breast milk and animal milk products.[15] The IARC recognized aflatoxins as a group 1 human carcinogen for their hepatocarcinogenic potential.[16] An estimated 25,000–155,000 annual HCC cases can be attributed to aflatoxin (approx. 3–20% of all HCC cases),[14] 40% of which occur in sub-Saharan Africa.[17] Urinary biomarkers and serum albumin adduct levels can be measured to determine the level of exposure.[18,19]

AFB1 by-products produced by liver metabolism are powerful genotoxins and cytotoxins and have been shown to cause HCC in all animal models tested. Studies have also shown a dose-response association between AFB1 exposure and HCC risk.[20] In humans, an association between dietary AFB1 and HCC has been established, while one with airborne AFB1 has been suggested. Route of entry can be difficult to parse, as workers who may inhale AFB1 tend to also ingest it in their diets, as well as absorb the toxin through their skin. These studies did not include genetic testing for *TP53* mutations (ARG>SER) among the concerned worker populations, meaning that molecular evidence for inhaled aflatoxin carcinogenesis remains outstanding.[21–24] Laborers in paper mills, waste management, animal husbandry, and textiles in certain countries like Egypt may have increased exposure to AFB1 and demonstrate an increased risk of HCC, lending support to an airborne route of transmission.[19,21–24]

A synergistic hepatocarcinogenic relationship with hepatitis B has been hypothesized based on genetic analysis, namely the prevalence of *TP53* mutations, among HCC cases in many developing nations, along with education on safe farming practices, may therefore decrease the burden of aflatoxin-associated HCC.[25,26]

Vinyl Chloride Monomer

Vinyl Chloride Monomer (VCM) is a hydrocarbon used in the production of polyvinyl chloride (PVC), an important component in the plastics industry. PVC is harmless and can be found in everything from water pipes, window frames, insulation, and waterproof clothes to medical and dental appliances. However, thousands of workers involved in the production of plastics have been exposed to VCM, the monomeric, and reactive form of vinyl chloride. Likewise, autoclave workers are at risk of VCM exposure. An estimated 40,000 workers in Europe and

80,000 in the US were exposed to VCM before 1997. VCM is also found in cigarette smoke. The VCM metabolite thioglycolic acid is detected in the urine to assess occupational exposure.[27,28]

VCM toxicity has been found to disturb the liver endothelium, causing portal hypertension as well as the rare malignancy angiosarcoma of the liver (ASL).[28] ASL is a proliferation of endothelial cells only associated with VCM exposure. In fact, VCM exposure has been found to have a dose-dependent effect on ASL risk.[29] VCM has also been shown to increase the risk of cirrhosis, HCC, and overall liver cancer mortality, displaying a synergistic effect with alcohol.[30,31]

VCM is absorbed through inhalation and metabolized by the liver into numerous mutagenic and carcinogenic compounds such as ethylene dichloride and chloro-ethylene oxide.[27,32] These by-products, such as carbamates, induce DNA breaks and chromosomal aberrations and are most concentrated in the liver where processing occurs.[33]

The IACM group 1 carcinogen designation of VCM comes from an abundance of animal and human studies. On top of liver cancers, occupational VCM exposure has been demonstrated in humans to increase the risk of cancers of the brain,[34] lungs,[35] and hematological system.[36] In VCM exposed workers with HCC, oncogenic mutations in KRAS and p53 have been observed.[37]

Arsenic

Arsenic (As) is a heavy metal classified as a group 1 carcinogen by the IARC. The primary source of exposure is the leakage of inorganic Arsenic into groundwater. Regions of the world with high prevalence of As in groundwater include Bangladesh, West Bengal and the Antofagasta province in Northern Chile.[38,39]

Occupations with exposure to Arsenic include coal-based energy production, timber manufacturing, glass production, pharmaceutical production, agrichemical production, and exposure to pesticides, lead, and antifouling paint. The highest exposure is among workers in carpentry with arsenic-pressure-treated lumber or lead and copper smelters, as Arsenic in naturally found in these ores. As is used as a pesticide for cotton plants, and in the treatment of acute promyelocytic leukemia. High levels of Arsenic in the air can be found in the surroundings of metal smelters and coal-fired power plants. Urinary As levels may be used to assess exposure.[40,41]

As is absorbed through the gastrointestinal tract and detoxified by glutathione in the liver. Glutathione can act as an antioxidant, or become conjugated to Arsenic and excreted in the bile. Arsenic is also methylated in the liver.[42,43]

According to the IACR, As has been implicated in cancers of the skin, lungs, bladder, prostate, kidneys, and liver in humans. As has also been implicated in the development of vascular disease, including stroke and ischemic heart disease.[44] Recent studies have also suggested diabetic, neurological, and reproductive sequela.[45] Animal and cell model systems have demonstrated carcinogenesis promoted by Arsenic, while epidemiological studies have shown an association between exposure and a spectrum of hepatic disorders, including hepatomegaly, sclerosis, fibrosis, cirrhosis, and liver cancer.[38,43]

As is known to accumulate in the liver, and several mechanisms of carcinogenesis have been proposed, including genotoxicity, generation of free radicals and oxidative stress, disturbance of signal transduction and cellular proliferation, massive alteration in DNA methylation, and direct cytotoxicity, though the exact mechanism is poorly understood.[46,47]

Cadmium

Cadmium (Cd) is a heavy metal found naturally as a grey-white powder. While first discovered as a yellow/orange pigment, Cd has since become an important component in Nickel-Cd rechargeable batteries. Cd is also used as an anti-corrosive veneer for iron and steel.

Occupational exposure to Cd is typically through airborne particles. Occupations at risk include miners and processors of Cd ores, and manufacturers of Cd containing products, such as painters, smolders, welders, and battery and polyvinyl chloride (PVC) manufacturers. Workers involved in garbage disposal, such as waste collection, disposal or incineration, or recycling of electronics and plastics, are likewise exposed to Cd. Cd can also be found in food and cigarette smoke.[48]

Cd has been shown to accumulate in the liver, lungs, kidneys, and pancreas, and has been shown in animals to cause adverse events on these organs, as well as the immune system, nervous system, and blood.[49] Liver concentrations of workers peak at 40–60 years, demonstrating a gradual accumulation. Chronic inhalation can result in damage to the lungs, including bronchiolitis and emphysema. Occupational Cd exposure can be assessed in blood or urine.[48,50]

Animal studies have revealed the hepatocarcinogenic potential of Cd via multiple mechanisms. In cell and animal models, Cd has shown involvement in many stages of

carcinogenesis, including generation of mutations via oxidative stress, induction of inflammatory IL-6 by Kupffer cells, protooncogene activation via DNA hypomethylation, impaired DNA repair, and E-cadherin dysfunction, facilitating metastasis.[51,52] In humans, a cross-sectional study from China investigating Aflatoxins found an association between dietary intake of Cd and HCC mortality[53] The impact of Cd on liver carcinogenesis has not been further elucidated in human investigations. Human case-control studies are necessary to establish whether occupational Cd exposure may help account for the sex-discrepancy in liver cancer incidence.[4]

Organic Solvents

Organic solvents (OS) are volatile, carbon-based solvents used to extract, dissolve, or suspend insoluble substances. These solvents are widely used in paints, glues, adhesives, cleaning agents, coatings, dyes, plastics, and pharmaceuticals. Millions of workers in the US and Europe, and likely hundreds of millions around the world, are exposed to these solvents.[54] Various OS have been associated with numerous cancers, and parental exposure has even been shown to portend a risk to children.[55,56]

An increased risk of liver cancer mortality has been reported among workers exposed to OS, such as painters, in a meta-analysis of cohort studies.[57] Few studies have investigated the association between specific OS and liver cancer risk, except for studies into perchloroethylene (PCE) and trichloroethylene (TCE).

TCE is broadly used in dry cleaning, paint stripping, metal degreasing, and manufacture of chlorinated compounds. TCE has been detected in 1/3 of hazardous waste sites and 10% of groundwater sources.[58] TCE has been shown to induce renal cell carcinoma (RCC) and HCC in rodents and has been associated with RCC in human studies,[59] leading to a group 1 carcinogen designation by the IACR. A recent human study has also found an association with liver cancer.[60] Numerous mechanisms have been suggested for TCE carcinogenesis, including its mutagenic potential, proliferative signaling by disrupting proliferator-activated receptor (PPAR)α,[61,62] and dysregulation of DNA expression and repair via homologous recombination (HR) genes and c-myc oncogenes.[63,64]

PCE is used in dry cleaning, textile processing, and degreasing. Exposure by inhalation, particularly among dry-cleaning workers, has been linked with many neoplasms, including bladder cancer, lymphoma, multiple myeloma, and possible esophageal, kidney, cervical, and breast cancers.[65] Increased risk of liver cancer has also been demonstrated in animals and humans. The IARC gives PCE a category 2A designation (probably carcinogenic).

Other industrial toxins associated with liver cancer risk include polychlorinated dibenzo-*p*-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF),[66,67] polychlorinated biphenyls (PCB),[68] all of which have category 1 designation from the IACR. Polybrominated biphenyls (PBB)[69] and chloral and chloral hydrate[70] have also been suggested to increase liver cancer risk, but have not been proven in human studies.

Pesticides

An estimated 500,000 tons of pesticide ingredients are used annually in the US, and an estimated 10,000–20,000 pesticide poisonings are diagnosed each year.[71] Several epidemiological studies have found pesticides to increase HCC risk in agricultural workers, and many of the commonly used compounds have been proven carcinogenic in animal models.[72–74] However, 1,1,1-Trichloro-2,2-bis (p-chlorophenyl)-ethane (DDT) is the only specific pesticide that has been investigated and shown an association with liver cancer in humans.

DDT has been demonstrated to cause hepatic damage and carcinogenesis in animal models.[75,76] Based on these studies, the IARC has designated DDT as group 2B, a possible carcinogen in humans.[77]

While widely used as an insecticide, DDT was banned in numerous developed countries in the 1970s due to toxic effects on the environment and suspected toxicity for humans. It continues to be used for control of malaria, termites, and other insect-based health and agricultural purposes in much of Africa and Asia. Using a cost-benefit analysis, the world health organization (WHO) supports this use of DDT until other means become accessible.[78,79]

DDT in food products is absorbed through the GI tract, while occupational exposure typically occurs through inhalation and dermal contact. The half-life of DDT in humans is 7 years. DDT has been found to induce numerous health effects in humans, involving the reproductive and neurological systems and disturbing normal human development.[80,81]

Three studies assessing DDT and HCC found a correlation between levels of DDT in blood and adipose tissue and the risk of liver cancer.[82–84] One suggested explanation is that DDT disrupts the endocrine system, promoting estrogenic effects.[83] DDT has also been

shown in mice to upregulate CYP family members involved in an inflammatory response and disrupt normal immune function.[85,86] The validity of these findings has been questioned due to the high prevalence of aflatoxin and hepatitis B, other promotes of HCC, in the studied populations (South and Southeast Asia, Africa). Both aflatoxin and Hep B have been suggested to have synergistic effects for HCC.[82–84]

The development of effective, safe, and affordable insecticides is essential to replace DDT usage in the developing world and reduce the likely increased risk of HCC.

N-Nitrosamines

N-Nitrosamines are a class of chemical compounds created from nitrogen dioxide in food storage, preparation, or digestion. Nitrosamines, and their precursors, are commonly found in agricultural products, tobacco, plastics, tanned leather goods, solvents, pharmaceuticals, textiles, rubber additives, and cosmetics.[87] Nitrosamines are most commonly ingested in food as products of nitrites and nitrates used as meat preservatives. The formation of nitrosamines contributes to the increased risk of GI cancers from preserved and smoked meats high in nitrites and nitrates.[88]

Occupational exposure to nitrosamines is particularly prevalent in the rubber manufacturing industry, where an increased risk of multiple cancers has been observed. Occupational exposure to chemicals in the rubber industry, such as nitrosamines, has a group 1 carcinogen designation from the IARC. Urinary N-nitrosamine levels can be measured to determine exposure.[89,90]

N-nitrosamines have been shown to shorten telomeres, protective caps at the ends of chromosomes, culminating in cellular senescence, or less commonly, telomerase activation and cell immortalization.[91] Nitrosamines have been shown to induce liver damage and increase the risk of liver cancer in rodents.[92] High dietary and cigarette nitrosamines have been associated with an increased risk of liver cancer in Thailand, though confounding factors such as viral hepatitis, and a liver fluke known as Opisthorchis viverrine implicated in intrahepatic cholangiocarcinoma, may be at play.[93,94]

Medications

Oral Contraceptives

Over 750 cases of HCC or hepatic adenomas have been reported by case studies among women with long-term oral contraceptive use.[95] However, a meta-analysis of 17 studies found no significant association between oral contraceptive use and liver cancer risk.[96] Oral contraceptives are known to increase the risk of benign hepatic adenomas, though the malignant potential is variable.[97] Hepatic adenomas with beta-catenin mutations have been shown to have malignant potential.[98]

Anabolic Steroids

Development of hepatic adenomas and HCC among those with long-term, high-dose anabolic androgenic steroid (AAS) use, such as body-builders, has been described in the literature. These case reports describe AAS-associated HCC without cirrhosis or history of alcohol or viral hepatitis.[95,99,100]

AAS are typically used to increase muscle mass but have a diverse array of effects on organ function. In the liver, 17α-alkylated AAS such as stanozolol are known to induce cholestasis, peliosis hepatis, liver cell proliferation.[95] One such case report described testosterone-receptor positive HCC, reaffirming the theory that AAS use helps stimulate carcinogenesis.[100] While AAS use more commonly induces benign hepatic adenomas, these are difficult to distinguish from HCC on imaging and may have the potential for malignant transformation.[95]

Aristolochic Acid

Aristolochic Acid (AA) is a component of many traditional East Asian herbal medicines that has been shown to increase the risk of HCC among those with HCV infection. A prospective cohort study from Taiwan, published in 2019, showed a dose dependent increase in HCC risk with 1–1000 mg of AA consumption (HR= 1.21–1.88). Confounding variables such as obesity, alcohol consumption, and aflatoxin exposure were not included in the analysis.[101]

Conclusion

Primary liver cancer is a common and growing cause of cancer incidence and mortality around the world. Due to increased hepatitis B vaccination, heavy alcohol consumption is becoming the leading cause of liver pathology and cancer. Tobacco is another likely lifestyle contributor to liver cancer, while oral contraceptives and anabolic steroids are suggested but not proven to increase risk. Occupational chemicals increasing the risk of liver cancer include aflatoxin and DDT in developing agricultural laborers, vinyl chloride in plastic manufacturers, and arsenic, cadmium, N-nitrosamines, and

organic solvents in a variety of metal-working, waste-disposing, and manufacturing industries. A stronger understanding of alcohol pathophysiology is driving the development of treatments to mitigate inflammation and HCC risk, while preventive interventions such as hepatitis B vaccination, workplace safety standards and testing of employee exposure levels, and agricultural reform can help curb the growing global burden of liver cancer.

Ethics Approval

No ethics approval needed

Author Contributions

All authors made substantial contributions to conception and design, analysis and interpretation of data; took part in drafting the article; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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