

Hepatocellular carcinoma and the risk of occupational exposure

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. The main risk factors for HCC are alcoholism, hepatitis B virus, hepatitis C virus, nonalcoholic steatohepatitis, obesity, type 2 diabetes, cirrhosis, aflatoxin, hemochromatosis, Wilson's disease and hemophilia. Occupational exposure to chemicals is another risk factor for HCC. Often the relationship between occupational risk and HCC is unclear and the reports are fragmented and inconsistent. This review aims to summarize the current knowledge regarding the association of infective and non-infective occupational risk exposure and HCC in order to encourage further research and draw attention to this global occupational public health problem.

Key words: Hepatocellular carcinoma; Autophagy; Epigenetic events; Hepatitis B virus; Hepatitis C virus; Occupational exposure; Chemical agents; Mitophagy;

Arsenic; Cadmium

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Core tip: Hepatocellular carcinoma (HCC) is the fifth most common human cancer. This review summarizes current knowledge regarding the occupational risk factors of HCC. In particular, we underline not only the infective but also non-infective occupational risk exposure, including chemical agents and toxic metabolites which are a major cause of liver damage.

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INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is increasing worldwide. There are geographical areas with a high prevalence, as in Asia and Africa, and death from HCC has increased in the United States and Europe^[1-5].

Aflatoxin^[6], alcohol intake^[7], hepatitis B virus (HBV)^[4], hepatitis C virus (HCV) infection^[5] and oral contraception^[8,9] are known risk factors for HCC, whereas cigarette smoke, anabolic steroids and insulin resistance are suspected to be contributing factors^[10-16].

The relationship between occupational risk and HCC is often unclear and the reports are fragmented and inconsistent^[17-19]; however, it is very commonly reported that vinyl chloride monomer (VCM) induced angiosarcoma of the liver^[20].

HCC mortality, assessed by standardized mortality ratio, has been reported in different categories of workers: Building and chemical workers, painters, subjects exposed to solvents and workers in the textile industry have often been reported to be at high risk for HCC^[21-30]. However, such studies have often failed to identify a single agent responsible for the heightened HCC risk. There have been few investigations of occupational exposure and liver cancer. A number of factors and confounders have precluded drawing firm conclusions^[31].

The possible associations between the risk of infection and non-infectious occupational hazards and HCC will be discussed, in the hope of drawing attention to this global public health problem.

REVIEW METHOD

The PubMed, Scopus and Web of Science databases were searched using the following keywords: "HCC", "occupational exposure", "chemical agents", "arsenic",

"cadmium", "HBV", "HCV", "molecular hepatocarcinogenesis", "molecular immunological targets", "autophagy", "mitophagy" and "epigenetic events". Published data at the International Agency for Research on Cancer (IARC) were consulted.

INFECTIVE RISK FACTORS FOR HCC

Infection is one of the main contributors to cancer development^[32]. There are 11 biological agents classified as IARC group 1 carcinogens^[33,34]. HBV, HCV and AFB1 are responsible for HCC development^[35]. The vast majority of the global cancer burden attributable to infection occurs in less developed regions (Table 1).

HEPATITIS INFECTIONS

Infection with HBV and HCV can be through parenteral or unapparent transmission^[36-42].

Occupational exposure to hepatitis B

The risk of hepatitis from needlestick injury from an hepatitis B envelope antigen positive (HBsAg+) source is 22%-31%, whereas the risk of contracting clinical hepatitis from a needlestick injury involving an hepatitis B surface antigen positive (HBsAg+), eAg- source is 1%-6%. Post-exposure prophylaxis (PEP), including HBIG and the HBV vaccine, is believed to be 85%-95% effective. HBV vaccine or HBIG alone is thought to be 70%-75% effective^[43-45].

Occupational exposure to hepatitis C

The risk of HCV transmission from percutaneous exposure is approximately 2%. HCV is rarely transmitted from mucous membrane exposure to blood (both documented cases have been when the source patient was human immunodeficiency virus/HCV co-infected) and it has never been documented following blood exposure to intact or non-intact skin. There is no known PEP for HCV exposure. According to a European case-control study, assessment of the risk of transmission after occupational HCV exposure should take into account the injury severity, device involved and the HCV RNA status of the source patient^[46-50].

DEVELOPMENT OF HCC IN CHRONIC HBV INFECTION

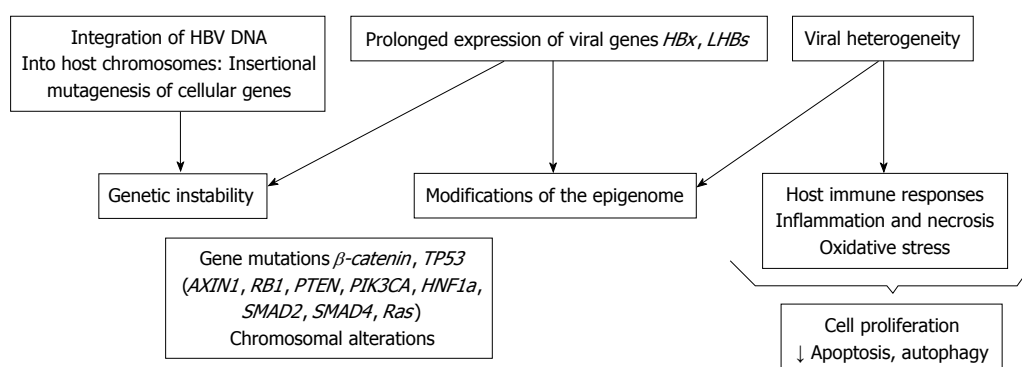
Chronic HBV infection has a causal role in HCC development^[36] since it promotes carcinogenesis through liver injury (necrosis and inflammation) and cirrhosis development (fibrosis and regeneration)^[41,43-45]. Moreover, HBV and HCV co-infection causes a higher than 50-fold risk compared to HCC^[51-54].

Risk factors for liver cancer in HBV patients include: (1) host-related risk factors: Older age, Asian ethnicity, male sex, alcohol intake and advanced liver disease^[55-57]; (2) viral risk factors: HBV genotype C, mutations of pre-S, enhancer-H, core promoter, HCV or hepatitis

Table 1 Hepatocellular carcinoma and occupational exposure to infective agents

Risk agent	CAS No.	Occupational exposure	IARC class
Infective risk			
HBV	-	Health care workers ^[4,38,41,44] , waste operators ^[38,44]	Group 1 ^[34]
HCV	-	Health care workers ^[38,39,61]	Group 1 ^[34]
Aflatoxin B1	1162-65-8	Paper mill and sugar factory; poultry production; rice mill; waste management; swine industry; agri-food industry; wheat handling; textile manufacturing ^[77,78,87-91,93,96]	Group 1 ^[76]

IARC: International Agency for Research on Cancer; CAS No.: Chemical abstract service number; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

**Figure 1** Pathogenesis of hepatitis B virus-related hepatocellular carcinoma. HBV: Hepatitis B virus.

Delta virus infection and PC/BCP HBV variants^[45,58]; and (3) risk factors related to host-virus interaction: Cirrhosis, high HBV-DNA serum levels, prolonged HBeAg positivity, prolonged HBsAg positivity and high HBsAg serum levels^[59-62].

Lastly, the HCC risk factors in chronic HBV infection are different and the pathogenesis is characterized by the combined action of different alterations involving genetic, epigenetic and immunological factors^[63-71] (Figure 1).

DEVELOPMENT OF HCC IN CHRONIC HCV INFECTION

The mechanism by which HCV causes HCC is not wholly clear. It has been suggested that HCV proteins have direct oncogenic properties^[5]. Chronic HCV infection leads to cirrhosis in 10%-20% of patients of whom 1%-5% develop liver cancer^[5]. Central tumor suppressor genes and a number of proto-oncogenes, such as retinoblastoma tumor suppressor (*Rb*) and *P53*, have been suggested as targets of direct alteration by HCV proteins; the wnt/ β -catenin and transforming growth factor- β pathways may also be directly affected^[5].

Moreover, chronic infection, necrosis and cell regeneration, fibrosis and cirrhosis are, together with the direct mechanisms, the high risk factors for HCC. Finally, HBV or HCV chronic infection has immunomodulatory and immunosuppressive effects^[71-73].

AFLATOXINS

The aflatoxins are metabolic products of certain fungi, *Aspergillus flavus* and *parasiticus* that develop in cereals

(maize), oilseeds (groundnuts) and dried fruit and are chemicals of the furanocoumarins type. To date, we have isolated 17 aflatoxins and 5 are relevant to dissemination and toxicity. High exposure concentrations cause acute hepatitis. Chronic exposure causes the development of liver cancer. This could be caused by the aflatoxin ability to determine the mutation of the p53 tumor suppressor gene, which in normal conditions induces the apoptosis processes^[74-77].

The risk of HCC increases when the exposure occurs in the presence of HBV infection, as occurs in the Chinese population^[78-96].

NON-INFECTIVE RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

A wide range of occupational activities may involve worker exposure to a variety of chemical agents. The liver is the main organ involved in metabolism and in toxicokinetics of a xenobiotic. However, it is frequently also a target organ because of its blood supply and the many metabolic and excretory processes in which it has a role. Adverse effects of chemical exposure involving the liver (hepatotoxicity) comprise hepatocellular damage, cholestatic injury, fatty liver, granulomatous disease, cirrhosis and malignancies, including HCC. A variety of chemicals comprising VCM, organic solvents, chlorinated pesticides and arsenic exert adverse effects on the liver^[97] (Tables 2 and 3).

VCM AND POLYVINYL CHLORIDE

VCM, chemical abstract service number (CAS No.

Table 2 Hepatocellular carcinoma and occupational exposure to chemical agents

Risk agent	CAS No.	Occupational exposure	IARC class
Non-infective risk			
VCM	75-01-4	Plastics, plumbing, cabling, house framing, waterproof clothing, medical devices and food packaging industry ^[98,99,102,103,105-108,111,112,114-120]	Group 1 ^[76]
TCE	79-01-6	Dry cleaning; paint stripping; metal degreasing; production of chlorinated chemical compounds; shoe manufacturing; aircraft/aerospace, electronics and printing industry ^[125,127]	Group 1 ^[129]
PCE	127-18-4	Dry cleaning; textile processing; metal degreasing ^[138]	Group 2A ^[129]
DDT	50-29-3	Farming industry ^[141,145]	Group 2B ^[148]
N-nitrosamines	35576-91-1	Plastic, rubber and pharmacological manufacturing; farming industry; metalworking; electrical component production and use; gasoline and lubricant additives, production and use ^[159-165]	Group 1 ^[160,161]
TCDD	1746-01-6	Waste management; paper mill; timber manufacturing; iron and steel manufacturing; electric power industry ^[175,179]	Group 1 ^[76]
PeCDF	57117-31-4	Cement and metalworking industry; chemical manufacturing ^[171,172,175]	Group 1 ^[76]
PCB	1336-36-3	Electrical industry, plastic and chemical industry; maintenance/repair technicians of PCB devices ^[175,186-190]	Group 1 ^[76,207]
PBB		Electronics recycling industry; maintenance/repair technicians of PBB devices ^[209-212]	Group 2A ^[207]
Chloral	75-87-6	Insecticides and herbicide production; polyurethane foam production and use ^[125,214,215]	Group 2A ^[216]
Chloral hydrate	302-17-0	Pharmaceutical producing; health care workers; laboratory research; water disinfection by chlorination ^[129,216]	Group 2A ^[216]
O-toluidine	95-53-4	Dye production and use; herbicide and pharmaceutical production; rubber industry; clinical laboratories ^[220-222,227,228]	Group 1 ^[76]
MOCA	101-14-4	Rubber and polyurethane industry ^[220,230-232]	Group 1 ^[76]
4-ABP	92-67-1	Rubber industry; dyes production ^[220,235-238]	Group 1 ^[76]
BZD and dyes metabolized to BZD	92-87-5	Dye production and use; clinical laboratories ^[220,247]	Group 1 ^[76]

¹Not all of them are to be referred to group 1. VCM: Vinyl chloride monomer; TCE: Trichloroethylene; PCE: Perchloroethylene; DDT: 1,1,1-Trichloro-2,2-bis (p-chlorophenyl)-ethane; TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin; PeCDF: 2,3,4,7,8-Pentachlorodibenzofuran; PCB: Polychlorinated biphenyls; PBB: Polybrominated biphenyls; O-toluidine: Ortho-toluidine; MOCA: 4,4'-Methylene bis (2-chlorobenzeneamine); 4-ABP: 4-aminobiphenyl; BZD: Benzidine; IARC: International Agency for Research on Cancer; CAS No.: Chemical abstract service number.

Table 3 Hepatocellular carcinoma and occupational exposure to metals

Risk agent	CAS No.	Occupational exposure	IARC class
Non-infective risk			
As	7440-38-2	Timber manufacturing; pesticide use; As extraction industry; lead processing; pharmaceutical industry; glass industry; leather preservatives; antifouling paints; agrochemical production; microelectronics and optical industries; non-ferrous metal smelters; coal-fired power plants ^[254-258]	Group 1 ^[263]
Cd	7440-43-9	Cd mining; manufacturing of Cd-containing ores and products; Ni-Cd battery manufacturing, Cd alloy production ^[275,277,278]	Group 1 ^[263]

As: Arsenic; Cd: Cadmium; IARC: International Agency for Research on Cancer; CAS No.: Chemical abstract service number.

75-01-4), is a chlorinated organic compound. VCM is found in cigarette smoke and is mainly used in the production of polymer polyvinyl chloride (PVC). VCM is rapidly absorbed after inhalation and is primarily metabolized by the liver.

Since PVC is harmless in its polymeric form, workers handling the finished goods are not at risk of exposure. The risk phases are those in which the workers are in contact with the material when still in the monomeric state. Many epidemiological studies have demonstrated the high prevalence of exposure to VCM in those working with the chemical. Thiodiglycolic acid is the main VCM metabolite detected in the urine of occupationally exposed subjects.

It has been shown in both human and animal models that VCM is able to induce liver angiosarcoma and HCC^[98-104].

Maroni *et al.*^[105] reported the hepatotoxicity of VCM and other studies have shown the capacity of VCM to

induce specific gene mutations in the liver^[105-117].

Various European and Italian studies have reported the apparent association between the amount and timing of exposure to VCM and development of HCC in those exposed^[118-120].

ORGANIC SOLVENTS

Organic solvents are substances that contain carbon and are capable of dissolving or dispersing one or more other substances. Millions of workers are exposed to organic solvents contained in products such as varnishes, adhesives, glues, plastics, textiles, printing inks, agricultural products and pharmaceuticals.

Many organic solvents are recognized by NIOSH as carcinogens (carbon tetrachloride, benzene and trichloroethylene), reproductive hazards and neurotoxins. Among the organic solvents, trichloroethylene (TCE) and perchloroethylene (PCE) have been reported to be

capable of promoting cancer in humans^[121,122].

TCE (CAS 06/01/79) has been associated with a high prevalence of liver tumors in exposed workers. Although the hepatic metabolism of this solvent is known, the molecular alterations that cause liver cancer are not completely known^[123-127].

It is hypothesized that TCE may be involved in various mechanisms, such as the reduction of programmed cell apoptosis and the uncontrolled proliferation induced by peroxisome activated receptor (PPAR). In fact, it has been proved that TCE is able to bind PPAR^[128-132].

RAD51 is a eukaryote gene. The protein encoded by this gene is a member of the RAD51 protein family which assists in the repair of DNA. TCE binds the *RAD51*, consequently alters the DNA repair and can cause a certain degree of genomic instability.

Finally, it was reported that TCE can cause hypomethylation of DNA and hyperexpression of oncogenes (*e.g.*, *MYC* and *JUG*), responsible for uncontrolled cell proliferation^[133-137].

A high prevalence of liver cancer was found in animal models exposed to PCE (CAS 127-18-4)^[138,139].

Porru *et al.*^[140] showed that, in workers chronically exposed to organic solvents (toluene and xylene), there is an increased risk of HCC and that the risk is time-dependent.

PESTICIDES

Pesticides are widely used in agriculture to get the best quality products and appearance. Farmers and many workers in the agro-food chain are exposed to these substances as well as consumers who eat agricultural products that are not properly cleaned and decontaminated.

Among these substances, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-ethane (DDT) and its metabolite 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (DDE) have been extensively studied. DDT was used both in agriculture and for environmental disinfection until its use was later forbidden in both America and Europe because of its toxic effects on humans. However, in Africa and many parts of Asia it is currently used to control diseases delivered by an insect as a vector (*e.g.*, Leishmaniasis, malaria).

In humans, DDT contamination occurs through contact with the skin, mucous membranes and inhalation. After DDT absorption, it is distributed to all organs and a portion will be stored in fatty tissues, especially if the exposure was massive^[141-146].

Many insecticides, including DDT, were reported to be responsible for leading the development of HCC^[147-152]. This occurs through different mechanisms not yet completely understood. Moreover, DDT has an estrogenic effect, while DDE has anti-androgenic effects. DDT may also interfere with the *CYP3A1* gene involved in the inflammatory and immune responses in the liver.

Probably none of these mechanisms is individually able to result in HCC but the simultaneous presence of these alterations may lead to the development of liver cancer. Furthermore, the presence of important cofactors, such as HBV, HCV and AFB1, amplifies the risk in exposed populations^[152-158].

N-NITROSAMINES

Nitrosamines are carcinogenic chemical compounds produced when nitrite, a preservative added to certain foods (fish, fish byproducts, certain types of meat, cheese products, beer), combines with amino acids in the stomach. Nitrosamines can be also found in latex products and tobacco smoke. Moreover, nitrosamines are produced in research laboratories, in rubber and tyre manufacturing processes and may be found as contaminants in the final rubber product. Some nitrosamines have been found to be effective for a variety of purposes, including antimicrobial (No. 11) or chemotherapeutic agents (Nos. 5 and 9) in conjunction with others, herbicides (Nos. 5 and 6), additives to soluble and synthetic metalworking fluids (No. 3), solvents or gasoline and lubricant additives (No. 4), antioxidants, stabilizers in plastics, fiber industry solvents and copolymer softeners, and to increase dielectric constants in condensers. Contamination can occur with skin contact and by ingestion and/or inhalation.

Nitrosamines are carcinogenic and are implicated in nasopharyngeal, esophageal, stomach, liver and urinary bladder cancers^[159].

From 1981 to 1991, the United States - National Toxicology Program conducted several investigations to characterize and assess the toxicological potential and carcinogenic activity of N-nitrosamines in laboratory animals (rats and mice). The results were reported in the second (1981) (N-nitrosamines: 2-7, 9-15) and sixth (1991) (N-nitrosamines: 1-8) annual report on carcinogens^[159-163].

In environmental surveys of some European rubber factories, de Vocht *et al.*^[164] found the average N-nitrosamine levels well below the regulatory limits in force but high accidental exposures have still occurred. In fact, they detected high levels of urinary N-nitrosamines in exposed workers^[162,164-166]. Recent studies have reported a correlation between exposure to N-nitrosamines and HCC which might be due to the shortening of telomeres among workers in the rubber industry. Telomeres are critical to maintaining the integrity of chromosomes and telomere length abnormalities are associated with carcinogenesis^[163,165,167-169].

DIOXINS AND DIOXIN-LIKE COMPOUNDS

The dioxins and dioxin-like compounds are a class of heterocyclic organic compounds whose molecular structure fundamentally consists of a ring of six atoms, four carbon and two oxygen atoms; dioxin in the strict

sense is differently stable and comes in two different positional isomers. Commonly referred to dioxins are also compounds derived from furan, in particular dibenzofurans. Therefore, part of the dioxin-like compounds are polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans and among them, the most toxic is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It has been shown that compounds of the family of dioxins are formed during the initial stage of the waste combustion when combustion generates gaseous HCl in the presence of catalysts, such as copper and iron. Organic chlorine, which is bound to organic compounds of polymers such as PVC, is mainly responsible for the formation of compounds belonging to the family of dioxins. Dioxins are generated even in the absence of combustion, for example in bleaching paper and tissues with chlorine.

About 90% of human dioxin, except for cases of exposure to specific sources such as industrial plants and incinerators, takes place through food (in particular the fat of animals exposed to dioxin) and not directly by air. The phenomenon of bioaccumulation is very important, *i.e.*, the possibility that dioxin enters into the human food chain from plants, through herbivores, carnivores and finally humans^[170-176]. Dioxins are classified as definitely carcinogenic and are in the IARC group 1 carcinogenics for humans.

The National Institute for Occupational Safety and Health (NIOSH) has classified TCDD as an occupational carcinogen that can cause space-occupying liver lesions, both non-neoplastic and neoplastic, such as in HCC^[177-181].

Many studies have indicated that the carcinogenic capacity of TCDD may be due to the interaction between TCDD and the aryl hydrocarbon receptor (AhR). This receptor is implicated in several xenobiotic metabolisms but there is evidence that AhR is able to control other genes, some of which have a pro-oncogenic capacity^[182-184]. The TCDD is an important AhR agonist and is therefore able to induce and enhance HCC development and diffusion^[184].

POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyls (PCB) are synthetic chlorinated aromatic hydrocarbons, chemically stable and therefore persistent environmental contaminants. The contamination occurs by skin contact or inhalation, which also allows the possibility of developing vapors for equipment containing PCB overheating^[185].

Studies in animal models have shown that these chemical compounds can cause chronic hepatitis as well as cancers, such as HCC and cholangiocarcinoma, especially if there is high exposure and a prolonged time. However, there is little data on liver injury in humans. In one case, exposure to olive oil accidentally contaminated with PCB resulted in death from hepatic cirrhosis. Other studies in workers exposed to the PCB have reported an increased incidence of liver tumors^[185-188].

Some possible mechanisms by which PCB can cause cancer have been assumed: Reactive oxygen species (ROS) is produced through the enzymatic oxidation or autooxidation of PCB; PCB determines the increased expression of genes responsible for inflammation and apoptosis in the liver; and PCB has "toxic" effects on certain genes, such as the loss of part of a chromosome and chromosome breakage^[189-199]. ROS are also able to reduce telomerase activity which can determine telomere shortening. The contribution of all or part of these alterations may facilitate the onset of tumors and more specifically HCC^[200-205]. At present we have no conclusive data on the relationship between PCBs and HCC and further studies will be needed to establish the causal link. However, the evidence reported by animal model studies have made it possible to classify PCB in IARC group 1^[206,207].

POLYBROMINATED BIPHENYLS

Polybrominated biphenyls are polyhalogenated derivatives of a biphenyl core^[208] that are chemically stable and therefore persistent environmental contaminants. Whereas they were widely used just a few years ago, they are now subject to restrictive rules that limit their use in the European Union (Restriction of Hazardous Substances Directive).

Contamination can occur through skin contact, inhalation and ingestion^[209-212]. Based on data obtained from animal research, PDDs are considered potential human carcinogens and can result in hematological, digestive system and liver malignancies. The pathogenic mechanisms by which they can result in PDD cancer are similar to those described for PCB which allows them to be defined as "probably carcinogenic for humans" (group 2A)^[207].

CHLORAL AND CHLORAL HYDRATE

Chloral (or trichloroacetaldehyde) is a chemical compound with the formula C_2HCl_3O and CAS (chemical abstracts service) 75-87-6. Chloral is produced by the chlorination of ethanol and is also produced as an intermediate in the synthesis of various products, for example DDT. Chloral is used for production of chloral hydrate (formula $C_2H_3Cl_3O_2$ and CAS No. 302-17-0).

Chloral hydrate is an ingredient used in Hoyer's solution^[213-216]. In mouse studies, oral administration of chloral in water induced liver nodules as well as hyperplastic nodules and HCC after 92 wk. Significant increases in HCC incidence were seen in treated mice surviving 104 wk^[217,218]. Some studies indicate that chloral hydrate is able to produce genomic alterations, such as chromosomal aberrations, loss of cell apoptosis and rupture of the gap junction. There are limited studies on carcinogenicity in humans. However, thanks to evidence in animal studies, chloral and chloral hydrate are currently classified in group A2^[216-219].

ORTHO-TOLUIDINE

Ortho-toluidine (O-toluidine) (CAS No. 95-53-4) is used in the chemical and rubber industry and is found in some colorants, herbicides and pesticides. O-toluidine can be an environmental contaminant if in the water used for irrigation of the cultivated fields. It has also been found in tobacco cigarettes. In animal models, O-toluidine caused bladder cancer and its exposure increased the incidence of HCC. Its carcinogenic power is probably due to the ability to determine the formation of DNA adducts, causing damage to the DNA structure. Therefore, O-toluidine is classified in group A^[220-229].

4,4'-METHYLENE BIS (2-CHLOROBENZENAMINE)

4,4'-Methylene bis (2-chlorobenzylamine) (MOCA) (CAS No. 101-14-4), used in the rubber industry, can be absorbed through the skin in workers, while population exposure occurs by ingestion of vegetables grown in contaminated soil. The ingestion or subcutaneous injection of MOCA in rats results in an increased incidence of HCC and lung cancer^[230-232]. MOCA has a documented detrimental effect on the genome; in fact, it is able to determine chromatin alterations and deletions^[76,233]. MOCA is classified in IARC group 1.

4-AMINOBIIPHENYL

4-aminobiphenyl (4-ABP) is used in the rubber industry as an antioxidant and a dye and is also found in cigarettes. It is classified in IARC group 1^[76]. In rats, 4-ABP ingestion causes bladder cancer, angiosarcoma and HCC; subcutaneous or intraperitoneal exposure determines a high incidence of HCC^[234]. The metabolism of 4-ABP determines the formation of N-hydroxyl ABP which is a mutagen. 4-ABP can form a DNA adduct. In human liver tissue, higher 4-ABP-DNA levels were observed in HCC cases compared with controls^[235-241]. Although there was a dose-related increase in 4-ABP DNA (cigarettes smoked/day) and an association with mutant p53 protein expression in bladder cancers, there are currently no reports of p53 or other specific gene mutations caused by exposure to PAH or 4-ABP in HCC^[242-244].

BENZIDINE AND DYES METABOLIZED TO BENZIDINE

In the past, benzidine (BZD) (CAS No. 92-87-5) and dyes metabolized to benzidine have been widely used in the production of dyes. Their use is currently banned in the United States and Europe. However, the use of products containing these substances may expose people to health risks^[245-248]. Epidemiological data on the risk of tumors in humans are limited, but the ingestion of BZD in rats increases the incidence of HCC^[249-252].

BZD and dyes metabolized to BZD are classified in group 1 carcinogens^[76].

ARSENIC

Arsenic (As) (CAS 7440-38-2) is widespread in nature and, combined with other elements, forms very toxic inorganic compounds that can pollute the water and contaminate the population. The workers in mechanical industries are exposed to the risk of illness from dyes, chemicals and glass^[253-258].

After oral intake and gastrointestinal absorption, it is metabolized in the liver where it is conjugated with glutathione and methylated^[259,260]. The chronic exposure to small amounts produces chronic liver disease, cirrhosis and HCC.

In the 2004 IARC monograph, the result of inorganic As in HCC formation was called "limited". In contrast, more recent data from animal models have shown the possibility of a strong bond with liver tumor formation^[261-268].

Various carcinogenic mechanisms, genetic and epigenetic, have been proposed: DNA methylation, oxidative damage, genomic instability and reduction of programmed cell death^[269-274].

CADMIUM

Cadmium (Cd) (CAS No. 7440-43-9) is a chemical element used as an anti-corrosion coating and a pigment. It is combined with lithium in rechargeable batteries and is also in cigarette tobacco. In fact, a cigarette contains about 2.0 µg Cd, of which 10.2% is transferred to the smoke^[275]. Cd in the blood and body of smokers are typically double those found in non-smokers^[276]. Burning municipal waste leads to inhalation of Cd. Workers in the metal and plastic product industry and workers involved in the construction of solar panels are exposed to Cd^[277,278].

In 2011, Cd production was estimated to be 600 metric tons in United States. Most of the Cd produced today is obtained from zinc and products recovered from spent Ni-Cd batteries. China, South Korea and Japan are the leading producers, followed by North America^[278]. According to OSHA estimates, 300000 workers are exposed to Cd in the United States. Cd found in food and cigarette smoke accumulates in the liver, kidney and pancreas. Liver concentrations increase with age, peaking at 40-60 years.

Based on epidemiological data, the IARC states that there is no evidence of unequivocal carcinogenic effects of Cd^[278-282].

However, many animal studies have demonstrated the ability of Cd to determine various tumors, including HCC. This risk is dose and time-dependent and it is conditioned on the exposure mode. Oxidative stress, DNA methylation, the failure of DNA repair, activation of oncogenes, uncontrolled cell growth and the loss of apoptosis are among the mechanisms hypothesized by

researchers^[283-286]. Interestingly, Sabolić *et al.*^[287] have shown that the Cd can be internalized in the Kupffer cells which begin to produce cytokines, some of these are indicated as cofactors in the development of HCC.

Some studies have reported that chronic exposure to Cd increases the risk of tumors in humans^[288-290]. However, large epidemiological studies are necessary to demonstrate whether long term Cd contamination is responsible for HCC development in humans, as in animal models.

DISCUSSION

Workplace risk prevention and safety rely chiefly on eliminating the risk itself (primary prevention) and, when it is not technically feasible, measures have to be enacted to reduce risk to a minimum^[291].

When chemical agents are involved, primary prevention entails replacing a toxic agent with a non-toxic one. However, some mutagenic/carcinogenic agents can be produced in synthetic processes as intermediates or waste products^[292]. As regards biological agents, it is critical to distinguish deliberate introduction of an agent into the working cycle, as in research centers, from the potential exposure resulting from its unwanted presence, as in the case of health care workers. Whereas the biological agent can be replaced in the former case, other measures have to be enacted in the latter^[293].

When risk assessment determines the existence of a healthy risk, adequate risk control systems have to be implemented. Such systems are divided into general and personal protection devices (PPD). The former include adoption of technical and procedural measures, for instance the reduction of environmental pollutants, whereas PPD largely consist of devices worn by workers (*e.g.*, masks, gloves), preventing direct contact with vapors, fumes and/or potentially contaminated material, *e.g.*, biological fluids^[294]. Biological risk prevention may involve mandatory vaccine prophylaxis, as in the case of HBV infection. Moreover, the fast pace of advances in vaccine development and protection equipment and devices requires continuous re-assessment of workplace protection systems^[295,296].

In workplaces where risks are documented, safety procedures must be instituted in accordance with national guidelines. In case of flaws or deficiencies in such guidelines, those in charge of workplace safety are required to refer to the guidelines of internationally recognized organizations such as the Centers for Disease Control and Prevention, American Conference of Industrial Hygienists, NIOSH, *etc.*

The employer and occupational physician have key roles in preventing occupational risk and diseases. The occupational physician, besides carrying out biological monitoring and health surveillance (secondary prevention), is responsible for promoting workplace health^[291].

As regards HCC prevention, all exposed workers should have HBV vaccination. In addition, campaigns

against smoking and alcohol drinking should be organized, providing an explicit warning that these factors may contribute to the development of liver cancer^[10-12,101].

Development and progression of HCC is still not a completely known multistage process. Genetic, epigenetic and immunological factors probably contribute to the development of HCC^[7,11,13,37,38,50,51,101,297,298].

CONCLUSION

In conclusion, the precancerous milieu of chronic liver disease is characterized by neo-angiogenesis, inflammation with ROS production and fibrosis. Synchronous events occurring in this setting also include hypoxia, oxidative stress, apoptosis, mitophagy and autophagy^[299-302].

Autophagy shows a double face in HCC. While autophagy helps to prevent tumorigenesis, it is also used by the cancer cells for survival against apoptosis by traditional chemotherapeutic drugs^[303,304]. Initially, autophagy functions as a tumor suppressor and later, when HCC has developed, the autophagy may contribute to its growth^[303,305].

Microbes have evolved mechanisms to evade and exploit autophagy and both HBV and HCV use autophagy for their own survival^[306]. Studies have shown that autophagy enhances viral replication at most steps of HBV replication and that autophagy proteins are likely to be factors for the initial steps of HCV replication^[307,308]. In tumor cells with defects in apoptosis, autophagy allows prolonged survival.

Future directions

All these mechanisms are still being studied in order to provide new therapeutic approaches to HCC^[309]. Despite the progress achieved in understanding the cancer process and the impact of this knowledge on treatment, primary prevention remains the most effective approach to reduce cancer mortality in both developed and developing countries for the near future^[9,37,38,50,51,56,309].

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