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**Hepatocellular carcinoma and risk of occupational exposure**

Rapisarda V *et al.* HCC and occupational exposure risk

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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, 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 often fragmented and inconsistence. This review wants to unify the current knowledge regarding the association of infective and non-infective occupational risk exposure and HCC, to encourage further research and draw attention to this global occupational public health problem.

**Key words:** Hepatocellular carcinoma; Autophagy; Mitophagy; Epigenetic events; Hepatitis B virus; Hepatitis C virus; Occupational exposure; Chemical agents; 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 the major cause of liver damage.

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**INTRODUCTION**

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

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

The relationship between occupational risk and HCC is often unclear and the reports are fragmented and inconsistence[17-19]; however it is very common vinyl chloride (VCM) induced hepatic angiosarcoma (ASL)[20].

HCC mortality, assessed with standardized relate mortality (SMR), has been reported in different categories of workers: Workers at the building, chemical workers, painters, subjects exposed to solvents, and workers of textile industry were often reported at high risk for HCC incidence[21-30]. However, such studies have often failed to identify a single agent responsible for the heightened HCC risk. Investigations of occupational exposure and liver cancer are few. A number of factors and confounders have precluded drawing firm conclusions[31].

Below it will be discussed the possible associations between risk of infection and non-infectious occupational hazard and HCC, hoping to draw attention to this global problem of public health.

**REVIEW METHOD**

The PubMed, Scopus, and Web of Science (WOS) database was used for the following keywords: “hepatocellular carcinoma”, “occupational exposure”, “chemical agents”, “arsenic”, “cadmium”, “HBV”,”HCV”, “molecular hepatocarcinogenesis”, “molecular immunological targets,” “autophagy”, “mitophagy”, “epigenetic events”. Data published 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]. Those responsible for HCC development in the world are HBV, HCV and AFB1[35].The vast majority of the global cancer burden attributable to infection involves less developed regions (Table 1).

**HEPATITIS INFECTIONS**

HBV and HCV can infect for parenteral or unapparent transmission[36-42].

***Occupational exposure to hepatitis B***

The risk of hepatitis from needlesticks from an HBeAg+ source is 22%-31%, whereas the risk of contracting clinical hepatitis from a needlestick involving an 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 are thought to be 70%-75% effective[43-45].

***Occupational exposure to hepatitis C***

The risk of HCV transmission from a 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 HIV/HCV co-infected), and it never has been documented following a blood exposure to intact or non-intact skin. There is no known PEP to HCV exposure. According to a European case-control study, assessment of the risk of transmission after occupational HCV exposure should take into account injury severity, the 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 the liver injury (necrosis and inflammation), and cirrhosis development (fibrosis and regeneration)[41,43,44,45]. Moreover, HBV and HCV co-infection causes a risk more than 50-fold relative HCC risks[51-54].

Risk factors for liver cancer in HBV patients include: (1) host-related risk factor: 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 HDV infection, 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, high HBsAg serum levels[59-62].

Lastly, the HCC risk factor in chronic HBV infection are different and pathogenesis is characterized by the combined action of different alterations involving genetic, epigenetic and immunological[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% develops 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 TGF-β pathways may also be directly affected[5].

Moreover chronic infection, necrosis and cell regeneration, fibrosis and finally cirrhosis are, together with the direct mechanisms, the high risk factors of HCC. Finally, the 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), in oilseeds (groundnuts), in dried fruit. Are chemicals of difuranocumarina type. Until now we were 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).

**VINYL CHLORIDE MONOMER AND POLYVINYL CHLORIDE**

Vinyl chloride monomer (VCM) - Chemical Abstract Service Number (CAS No.) 75-01-4 is a chlorinated organic compound. VMC is found in cigarette smoke and it is also mainly used in the production of polymer polyvinyl chloride (PVC). VCM is rapidly absorbed after inhalation and it 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 all those in which the worker are in contact with the material still in the monomeric state. Many epidemiological studies have demonstrated the high prevalence of exposure to VCM in the workers of the chemical. Thiodiglycolic acid is the main VCM metabolite detected in urine of occupationally exposed subjects.

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

Maroni *et al*[113] reported the hepato toxicity 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 the exposed[118-120].

**ORGANIC SOLVENTS**

The 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, trichlorethylene (TCE) and perchlorethylene (PCE) have been reported capable of promoting cancer in man[121,122].

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

It is hypothesized that TEC may be involved various mechanisms such as, for example, the reduction of the 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 the 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. TEC binds the RAD51 and consequently alters the DNA repair and can cause a certain degree of genomic instability.

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

High prevalence of liver cancer had been 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 increase of HCC and 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, but also consumers who eat agricultural products not properly cleaned and decontaminated may be exposed as well.

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

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

Many insecticides, including DDT, had been reported to be responsable to lead the development of HCC[147-152]. This would occur through different mechanisms not yet completely understood. Moreover, DDT is able to have a similar-estrogenic effect, while the DDE has anti-androgenic effects. DDT may also interfere with the CYP3A1 gene, involved in the inflammatory and immune response in the liver. Probably none of these mechanisms is individually able to determine the 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, is important to amplify 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 tire manufacturing processes, and they 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 the skin contact, by ingestion and/or inhalation.

Nitrosamines are carcinogenic and they are implicated in nasopharynx, oesophagus, stomach, liver, and urinary bladder cancers[159].

From 1981 to 1991, the US NTP 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[159-161].

In environmental surveys of some European rubber factories, De Vocht *et al*[162] and Jönsson *et al*[163] found the average N-nitrosamine levels well below regulatory limits in force, but still high accidental exposures have occurred. In fact, they were 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 and this might be much due to the shortening of telomeres among workers in the rubber industry. Telomeres are critical to maintaining the integrity of chromosomes, and abnormalities of telomere length 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 fundamental consists of a ring of six atoms, four carbon atoms and two oxygen; dioxin in the strict sense, differently stable, 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 polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF). Among them, the most toxic is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It is 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. Main responsible for compounds formation belonging to the family of dioxins is the organic chlorine, which is bound to organic compounds of polymers, for example PVC. Dioxins are generated even in the absence of combustion, for example in the bleaching of paper and tissue performed 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. Very important is the phenomenon of bioaccumulation, i.e. the possibility that dioxin enter in human food chain from plants, through herbivores, carnivores and finally human[170-176]. Dioxins are classified as definitely carcinogenic and in Group 1 Carcinogenic to humans by IARC.

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

Many studies indicate 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 metabolism, but there is evidence that AhR is able to control other genes, some of which with capacity pro-oncogenic[182-184]. The TCDD is an important AhR agonist and, therefore, able to induce and enhance the 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 by inhalation, this last also for the possibility of developing vapors for the equipments containing PCB overheating[185].

Studies in animal models have shown that these chemical compounds can cause chronic hepatitis, but also cancers, such as the HCCand cholangiocarcinoma, especially if the amount of high exposure and time is prolonged. Instead, we have little data on liver injury in man. In one case the exposure to olive oil accidentally contaminated with PCB has determined, in subjects exposed, death for hepatic cirrhosis. Other studies in workers exposed to the PCB, have reported an increased incidence of liver tumors[185-188].

It has been assumed some possible mechanisms by which PCB can cause cancer: through the enzymatic oxidation or autoxidation of the PCB it produces reactive oxygen species (ROS); PCB determines the increased expression of genes responsible for inflammation and apoptosis in the liver; PCB has “toxic” effects of certain genes such as, for example, the loss of part of 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 of the HCC[200-205]. However, at present we have no conclusive data on the relationship between PCBs and HCC. Further studies will be needed to establish the causal link; however, the evidence reported by studies in animal models have made possible to classify the PCB in IARC Group 1[206,207].

**POLYBROMINATED BIPHENYLS**

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

The contamination can occur through skin contact, inhalation, and ingestion[209-212]. Based on data obtained from animal research, the PDDs are considered as potential human carcinogens and they can determine hematologic malignancies, the digestive system and liver. The pathogenic mechanisms by which they can determine PDDs cancer are similar to those described for the PCB and this allows you to define them as “probably carcinogenic for humans” (Group 2A)[207].

**CHLORAL AND CHLORAL HYDRATE**

Chloral (or trichloroacetaldehyde) is a chemical compound having the formula C2HCl3O and CAS (Chemical Abstracts Service) 75-87-6. The chloral is produced by chlorination of ethanol. It is also produced as an intermediate in the synthesis of various products, for example DDT. Chloral is used for production of chloral hydrate (formula C2H3Cl3O2 and CAS number 302-17-0).

The chloral hydrate is an ingredient used for 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 have been 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, the chloral and chloral hydrate are currently classified in Group A2[216-219].

**ORTHO-TOLUIDINE (O-TOLUIDINE)**

O-Toluidine (CAS No. 95-53-4) is used in the chemical and rubber industry and it is located in some colorants, herbicides, and pesticides. O-Toluidine can be an environmental contaminant if it is found in the water used for the irrigation of the cultivated fields. It has also been found in tobacco cigarettes. O-Toluidine is responsible of bladder cancer in the animal model and its exposure increases the incidence of HCC. Its carcinogenic power is probably due to the ability to determine the formation of DNA adducts and cause 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 by the workers through the skin, while the 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 Group 1 IARC.

**4-AMINOBIPHENYL**

4-Aminobiphenyl (4-ABP) is not only used in the rubber industry as an antioxidant and as a dye, but it is also found in cigarettes. It is classified in Group 1 IARC[76]. In rats, 4-ABP ingestion causes bladder cancer, angiosarcoma and HCC; subcutaneous or intraperitoneal determines 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]. Nevertheless 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. Currently their use is 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 human 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, combining with other elements, it forms very toxic inorganic compounds that can pollute the water and contaminate the population. The workers of the mechanical industries are exposed to the risk of illness, dyes, chemicals, and glass[253-258].

After oral intake and gastrointestinal absorption, as 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 IARC monograph of 2004, the responsibility of inorganic As in HCC formation has been called “limited”. In contrast, more recent data from animal models have shown the possibility of a strong bond with the liver tumor formation[261-268].

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

**CADMIUM**

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

In 2011, Cd production was estimated at 600 metric tons in US. Most of the Cd produced today is obtained from zinc and by 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 US. 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 effect of Cd[278-282].

However, many studies conducted in animals have demonstrated the ability of Cd to determine various tumors including HCC. This risk is dose, time-dependent and it is conditioned on the exposure mode. Among the mechanisms hypothesized, researchers have indicated: oxidative stress, DNA methylation, and the failure of DNA repair, the activation of oncogenes, the uncontrolled cell growth, and the loss of apoptosis[283-286]. Interestingly, Sabolic and co-workers have shown that the Cd can be internalized in the Kupffer cells which begin to produce cytokines, some of these indicated as cofactors in the development of HCC[287].

Some studies have reported that chronic exposure to Cd increases the tumors risk in human[288-290]. However large epidemiological studies are necessary to demonstrate whether the long period Cd contamination is responsible of HCC development in human, as it happen for 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 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 as 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 HCW. 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 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: Centers for Disease Control and Prevention (CDC), ACGIH (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 specifically HCC prevention, all exposed workers should have HBV vaccination. In addition, campaigns against smoking and alcohol drinking should be organized, providing explicit warning that these factors may contribute to the development of liver cancer[10,11,12,101].

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

**CONCLUSION AND FUTURE DIRECTIONS**

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, mytophagy and autophagy[299-302].

Autophagy shows a double face in HCC. While autophagy helps to prevents tumorigenesis, it is also used by the cancer cells for survival against apoptosis by traditional chemotherapeutic drugs[303,304]. Initially autophagy functions are as tumor suppressor, later when the 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 authophagy 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, in near future primary prevention remains the most effective approach to reduce cancer mortality in either developed and developing countries[9,37,38,50,51,56,309].

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**Table 1 Hepatocellular carcinoma and occupational exposure to infective agents**

|  |  |  |  |
| --- | --- | --- | --- |
| **Risk agent** | **CAS No.** | **Occupational exposure** | **IARC class** |
| **Infective risk** |  |  |  |
| Hepatitis B virus | - | Health care workers[4,38,41,44],waste operators[38,44] | Group 1[34] |
| Hepatitis C virus | - | 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[77,78,87-90,91 93,96] | Group 1[76] |

IARC: International Agency for Research on Cancer; CAS No.: Chemical Abstract Service Number.

**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[98,99,102,103,105-107,110-120] | 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] |
| Tetrachloroethylene (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 components production and use; gasoline and lubricant additives, production and use[159,160,161, 162-165] | Group [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[175,186,187-190] | Group1 [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] |
| ortho-Toluidine | 95-53-4 | Dyes 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 | Dyes 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: Perchlorethylene DDT: 1,1,1-Trichloro-2,2-bis (p-chlorophenyl)-ethane; TCDD: [2,3,7,8-Tetrachlorodibenzo-p-dioxin](http://en.wikipedia.org/wiki/2,3,7,8-Tetrachlorodibenzodioxin); PeCDF: 2,3,4,7,8-Pentachlorodibenzofuran; PCB: Polychlorinated biphenyls; PBB: Polybrominated biphenyls; MOCA: 4,4′-Methylene bis(2-chlorobenzenamine); 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; pesticides use; As extraction industry; lead processing; pharmaceutical industry; glass industry; leather preservatives; antifouling paints; agrochemicals 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.

**Host immune responses**

**Inflammation and necrosis**

**Oxydative stress**

**Viral**

**Heterogeneity**

**Prolonged**

**expression**

**of viral genes**

**HBx, LHBs**

**Modifications of the epigenome**

**Genetic**

**instability**

**Integration of HBV DNA**

**Into host chromosomes:**

**Insertional mutagenesis**

**of cellular genes**

**Cell proliferation**

**Apoptosis, Autophagy**

**Gene Mutations**

**β-catenin, TP53**

**(AXIN1, RB1, PTEN, PIK3CA, HNF1a, SMAD2 and 4, Ras)**

**Chromosomal alterations**

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