**Name of Journal: *World Journal of Hepatology***

**ESPS Manuscript NO: 20719**

**Manuscript Type: Review**

**Hepatocellular carcinoma and risk of occupational exposure**

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

**Venerando Rapisarda, Carla Loreto, Michele Malaguarnera, Annalisa Ardiri, Maria Proiti, Giuseppe Rigano, Evelise Frazzetto, Maria Irene Ruggeri, Giulia Malaguarnera, Nicoletta Bertino, Mariano Malaguarnera, Vito Emanuele Catania, Isidoro Di Carlo, Adriana Toro, Emanuele Bertino, Dario Mangano, Gaetano Bertino**

**Venerando Rapisarda, Dario Mangano,** Occupational Medicine Unit, Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy

**Carla Loreto,** Department of Bio-Medical Sciences, Human Anatomy and Histology Section, University of Catania, 95100 Catania, Italy

**Michele Malaguarnera,** Department of Biomedical Sciences, University of Catania, 95100 Catania, Italy

**Annalisa Ardiri, Maria Proiti, Giuseppe Rigano, Evelise Frazzetto, Gaetano Bertino,** Hepatology Unit, Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy

**Maria Irene Ruggeri,** Internal Medicine Unit ARNAS Civic Hospital, 90142 Palermo, Italy

**Giulia Malaguarnera, Mariano Malaguarnera, Vito Emanuele Catania,** Research Centre “La Grande Senesce” University of Catania, 95100 Catania, Italy

**Nicoletta Bertino, Emanuele Bertino,** Faculty of Pharmacy, University of Catania, 95123 Catania, Italy

**Isidoro Di Carlo, Adriana Toro,** Department of Surgical Sciences, Organ Transplantation and Advanced Technologies, University of Catania, 95100 Catania, Italy

**Author contributions:** All authors contributed to this paper.

**Conflict-of-interest** **statement:** No potential conflicts of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Gaetano Bertino, Professor,** Hepatology Unit, Department of Clinical and Experimental Medicine, University of Catania, Policlinic - Via S. Sofia n. 78, 95123 Catania, Italy. gaetanobertinounict@libero.it

**Telephone:** +39-095-3781573

**Fax:** +39-095-3781572

**Received:** June 17, 2015

**Peer-review started:** June 19, 2015

**First decision:** August 10, 2015

**Revised:** April 1, 2016

**Accepted:** April 14, 2016

**Article in press:**

**Published online:**

**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

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Rapisarda V, Loreto C, Malaguarnera M, Ardiri A, Proiti M, Rigano G, Frazzetto E, Ruggeri MI, Malaguarnera G, Bertino N, Malaguarnera M, Catania VE, Di Carlo I, Toro A, Bertino E, Mangano D, Bertino G. Hepatocellular carcinoma and risk of occupational exposure. *World J Hepatol* 2016; In press

**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].

**REFERENCES**

1 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans**. Biological agents. Volume 100 B. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 2012; **100**: 1-441 [PMID: 23189750]

2 **McGlynn KA**, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis* 2015; **19**: 223-238 [PMID: 25921660 DOI: 10.1016/j.cld.2015.01.001]

3 **Wallace MC**, Preen D, Jeffrey GP, Adams LA. The evolving epidemiology of hepatocellular carcinoma: a global perspective. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 765-779 [PMID: 25827821 DOI: 10.1586/17474124.2015.1028363]

4 **Papatheodoridis GV**, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol* 2015; **62**: 956-967 [PMID: 25595883 DOI: 10.1016/j.jhep.2015.01.002]

5 **Lemon SM**, McGivern DR. Is hepatitis C virus carcinogenic? *Gastroenterology* 2012; **142**: 1274-1278 [PMID: 22537433 DOI: 10.1053/j.gastro.2012.01.045]

6 **Saad-Hussein A**, Taha MM, Beshir S, Shahy EM, Shaheen W, Elhamshary M. Carcinogenic effects of aflatoxin B1 among wheat handlers. *Int J Occup Environ Health* 2014; **20**: 215-219 [PMID: 25000109 DOI: 10.1179/2049396714Y]

7 **Askgaard G**, Grønbæk M, Kjær MS, Tjønneland A, Tolstrup JS. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. *J Hepatol* 2015; **62**: 1061-1067 [PMID: 25634330 DOI: 10.1016/j.jhep.2014.12.005]

8 **Bassuk SS**, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. *Ann Epidemiol* 2015; **25**: 193-200 [PMID: 25534509 DOI: 10.1016/j.annepidem.2014.11.004]

9 **Bertino G**, Demma S, Ardiri A, Toro A, Calvagno Gs, Malaguarnera G, Bertino N, Malaguarnera M, Malaguarnera M, Di Carlo I. Focal nodular hyperplasia from the surgery to the follow-up. Change of therapeutic approach. *Acta Medica Mediterranea* 2014; **30**: 1329-1336

10 **Lv Y**, Liu C, Wei T, Zhang JF, Liu XM, Zhang XF. Cigarette smoking increases risk of early morbidity after hepatic resection in patients with hepatocellular carcinoma. *Eur J Surg Oncol* 2015; **41**: 513-519 [PMID: 25656703 DOI: 10.1016/j.ejso.2015.01.015]

11 **Purohit V**, Rapaka R, Kwon OS, Song BJ. Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. *Life Sci* 2013; **92**: 3-9 [PMID: 23123447 DOI: 10.1016/j.lfs.2012.10.009]

12 **Hsieh YH**, Chang WS, Tsai CW, Tsai JP, Hsu CM, Jeng LB, Bau DT. DNA double-strand break repair gene XRCC7 genotypes were associated with hepatocellular carcinoma risk in Taiwanese males and alcohol drinkers. *Tumour Biol* 2015; **36**: 4101-4106 [PMID: 25944161 DOI: 10.1007/s13277-014-2934-5]

13 **Loomba R**, Yang HI, Su J, Brenner D, Barrett-Connor E, Iloeje U, Chen CJ. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. *Am J Epidemiol* 2013; **177**: 333-342 [PMID: 23355498 DOI: 10.1093/aje/kws252]

14 **Bertino G**, Ardiri AM, Alì FT, Boemi PM, Cilio D, Di Prima P, Fisichella A, Ierna D, Neri S, Pulvirenti D, Urso G, Mauceri B, Valenti M, Bruno CM. Obesity and related diseases: an epidemiologic study in eastern Sicily. *Minerva Gastroenterol Dietol* 2006; **52**: 379-385 [PMID: 17108868]

15 **Hardt A**, Stippel D, Odenthal M, Hölscher AH, Dienes HP, Drebber U. Development of hepatocellular carcinoma associated with anabolic androgenic steroid abuse in a young bodybuilder: a case report. *Case Rep Pathol* 2012; **2012**: 195607 [PMID: 22934212 DOI: 10.1155/2012/195607]

16 **Toro A**, Mahfouz AE, Ardiri A, Malaguarnera M, Malaguarnera G, Loria F, Bertino G, Di Carlo I. What is changing in indications and treatment of hepatic hemangiomas. A review. *Ann Hepatol* 2014; **13**: 327-339 [PMID: 24927603]

17 **Vinci M**, Malaguarnera L, Pistone G. RS3PE and ovarian cancer. *Ann Rheum Dis* 2001; **60**: 429-431 [PMID: 11284457]

18 **Czarnecki LA**, Moberly AH, Turkel DJ, Rubinstein T, Pottackal J, Rosenthal MC, McCandlish EF, Buckley B, McGann JP. Functional rehabilitation of cadmium-induced neurotoxicity despite persistent peripheral pathophysiology in the olfactory system. *Toxicol Sci* 2012; **126**: 534-544 [PMID: 22287023 DOI: 10.1093/toxsci/kfs030]

19 **Yang CJ**, Lin JL, Lin-Tan DT, Weng CH, Hsu CW, Lee SY, Lee SH, Chang CM, Lin WR, Yen TH. Spectrum of toxic hepatitis following intentional paraquat ingestion: analysis of 187 cases. *Liver Int* 2012; **32**: 1400-1406 [PMID: 22672665 DOI: 10.1111/j.1478-3231.2012.02829.x]

20 **Sherman M**. Vinyl chloride and the liver. *J Hepatol* 2009; **51**: 1074-1081 [PMID: 19836850 DOI: 10.1016/j.jhep.2009.09.012]

21 **Wong O**, Morgan RW, Kheifets L, Larson SR, Whorton MD. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. *Br J Ind Med* 1985; **42**: 435-448 [PMID: 2410010]

22 **Jansson C**, Alderling M, Hogstedt C, Gustavsson P. Mortality among Swedish chimney sweeps (1952-2006): an extended cohort study. *Occup Environ Med* 2012; **69**: 41-47 [PMID: 21705462 DOI: 10.1136/oem.2010.064246]

23 **Ward EM**, Fajen JM, Ruder AM, Rinsky RA, Halperin WE, Fessler-Flesch CA. Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. *Environ Health Perspect* 1995; **103**: 598-603 [PMID: 7556014]

24 **Malaguarnera M**, Vacante M, Russo C, Gargante MP, Giordano M, Bertino G, Neri S, Malaguarnera M, Galvano F, Li Volti G. Rosuvastatin reduces nonalcoholic fatty liver disease in patients with chronic hepatitis C treated with α-interferon and ribavirin: Rosuvastatin reduces NAFLD in HCV patients. *Hepat Mon* 2011; **11**: 92-98 [PMID: 22087124]

25 **Steenland K**, Palu S. Cohort mortality study of 57,000 painters and other union members: a 15 year update. *Occup Environ Med* 1999; **56**: 315-321 [PMID: 10472305]

26 **Chen R**, Seaton A. A meta-analysis of mortality among workers exposed to organic solvents. *Occup Med* (Lond) 1996; **46**: 337-344 [PMID: 8918147]

27 **Gibbs GW**, Amsel J, Soden K. A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride. *J Occup Environ Med* 1996; **38**: 693-697 [PMID: 8823660]

28 **Chow WH**, McLaughlin JK, Zheng W, Blot WJ, Gao YT. Occupational risks for primary liver cancer in Shanghai, China. *Am J Ind Med* 1993; **24**: 93-100 [PMID: 8352295]

29 **Toro A**, Ardiri A, Mannino M, Arcerito MC, Mannino G, Palermo F, Bertino G, Di Carlo I. Effect of pre- and post-treatment α-fetoprotein levels and tumor size on survival of patients with hepatocellular carcinoma treated by resection, transarterial chemoembolization or radiofrequency ablation: a retrospective study. *BMC Surg* 2014; **14**: 40 [PMID: 24993566 DOI: 10.1186/1471-2482-14-40]

30 **Heinemann K**, Willich SN, Heinemann LA, DoMinh T, Möhner M, Heuchert GE. Occupational exposure and liver cancer in women: results of the Multicentre International Liver Tumour Study (MILTS). *Occup Med* (Lond) 2000; **50**: 422-429 [PMID: 10994245]

31 **Chang CK**, Astrakianakis G, Thomas DB, Seixas NS, Ray RM, Gao DL, Wernli KJ, Fitzgibbons ED, Vaughan TL, Checkoway H. Occupational exposures and risks of liver cancer among Shanghai female textile workers--a case-cohort study. *Int J Epidemiol* 2006; **35**: 361-369 [PMID: 16373377]

32 **Oh JK**, Weiderpass E. Infection and cancer: global distribution and burden of diseases. *Ann Glob Health* 2014; **80**: 384-392 [PMID: 25512154 DOI: 10.1016/j.aogh.2014.09.013]

33 **Bouvard V**, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens--Part B: biological agents. *Lancet Oncol* 2009; **10**: 321-322 [PMID: 19350698]

34 **Coutlée F**, Franco EL. Infectious agents. *IARC Sci Publ* 2011; **(163)**: 175-187 [PMID: 22997862]

35 **Kew MC**. Aflatoxins as a cause of hepatocellular carcinoma. *J Gastrointestin Liver Dis* 2013; **22**: 305-310 [PMID: 24078988]

36 **Carr BI**, Guerra V, Steel JL, Lu SN. A comparison of patients with hepatitis B- or hepatitis C-based advanced-stage hepatocellular carcinoma. *Semin Oncol* 2015; **42**: 309-315 [PMID: 25843735 DOI: 10.1053/j.seminoncol.2014.12.019]

37 **Stroffolini T**, Spadaro A, Di Marco V, Scifo G, Russello M, Montalto G, Bertino G, Surace L, Caroleo B, Foti G, Portelli V, Madonia S, Sapienza M, Cosco L, Frugiuele P, Galdieri A, Brandolino N, Siciliano R, Bruno S, Almasio PL. Current practice of chronic hepatitis B treatment in Southern Italy. *Eur J Intern Med* 2012; **23**: e124-e127 [PMID: 22726382 DOI: 10.1016/j.ejim.2012.03.018]

38 **Askarian M**, Yadollahi M, Kuochak F, Danaei M, Vakili V, Momeni M. Precautions for health care workers to avoid hepatitis B and C virus infection. *Int J Occup Environ Med* 2011; **2**: 191-198 [PMID: 23022838]

39 **Hajarizadeh B**, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 553-562 [PMID: 23817321 DOI: 10.1038/nrgastro.2013.107]

40 **Bosques-Padilla FJ**, Vázquez-Elizondo G, Villaseñor-Todd A, Garza-González E, Gonzalez-Gonzalez JA, Maldonado-Garza HJ. Hepatitis C virus infection in health-care settings: medical and ethical implications. *Ann Hepatol* 2010; **9 Suppl**: 132-140 [PMID: 20714010]

41 **Sinn DH**, Lee J, Goo J, Kim K, Gwak GY, Paik YH, Choi MS, Lee JH, Koh KC, Yoo BC, Paik SW. Hepatocellular carcinoma risk in chronic hepatitis B virus-infected compensated cirrhosis patients with low viral load. *Hepatology* 2015; **62**: 694-701 [PMID: 25963803 DOI: 10.1002/hep.27889]

42 **Grosso G**, Mistretta A, Marventano S, Ferranti R, Mauro L, Cunsolo R, Proietti L, Malaguarnera M. Long-term persistence of seroprotection by hepatitis B vaccination in healthcare workers of southern Italy. *Hepat Mon* 2012; **12**: e6025 [PMID: 23087756 DOI: 10.5812/hepatmon.6025]

43 **Yang HI**, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, Wang LY, Lu SN, You SL, Chen DS, Liaw YF, Chen CJ. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 1134-1143 [PMID: 18695135 DOI: 10.1093/jnci/djn243]

44 **Malaguarnera G**, Vacante M, Drago F, Bertino G, Motta M, Giordano M, Malaguarnera M. Endozepine-4 levels are increased in hepatic coma. *World J Gastroenterol* 2015; **21**: 9103-9110 [PMID: 26290636 DOI: 10.3748/wjg.v21.i30.9103]

45 **Saitta C**, Tripodi G, Barbera A, Bertuccio A, Smedile A, Ciancio A, Raffa G, Sangiovanni A, Navarra G, Raimondo G, Pollicino T. Hepatitis B virus (HBV) DNA integration in patients with occult HBV infection and hepatocellular carcinoma. *Liver Int* 2015; **35**: 2311-2317 [PMID: 25677098 DOI: 10.1111/liv.12807]

46 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101]

47 **Hassan MM**, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206-1213 [PMID: 12395331]

48 **Cha C**, Dematteo RP. Molecular mechanisms in hepatocellular carcinoma development. *Best Pract Res Clin Gastroenterol* 2005; **19**: 25-37 [PMID: 15757803]

49 **Thorgeirsson SS**, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; **31**: 339-346 [PMID: 12149612]

50 **Malaguarnera M**, Scuderi L, Ardiri Al, Malaguarnera G, Bertino N, Ruggeri IM, Greco C, Ozyalcn E, Bertino E, Bertino G. Type II mixed cryoglobulinemia in patients with hepatitis C Virus: treatment with pegylated-interferon and ribavirin. *Acta Medica Mediterranea* 2015; **31**: 651

51 **Bertino G**, Demma S, Ardiri A, Proiti M, Gruttadauria S, Toro A, Malaguarnera G, Bertino N, Malaguarnera M, Malaguarnera M, Di Carlo I. Hepatocellular carcinoma: novel molecular targets in carcinogenesis for future therapies. *Biomed Res Int* 2014; **2014**: 203693 [PMID: 25089265 DOI: 10.1155/2014/203693]

52 **Bertino G**, Di Carlo I, Ardiri A, Calvagno GS, Demma S, Malaguarnera G, Bertino N, Malaguarnera M, Toro A, Malaguarnera M. Systemic therapies in hepatocellular carcinoma: present and future. *Future Oncol* 2013; **9**: 1533-1548 [PMID: 24106903 DOI: 10.2217/fon.13.171]

53 **Biondi A**, Malaguarnera G, Vacante M, Berretta M, D'Agata V, Malaguarnera M, Basile F, Drago F, Bertino G. Elevated serum levels of Chromogranin A in hepatocellular carcinoma. *BMC Surg* 2012; **12** Suppl 1: S7 [PMID: 23173843 DOI: 10.1186/1471-2482-12-S1-S7]

54 **Bertino G**, Ardiri AM, Boemi PM, Ierna D, Interlandi D, Caruso L, Minona E, Trovato MA, Vicari S, Li Destri G, Puleo S. A study about mechanisms of des-gamma-carboxy prothrombin's production in hepatocellular carcinoma. *Panminerva Med* 2008; **50**: 221-226 [PMID: 18927526]

55 **Bertino G**, Ardiri AM, Calvagno GS, Bertino N, Boemi PM. Prognostic and diagnostic value of des-γ-carboxy prothrombin in liver cancer. *Drug News Perspect* 2010; **23**: 498-508 [PMID: 21031166 DOI: 10.1358/dnp.2010.23.8.1444236]

56 **Bertino G**, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellualar carcinoma serum markers. *Semin Oncol* 2012; **39**: 410-433 [PMID: 22846859 DOI: 10.1053/j.seminoncol.2012.05.001]

57 **Bertino G**, Neri S, Bruno CM, Ardiri AM, Calvagno GS, Malaguarnera M, Toro A, Malaguarnera M, Clementi S, Bertino N, Di Carlo I. Diagnostic and prognostic value of alpha-fetoprotein, des-γ-carboxy prothrombin and squamous cell carcinoma antigen immunoglobulin M complexes in hepatocellular carcinoma. *Minerva Med* 2011; **102**: 363-371 [PMID: 22193346]

58 **Sartori M**, La Terra G, Aglietta M, Manzin A, Navino C, Verzetti G. Transmission of hepatitis C via blood splash into conjunctiva. *Scand J Infect Dis* 1993; **25**: 270-271 [PMID: 8511524]

59 **Bertino G**, Ardiri A, Proiti M, Rigano G, Frazzetto E, Demma S, Ruggeri MI, Scuderi L, Malaguarnera G, Bertino N, Rapisarda V, Di Carlo I, Toro A, Salomone F, Malaguarnera M, Bertino E, Malaguarnera M. Chronic hepatitis C: This and the new era of treatment. *World J Hepatol* 2016; **8**: 92-106 [PMID: 26807205 DOI: 10.4254/wjh.v8.i2.92]

60 **MacCannell T**, Laramie AK, Gomaa A, Perz JF. Occupational exposure of health care personnel to hepatitis B and hepatitis C: prevention and surveillance strategies. *Clin Liver Dis* 2010; **14**: 23-36, vii [PMID: 20123437 DOI: 10.1016/j.cld.2009.11.001]

61 **Yazdanpanah Y**, De Carli G, Migueres B, Lot F, Campins M, Colombo C, Thomas T, Deuffic-Burban S, Prevot MH, Domart M, Tarantola A, Abiteboul D, Deny P, Pol S, Desenclos JC, Puro V, Bouvet E. Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: a European case-control study. *Clin Infect Dis* 2005; **41**: 1423-1430 [PMID: 16231252]

62 **Malaguarnera G**, Giordano M, Nunnari G, Bertino G, Malaguarnera M. Gut microbiota in alcoholic liver disease: pathogenetic role and therapeutic perspectives. *World J Gastroenterol* 2014; **20**: 16639-16648 [PMID: 25469033 DOI: 10.3748/wjg.v20.i44.16639]

63 **Petrovic D**, Stamataki Z, Dempsey E, Golden-Mason L, Freeley M, Doherty D, Prichard D, Keogh C, Conroy J, Mitchell S, Volkov Y, McKeating JA, O'Farrelly C, Kelleher D, Long A. Hepatitis C virus targets the T cell secretory machinery as a mechanism of immune evasion. *Hepatology* 2011; **53**: 1846-1853 [PMID: 21452285 DOI: 10.1002/hep.24327]

64 **O'Bryan JM**, Potts JA, Bonkovsky HL, Mathew A, Rothman AL. Extended interferon-alpha therapy accelerates telomere length loss in human peripheral blood T lymphocytes. *PLoS One* 2011; **6**: e20922 [PMID: 21829595 DOI: 10.1371/journal.pone.0020922]

65 **Pardee AD**, Butterfield LH. Immunotherapy of hepatocellular carcinoma: Unique challenges and clinical opportunities. *Oncoimmunology* 2012; **1**: 48-55 [PMID: 22720211]

66 **Bertino G**, Ardiri A, Boemi PM, Calvagno GS, Ruggeri IM, Speranza A, Santonocito MM, Ierna D, Bruno CM, Valenti M, Boemi R, Naimo S, Neri S. Epoetin alpha improves the response to antiviral treatment in HCV-related chronic hepatitis. *Eur J Clin Pharmacol* 2010; **66**: 1055-1063 [PMID: 20652232 DOI: 10.1007/s00228-010-0868-4]

67 **Malaguarnera G**, Pennisi M, Gagliano C, Vacante M, Malaguarnera M, Salomone S, Drago F, Bertino G, Caraci F, Nunnari G, Malaguarnera M. Acetyl-L-Carnitine Supplementation During HCV Therapy With Pegylated Interferon-α 2b Plus Ribavirin: Effect on Work Performance; A Randomized Clinical Trial. *Hepat Mon* 2014; **14**: e11608 [PMID: 24910702 DOI: 10.5812/hepatmon.11608]

68 **Malaguarnera M**, Vacante M, Giordano M, Motta M, Bertino G, Pennisi M, Neri S, Malaguarnera M, Li Volti G, Galvano F. L-carnitine supplementation improves hematological pattern in patients affected by HCV treated with Peg interferon-α 2b plus ribavirin. *World J Gastroenterol* 2011; **17**: 4414-4420 [PMID: 22110268 DOI: 10.3748/wjg.v17.i39.4414]

69 **Malaguarnera M**, Vacante M, Bertino G, Neri S, Malaguarnera M, Gargante MP, Motta M, Lupo L, Chisari G, Bruno CM, Pennisi G, Bella R. The supplementation of acetyl-L-carnitine decreases fatigue and increases quality of life in patients with hepatitis C treated with pegylated interferon-α 2b plus ribavirin. *J Interferon Cytokine Res* 2011; **31**: 653-659 [PMID: 21923249 DOI: 10.1089/jir.2011.0010]

70 **Bruno CM**, Valenti M, Bertino G, Ardiri A, Amoroso A, Consolo M, Mazzarino CM, Neri S. Relationship between circulating interleukin-10 and histological features in patients with chronic C hepatitis. *Ann Saudi Med* 2011; **31**: 360-364 [PMID: 21808111 DOI: 10.4103/0256-4947.83215]

71 **Zhao F**, Korangy F, Greten TF. Cellular immune suppressor mechanisms in patients with hepatocellular carcinoma. *Dig Dis* 2012; **30**: 477-482 [PMID: 23108303 DOI: 10.1159/000341695]

72 **Cai L**, Zhang Z, Zhou L, Wang H, Fu J, Zhang S, Shi M, Zhang H, Yang Y, Wu H, Tien P, Wang FS. Functional impairment in circulating and intrahepatic NK cells and relative mechanism in hepatocellular carcinoma patients. *Clin Immunol* 2008; **129**: 428-437 [PMID: 18824414 DOI: 10.1016/j.clim.2008.08.012]

73 **El Ansary M**, Mogawer S, Elhamid SA, Alwakil S, Aboelkasem F, Sabaawy HE, Abdelhalim O. Immunotherapy by autologous dendritic cell vaccine in patients with advanced HCC. *J Cancer Res Clin Oncol* 2013; **139**: 39-48 [PMID: 22886490 DOI: 10.1007/s00432-012-1298-8]

74 **Strosnider H**, Azziz-Baumgartner E, Banziger M, Bhat RV, Breiman R, Brune MN, DeCock K, Dilley A, Groopman J, Hell K, Henry SH, Jeffers D, Jolly C, Jolly P, Kibata GN, Lewis L, Liu X, Luber G, McCoy L, Mensah P, Miraglia M, Misore A, Njapau H, Ong CN, Onsongo MT, Page SW, Park D, Patel M, Phillips T, Pineiro M, Pronczuk J, Rogers HS, Rubin C, Sabino M, Schaafsma A, Shephard G, Stroka J, Wild C, Williams JT, Wilson D. Workgroup report: public health strategies for reducing aflatoxin exposure in developing countries. *Environ Health Perspect* 2006; **114**: 1898-1903 [PMID: 17185282]

75 **Liu Y**, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: systematic review and meta-analysis. *Eur J Cancer* 2012; **48**: 2125-2136 [PMID: 22405700 DOI: 10.1016/j.ejca.2012.02.009]

76 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans**. Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum* 2012; **100**: 9-562 [PMID: 23189753]

77 **Viegas S**, Veiga L, Figueiredo P, Almeida A, Carolino E, Viegas C. Assessment of workers' exposure to aflatoxin B1 in a Portuguese waste industry. *Ann Occup Hyg* 2015; **59**: 173-181 [PMID: 25324565 DOI: 10.1093/annhyg/meu082]

78 **Autrup JL**, Schmidt J, Seremet T, Autrup H. Determination of exposure to aflatoxins among Danish workers in animal-feed production through the analysis of aflatoxin B1 adducts to serum albumin. *Scand J Work Environ Health* 1991; **17**: 436-440 [PMID: 1788537]

79 **Diaz GJ**, Murcia HW, Cepeda SM. Cytochrome P450 enzymes involved in the metabolism of aflatoxin B1 in chickens and quail. *Poult Sci* 2010; **89**: 2461-2469 [PMID: 20952710 DOI: 10.3382/ps.2010-00864]

80 **Lin ZH**, Chen JC, Wang YS, Huang TJ, Wang J, Long XD. DNA repair gene XRCC4 codon 247 polymorphism modified diffusely infiltrating astrocytoma risk and prognosis. *Int J Mol Sci* 2014; **15**: 250-260 [PMID: 24378850 DOI: 10.3390/ijms15010250]

81 **Long XD**, Yao JG, Zeng Z, Ma Y, Huang XY, Wei ZH, Liu M, Zhang JJ, Xue F, Zhai B, Xia Q. Polymorphisms in the coding region of X-ray repair complementing group 4 and aflatoxin B1-related hepatocellular carcinoma. *Hepatology* 2013; **58**: 171-181 [PMID: 23390017 DOI: 10.1002/hep.26311]

82 **Lai H**, Mo X, Yang Y, He K, Xiao J, Liu C, Chen J, Lin Y. Association between aflatoxin B1 occupational airway exposure and risk of hepatocellular carcinoma: a case-control study. *Tumour Biol* 2014; **35**: 9577-9584 [PMID: 24961349 DOI: 10.1007/s13277-014-2231-3]

83 **Hu T**, Du Q, Ren F, Liang S, Lin D, Li J, Chen Y. Spatial analysis of the home addresses of hospital patients with hepatitis B infection or hepatoma in Shenzhen, China from 2010 to 2012. *Int J Environ Res Public Health* 2014; **11**: 3143-3155 [PMID: 24637909 DOI: 10.3390/ijerph110303143]

84 **Villar S**, Ortiz-Cuaran S, Abedi-Ardekani B, Gouas D, Nogueira da Costa A, Plymoth A, Khuhaprema T, Kalalak A, Sangrajrang S, Friesen MD, Groopman JD, Hainaut P. Aflatoxin-induced TP53 R249S mutation in hepatocellular carcinoma in Thailand: association with tumors developing in the absence of liver cirrhosis. *PLoS One* 2012; **7**: e37707 [PMID: 22675488 DOI: 10.1371/journal.pone.0037707]

85 **Gouas D**, Shi H, Hainaut P. The aflatoxin-induced TP53 mutation at codon 249 (R249S): biomarker of exposure, early detection and target for therapy. *Cancer Lett* 2009; **286**: 29-37 [PMID: 19376640 DOI: 10.1016/j.canlet.2009.02.057]

86 **Kirk GD**, Lesi OA, Mendy M, Szymañska K, Whittle H, Goedert JJ, Hainaut P, Montesano R. 249(ser) TP53 mutation in plasma DNA, hepatitis B viral infection, and risk of hepatocellular carcinoma. *Oncogene* 2005; **24**: 5858-5867 [PMID: 16007211]

87 **Jargot D**, Melin S. Characterization and validation of sampling and analytical methods for mycotoxins in workplace air. *Environ Sci Process Impacts* 2013; **15**: 633-644 [PMID: 23738362]

88 **Viegas S**, Veiga L, Malta-Vacas J, Sabino R, Figueredo P, Almeida A, Viegas C, Carolino E. Occupational exposure to aflatoxin (AFB₁) in poultry production. *J Toxicol Environ Health A* 2012; **75**: 1330-1340 [PMID: 23095151 DOI: 10.1080/15287394.2012.721164]

89 **Burg WA**, Shotwell OL, Saltzman BE. Measurements of airborne aflatoxins during the handling of contaminated corn. *Am Ind Hyg Assoc J* 1981; **42**: 1-11 [PMID: 6784564]

90 **Viegas S**, Faísca VM, Dias H, Clérigo A, Carolino E, Viegas C. Occupational exposure to poultry dust and effects on the respiratory system in workers. *J Toxicol Environ Health A* 2013; **76**: 230-239 [PMID: 23514065 DOI: 10.1080/15287394.2013.757199]

91 **Autrup JL**, Schmidt J, Autrup H. Exposure to aflatoxin B1 in animal-feed production plant workers. *Environ Health Perspect* 1993; **99**: 195-197 [PMID: 8319623]

92 **Ghosh SK**, Desai MR, Pandya GL, Venkaiah K. Airborne aflatoxin in the grain processing industries in India. *Am Ind Hyg Assoc J* 1997; **58**: 583-586 [PMID: 9248032]

93 **Desai MR**, Ghosh S. Occupational exposure to airborne fungi among rice mill workers with special reference to aflatoxin producing A. flavus strains. *Ann Agric Environ Med* 2003; **10**: 159-162 [PMID: 14677906]

94 **Traverso A**, Bassoli V, Cioè A, Anselmo S, Ferro M. Assessment of aflatoxin exposure of laboratory worker during food contamination analyses. Assessment of the procedures adopted by an A.R.P.A.L. laboratory (Liguria Region Environmental Protection Agency). *Med Lav* 2010; **101**: 375-380 [PMID: 21105592]

95 **Long XD**, Huang XY, Yao JG, Liao P, Tang YJ, Ma Y, Xia Q. Polymorphisms in the precursor microRNAs and aflatoxin B1-related hepatocellular carcinoma. *Mol Carcinog* 2015 [PMID: 26152337 DOI: 10.1002/mc.22350]

96 **Saad-Hussein A**, Beshir S, Moubarz G, Elserougy S, Ibrahim MI. Effect of occupational exposure to aflatoxins on some liver tumor markers in textile workers. *Am J Ind Med* 2013; **56**: 818-824 [PMID: 23359393 DOI: 10.1002/ajim.22162]

97 **Levy BS**, Wegman DH, Baron SL, Sokas RK. Occupational and Environmental Health: Recognizing and Preventing Disease and Injury. 6th ed. New York: Oxford University Press, Inc., 2011

98 IARC monographs on the evaluation of carcinogenic risks to humans. Volume 97. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). *IARC Monogr Eval Carcinog Risks Hum* 2008; **97**: 3-471 [PMID: 20232717]

99 **Lopez V**, Chamoux A, Tempier M, Thiel H, Ughetto S, Trousselard M, Naughton G, Dutheil F. The long-term effects of occupational exposure to vinyl chloride monomer on microcirculation: a cross-sectional study 15 years after retirement. *BMJ Open* 2013; **3**: [PMID: 23794583 DOI: 10.1136/bmjopen-2013-002785]

100 **Uccello M**, Malaguarnera G, Corriere T, Biondi A, Basile F, Malaguarnera M. Risk of hepatocellular carcinoma in workers exposed to chemicals. *Hepat Mon* 2012; **12**: e5943 [PMID: 23162599 DOI: 10.5812/hepatmon.5943]

101 **Caponnetto P**, Russo C, Di Maria A, Morjaria JB, Barton S, Guarino F, Basile E, Proiti M, Bertino G, Cacciola RR, Polosa R. Circulating endothelial-coagulative activation markers after smoking cessation: a 12-month observational study. *Eur J Clin Invest* 2011; **41**: 616-626 [PMID: 21198559 DOI: 10.1111/j.1365-2362.2010.02449.x]

102 **Kauppinen T**, Toikkanen J, Pedersen D, Young R, Ahrens W, Boffetta P, Hansen J, Kromhout H, Maqueda Blasco J, Mirabelli D, de la Orden-Rivera V, Pannett B, Plato N, Savela A, Vincent R, Kogevinas M. Occupational exposure to carcinogens in the European Union. *Occup Environ Med* 2000; **57**: 10-18 [PMID: 10711264]

103 **Dobecki M**, Romanowicz B. [Occupational exposure to toxic substances during the production of vinyl chloride and chlorinated organic solvents]. *Med Pr* 1993; **44**: 99-102 [PMID: 8377644]

104 **Fred C**, Törnqvist M, Granath F. Evaluation of cancer tests of 1,3-butadiene using internal dose, genotoxic potency, and a multiplicative risk model. *Cancer Res* 2008; **68**: 8014-8021 [PMID: 18829559 DOI: 10.1158/0008-5472.CAN-08-0334]

105 **Dogliotti E**. Molecular mechanisms of carcinogenesis by vinyl chloride. *Ann Ist Super Sanita* 2006; **42**: 163-169 [PMID: 17033136]

106 **Fedeli U**, Mastroangelo G. Vinyl chloride industry in the courtroom and corporate influences on the scientific literature. *Am J Ind Med* 2011; **54**: 470-473 [PMID: 21456080 DOI: 10.1002/ajim.20941]

107 **Lewis R**, Rempala G, Dell LD, Mundt KA. Vinyl chloride and liver and brain cancer at a polymer production plant in Louisville, Kentucky. *J Occup Environ Med* 2003; **45**: 533-537 [PMID: 12762078]

108 **Hsieh HI**, Chen PC, Wong RH, Du CL, Chang YY, Wang JD, Cheng TJ. Mortality from liver cancer and leukaemia among polyvinyl chloride workers in Taiwan: an updated study. *Occup Environ Med* 2011; **68**: 120-125 [PMID: 20798004 DOI: 10.1136/oem.2010.056978]

109 **Mastrangelo G**, Martines D, Fedeli U. Vinyl chloride and the liver: misrepresentation of epidemiological evidence. *J Hepatol* 2010; **52**: 776-777 [PMID: 20347172 DOI: 10.1016/j.jhep.2010.01.017]

110 **Dragani TA**, Zocchetti C. Occupational exposure to vinyl chloride and risk of hepatocellular carcinoma. *Cancer Causes Control* 2008; **19**: 1193-1200 [PMID: 18560983 DOI: 10.1007/s10552-008-9188-8]

111 **Mastrangelo G**, Fedeli U, Fadda E, Valentini F, Agnesi R, Magarotto G, Marchì T, Buda A, Pinzani M, Martines D. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake. *Environ Health Perspect* 2004; **112**: 1188-1192 [PMID: 15289165]

112 **Malaguarnera M**, Motta M, Vacante M, Malaguarnera G, Caraci F, Nunnari G, Gagliano C, Greco C, Chisari G, Drago F, Bertino G. Silybin-vitamin E-phospholipids complex reduces liver fibrosis in patients with chronic hepatitis C treated with pegylated interferon α and ribavirin. *Am J Transl Res* 2015; **7**: 2510-2518 [PMID: 26807195]

113 **Maroni M**, Mocci F, Visentin S, Preti G, Fanetti AC. Periportal fibrosis and other liver ultrasonography findings in vinyl chloride workers. *Occup Environ Med* 2003; **60**: 60-65 [PMID: 12499459]

114 **Weihrauch M**, Lehnert G, Köckerling F, Wittekind C, Tannapfel A. p53 mutation pattern in hepatocellular carcinoma in workers exposed to vinyl chloride. *Cancer* 2000; **88**: 1030-1036 [PMID: 10699891]

115 **Weihrauch M**, Benicke M, Lehnert G, Wittekind C, Wrbitzky R, Tannapfel A. Frequent k- ras -2 mutations and p16(INK4A)methylation in hepatocellular carcinomas in workers exposed to vinyl chloride. *Br J Cancer* 2001; **84**: 982-989 [PMID: 11286481]

116 **Feron VJ**, Kruysse A, Til HP. One-year time sequence inhalation toxicity study of vinyl chloride in rats. I. Growth, mortality, haematology, clinical chemistry and organ weights. *Toxicology* 1979; **13**: 25-28 [PMID: 516069]

117 **Til HP**, Feron VJ, Immel HR. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem Toxicol* 1991; **29**: 713-718 [PMID: 1959825]

118 **Ward E**, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, De Santis M, Engholm G, Hagmar L, Langard S, Lundberg I, McElvenny D, Pirastu R, Sali D, Simonato L. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. *Epidemiology* 2001; **12**: 710-718 [PMID: 11679801]

119 **Wong RH**, Chen PC, Du CL, Wang JD, Cheng TJ. An increased standardised mortality ratio for liver cancer among polyvinyl chloride workers in Taiwan. *Occup Environ Med* 2002; **59**: 405-409 [PMID: 12040117]

120 **Gennaro V**, Ceppi M, Crosignani P, Montanaro F. Reanalysis of updated mortality among vinyl and polyvinyl chloride workers: Confirmation of historical evidence and new findings. *BMC Public Health* 2008; **8**: 21 [PMID: 18211695 DOI: 10.1186/1471-2458-8-21]

121 **Bebarta V**, DeWitt C. Miscellaneous hydrocarbon solvents. *Clin Occup Environ Med* 2004; **4**: 455-479, vi [PMID: 15325316]

122 **Malaguarnera G**, Cataudella E, Giordano M, Nunnari G, Chisari G, Malaguarnera M. Toxic hepatitis in occupational exposure to solvents. *World J Gastroenterol* 2012; **18**: 2756-2766 [PMID: 22719183 DOI: 10.3748/wjg.v18.i22.2756]

123 **Chen R**, Seaton A. A meta-analysis of painting exposure and cancer mortality. *Cancer Detect Prev* 1998; **22**: 533-539 [PMID: 9824376]

124 **Porru S**, Placidi D, Carta A, Gelatti U, Ribero ML, Tagger A, Boffetta P, Donato F. Primary liver cancer and occupation in men: a case-control study in a high-incidence area in Northern Italy. *Int J Cancer* 2001; **94**: 878-883 [PMID: 11745492]

125 **International Agency for Research on Cancer (IARC)**. Dry cleaning, some chlorinated solvents and other industrial chemicals. Lyon, France, 7-14 February 1995. *IARC Monogr Eval Carcinog Risks Hum* 1995; **63**: 33-477 [PMID: 9139128]

126 **Alexander DD**, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart M. A meta-analysis of occupational trichloroethylene exposure and liver cancer. *Int Arch Occup Environ Health* 2007; **81**: 127-143 [PMID: 17492303]

127 **Environmental Protection Agency (EPA)**. Trichloroethylene Toxicological Review and Appendices. Office of Pesticide Programs and Toxic Substances, 2011

128 **Bradford BU**, Lock EF, Kosyk O, Kim S, Uehara T, Harbourt D, DeSimone M, Threadgill DW, Tryndyak V, Pogribny IP, Bleyle L, Koop DR, Rusyn I. Interstrain differences in the liver effects of trichloroethylene in a multistrain panel of inbred mice. *Toxicol Sci* 2011; **120**: 206-217 [PMID: 21135412 DOI: 10.1093/toxsci/kfq362]

129 **International Agency for Research on Cancer (IARC)**. Trichloroethylene, tetrachloroethylene, and some other chlorinated agents. *IARC Monogr Eval Carcinog Risks Hum* 2014; **106**: 1-512 [PMID: 26214861]

130 **Hansen J**, Sallmén M, Seldén AI, Anttila A, Pukkala E, Andersson K, Bryngelsson IL, Raaschou-Nielsen O, Olsen JH, McLaughlin JK. Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies. *J Natl Cancer Inst* 2013; **105**: 869-877 [PMID: 23723420 DOI: 10.1093/jnci/djt107]

131 **Rusyn I**, Chiu WA, Lash LH, Kromhout H, Hansen J, Guyton KZ. Trichloroethylene: Mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. *Pharmacol Ther* 2014; **141**: 55-68 [PMID: 23973663 DOI: 10.1016/j.pharmthera.2013.08.004]

132 **Pogribny IP**, Rusyn I. Role of epigenetic aberrations in the development and progression of human hepatocellular carcinoma. *Cancer Lett* 2014; **342**: 223-230 [PMID: 22306342 DOI: 10.1016/j.canlet.2012.01.038]

133 **Chiu WA**, Ginsberg GL. Development and evaluation of a harmonized physiologically based pharmacokinetic (PBPK) model for perchloroethylene toxicokinetics in mice, rats, and humans. *Toxicol Appl Pharmacol* 2011; **253**: 203-234 [PMID: 21466818 DOI: 10.1016/j.taap.2011.03.020]

134 **Jiang Y**, Chen J, Tong J, Chen T. Trichloroethylene-induced gene expression and DNA methylation changes in B6C3F1 mouse liver. *PLoS One* 2014; **9**: e116179 [PMID: 25549359 DOI: 10.1371/journal.pone.0116179]

135 **Ramdhan DH**, Kamijima M, Wang D, Ito Y, Naito H, Yanagiba Y, Hayashi Y, Tanaka N, Aoyama T, Gonzalez FJ, Nakajima T. Differential response to trichloroethylene-induced hepatosteatosis in wild-type and PPARalpha-humanized mice. *Environ Health Perspect* 2010; **118**: 1557-1563 [PMID: 20709644 DOI: 10.1289/ehp.1001928]

136 **Dunlop MH**, Dray E, Zhao W, San Filippo J, Tsai MS, Leung SG, Schild D, Wiese C, Sung P. Mechanistic insights into RAD51-associated protein 1 (RAD51AP1) action in homologous DNA repair. *J Biol Chem* 2012; **287**: 12343-12347 [PMID: 22375013 DOI: 10.1074/jbc.C112.352161]

137 **Taira N**, Mimoto R, Kurata M, Yamaguchi T, Kitagawa M, Miki Y, Yoshida K. DYRK2 priming phosphorylation of c-Jun and c-Myc modulates cell cycle progression in human cancer cells. *J Clin Invest* 2012; **122**: 859-872 [PMID: 22307329 DOI: 10.1172/JCI60818]

138 **Gold LS**, De Roos AJ, Waters M, Stewart P. Systematic literature review of uses and levels of occupational exposure to tetrachloroethylene. *J Occup Environ Hyg* 2008; **5**: 807-839 [PMID: 18949603 DOI: 10.1080/15459620802510866]

139 **Guyton KZ**, Hogan KA, Scott CS, Cooper GS, Bale AS, Kopylev L, Barone S, Makris SL, Glenn B, Subramaniam RP, Gwinn MR, Dzubow RC, Chiu WA. Human health effects of tetrachloroethylene: key findings and scientific issues. *Environ Health Perspect* 2014; **122**: 325-334 [DOI: 10.1289/ehp.1307359]

140 **Porru S**, Placidi D, Carta A, Alessio L. Prevention of injuries at work: the role of the occupational physician. *Int Arch Occup Environ Health* 2006; **79**: 177-192 [PMID: 16187126]

141 **Centers for Disease Control and Prevention (CDC)**. Workplace safety and health topics. Pesticide illness and injury surveillance. 2013. Available from: URL: http://www.cdc.gov/niosh/topics/pesticides

142 **Costa C**, Rapisarda V, Catania S, Di Nola C, Ledda C, Fenga C. Cytokine patterns in greenhouse workers occupationally exposed to α-cypermethrin: an observational study. *Environ Toxicol Pharmacol* 2013; **36**: 796-800 [PMID: 23958972 DOI: 10.1016/j.etap.2013.07.004]

143 **Freire C**, Koifman RJ, Koifman S. Hematological and hepatic alterations in Brazilian population heavily exposed to organochlorine pesticides. *J Toxicol Environ Health A* 2015; **78**: 534-548 [PMID: 25849770 DOI: 10.1080/15287394.2014.999396]

144 **Gaikwad AS**, Karunamoorthy P, Kondhalkar SJ, Ambikapathy M, Beerappa R. Assessment of hematological, biochemical effects and genotoxicity among pesticide sprayers in grape garden. *J Occup Med Toxicol* 2015; **10**: 11 [PMID: 25759745 DOI: 10.1186/s12995-015-0049-6]

145 **Anwar WA**, Khaled HM, Amra HA, El-Nezami H, Loffredo CA. Changing pattern of hepatocellular carcinoma (HCC) and its risk factors in Egypt: possibilities for prevention. *Mutat Res* 2008; **659**: 176-184 [PMID: 18346933 DOI: 10.1016/j.mrrev.2008.01.005]

146 **Zhang R**, Niu Y, Du H, Cao X, Shi D, Hao Q, Zhou Y. A stable and sensitive testing system for potential carcinogens based on DNA damage-induced gene expression in human HepG2 cell. *Toxicol In Vitro* 2009; **23**: 158-165 [PMID: 19013231 DOI: 10.1016/j.tiv.2008.10.006]

147 **Rojanapo W**, Kupradinun P, Tepsuwan A, Tanyakaset M. Effect of varying the onset of exposure to DDT on its modulation of AFB1-induced hepatocarcinogenesis in the rat. *Carcinogenesis* 1993; **14**: 663-667 [PMID: 8097137]

148 **International Agency for Research on Cancer (IARC)**. Occupational exposures in insecticide application, and some pesticides. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 16-23 October 1990. *IARC Monogr Eval Carcinog Risks Hum* 1991; **53**: 5-586 [PMID: 1688189]

149 **National Toxicology Program (NTP)**. Report on Carcinogens. 12th ed: Research Triangle Park North Carolina: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program; 2011. Available from: URL: http://www.academia.edu/3788147/12th\_Report\_on\_Carcinogens

150 **van den Berg H**. Global status of DDT and its alternatives for use in vector control to prevent disease. *Cien Saude Colet* 2011; **16**: 575-590 [PMID: 21340333]

151 **van den Berg H**, Takken W. A framework for decision-making in integrated vector management to prevent disease. *Trop Med Int Health* 2007; **12**: 1230-1238 [PMID: 17956506]

152 **Persson EC**, Graubard BI, Evans AA, London WT, Weber JP, LeBlanc A, Chen G, Lin W, McGlynn KA. Dichlorodiphenyltrichloroethane and risk of hepatocellular carcinoma. *Int J Cancer* 2012; **131**: 2078-2084 [PMID: 22290210 DOI: 10.1002/ijc.27459]

153 **Zhao B**, Shen H, Liu F, Liu S, Niu J, Guo F, Sun X. Exposure to organochlorine pesticides is an independent risk factor of hepatocellular carcinoma: a case-control study. *J Expo Sci Environ Epidemiol* 2012; **22**: 541-548 [PMID: 21915153 DOI: 10.1038/jes.2011.29]

154 **Cocco P**, Kazerouni N, Zahm SH. Cancer mortality and environmental exposure to DDE in the United States. *Environ Health Perspect* 2000; **108**: 1-4 [PMID: 10620518]

155 **Zhao B**, Shen H, Liu F, Liu S, Niu J, Guo F, Sun X. Exposure to organochlorine pesticides is independent risk factor of hepatocellular carcinoma: a case--control study. *J Expo Sci Environ Epidemiol* 2011; **21**: 601-608 [PMID: 21750577 DOI: 10.1038/jes.2011.24]

156 **Cocco P**, Fadda D, Billai B, D'Atri M, Melis M, Blair A. Cancer mortality among men occupationally exposed to dichlorodiphenyltrichloroethane. *Cancer Res* 2005; **65**: 9588-9594 [PMID: 16230425]

157 **Chaturvedi NK**, Kumar S, Negi S, Tyagi RK. Endocrine disruptors provoke differential modulatory responses on androgen receptor and pregnane and xenobiotic receptor: potential implications in metabolic disorders. *Mol Cell Biochem* 2010; **345**: 291-308 [PMID: 20830510 DOI: 10.1007/s11010-010-0583-6]

158 **Angsubhakorn S**, Pradermwong A, Phanwichien K, Nguansangiam S. Promotion of aflatoxin B1-induced hepatocarcinogenesis by dichlorodiphenyl trichloroethane (DDT). *Southeast Asian J Trop Med Public Health* 2002; **33**: 613-623 [PMID: 12693600]

159 **National Toxicology Program (NTP)**. N-Nitrosamines (15 listings): N-Methyl-N'-Nitro-N-Nitrosoguanidine. *Rep Carcinog* 2011; **12**: 302-303 [PMID: 21860503]

160 **International Agency for Research on Cancer (IARC)**. Some inorganic substances, chlorinated hydrocarbons, aromatic Amines, N-Nitroso Compounds and natural products. IARC Monogr Vol. 1. Lyon: France, 1972

161 IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some N-nitroso compounds. *IARC Monogr Eval Carcinog Risk Chem Man* 1978; **17**: 1-349 [PMID: 150392]

162 **Gentry PR**, House-Knight T, Harris A, Greene T, Campleman S. Potential occupational risk of amines in carbon capture for power generation. *Int Arch Occup Environ Health* 2014; **87**: 591-606 [PMID: 23999744 DOI: 10.1007/s00420-013-0900-y]

163 **Andreotti G**, Silverman DT. Occupational risk factors and pancreatic cancer: a review of recent findings. *Mol Carcinog* 2012; **51**: 98-108 [PMID: 22162234 DOI: 10.1002/mc.20779]

164 **de Vocht F**, Sobala W, Wilczynska U, Kromhout H, Szeszenia-Dabrowska N, Peplonska B. Cancer mortality and occupational exposure to aromatic amines and inhalable aerosols in rubber tire manufacturing in Poland. *Cancer Epidemiol* 2009; **33**: 94-102 [PMID: 19679054 DOI: 10.1016/j.canep.2009.06.013]

165 **Bolognesi C**, Moretto A. Genotoxic risk in rubber manufacturing industry: a systematic review. *Toxicol Lett* 2014; **230**: 345-355 [PMID: 24275385 DOI: 10.1016/j.toxlet.2013.11.013]

166 **Li H**, Jönsson BA, Lindh CH, Albin M, Broberg K. N-nitrosamines are associated with shorter telomere length. *Scand J Work Environ Health* 2011; **37**: 316-324 [PMID: 21321788 DOI: 10.5271/sjweh.3150]

167 **Zhang X**, Lin S, Funk WE, Hou L. Environmental and occupational exposure to chemicals and telomere length in human studies. *Occup Environ Med* 2013; **70**: 743-749 [PMID: 23775864 DOI: 10.1136/oemed-2012-101350]

168 **Morales L**, Dachs J, González-Gaya B, Hernán G, Abalos M, Abad E. Background concentrations of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in the global oceanic atmosphere. *Environ Sci Technol* 2014; **48**: 10198-10207 [PMID: 25083749 DOI: 10.1021/es5023619]

169 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Polychlorinated Dibenzo-Para-Dioxins and Polychlorinated Dibenzofurans. Lyon, France, 4-11 February 1997. *IARC Monogr Eval Carcinog Risks Hum* 1997; **69**: 1-631 [PMID: 9379504]

170 **Ovando BJ**, Ellison CA, Vezina CM, Olson JR. Toxicogenomic analysis of exposure to TCDD, PCB126 and PCB153: identification of genomic biomarkers of exposure to AhR ligands. *BMC Genomics* 2010; **11**: 583 [PMID: 20959002 DOI: 10.1186/1471-2164-11-583]

171 Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCD and Related Compounds Part III: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. December 2003 NAS Review Draft. Available from: URL: http://www.epa.gov/ncea/pdfs/dioxin/nas-review/pdfs/part3/dioxin\_pt3\_full\_oct2004.pdf

172 **Rivera-Austrui J**, Martinez K, Marco-Almagro L, Abalos M, Abad E. Long-term sampling of dioxin-like substances from a clinker kiln stack using alternative fuels. *Sci Total Environ* 2014; **485-486**: 528-533 [PMID: 24742561 DOI: 10.1016/j.scitotenv.2014.03.021]

173 **Holma-Suutari A**, Ruokojärvi P, Laaksonen S, Kiviranta H, Nieminen M, Viluksela M, Hallikainen A. Persistent organic pollutant levels in semi-domesticated reindeer (Rangifer tarandus tarandus L.), feed, lichen, blood, milk, placenta, foetus and calf. *Sci Total Environ* 2014; **476-477**: 125-135 [PMID: 24463250 DOI: 10.1016/j.scitotenv.2013.12.109]

174 **Sweeney MH**, Mocarelli P. Human health effects after exposure to 2,3,7,8-TCDD. *Food Addit Contam* 2000; **17**: 303-316 [PMID: 10912244]

175 **Vezina CM**, Walker NJ, Olson JR. Subchronic exposure to TCDD, PeCDF, PCB126, and PCB153: effect on hepatic gene expression. *Environ Health Perspect* 2004; **112**: 1636-1644 [PMID: 15598615]

176 **Kulkarni PS**, Crespo JG, Afonso CA. Dioxins sources and current remediation technologies--a review. *Environ Int* 2008; **34**: 139-153 [PMID: 17826831]

177 **National Institute of Occupational Safety and Health (NIOSH)**. National occupational exposure survey. Cincinnati, Ohio: US Department of Health and Human Services, 2015. Available from: URL: http://www.cdc.gov/niosh

178 **National Toxicology Program (NTP)**. Toxicology and carcinogenesis studies of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (Cas No. 57117-31-4) in female Harlan Sprague-Dawley rats (gavage studies). *Natl Toxicol Program Tech Rep Ser* 2006; **525**: 1-198 [PMID: 17160103]

179 **Collins JJ**, Bodner K, Haidar S, Wilken M, Burns CJ, Lamparski LL, Budinsky RA, Martin GD, Carson ML. Chlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyl profiles of workers with trichlorophenol and pentachlorophenol exposures. *Chemosphere* 2008; **73**: S284-S289 [PMID: 18442847 DOI: 10.1016/j.chemosphere.2007.12.034]

180 **Bertino G**, Ardiri A, Demma S, GiuseppeCalvagno S, Toro A, Basile E, Campagna D, Ferraro G, Frazzetto E, Proiti M, Malaguarnera G, Bertino N, Malaguarnera M, Malaguarnera M, Amaradio MD, Pricoco G, Di Carlo I. Rare benign tumors of the liver: still rare? *J Gastrointest Cancer* 2014; **45**: 202-217 [PMID: 24510731 DOI: 10.1007/s12029-014-9580-4]

181 **Malaguarnera G**, Paladina I, Giordano M, Malaguarnera M, Bertino G, Berretta M. Serum markers of intrahepatic cholangiocarcinoma. *Dis Markers* 2013; **34**: 219-228 [PMID: 23396291 DOI: 10.3233/DMA-130964]

182 **Collins JJ**, Bodner KM, Wilken M, Haidar S, Burns CJ, Budinsky RA, Martin GD, Carson ML, Rowlands JC. Serum concentrations of chlorinated dibenzo-p-dioxins and dibenzofurans among former Michigan trichlorophenol and pentachlorophenol workers. *J Expo Sci Environ Epidemiol* 2007; **17**: 541-548 [PMID: 17426737]

183 **Aylward LL**, Bodner KM, Collins JJ, Wilken M, McBride D, Burns CJ, Hays SM, Humphry N. TCDD exposure estimation for workers at a New Zealand 2,4,5-T manufacturing facility based on serum sampling data. *J Expo Sci Environ Epidemiol* 2010; **20**: 417-426 [PMID: 19491942 DOI: 10.1038/jes.2009.31]

184 **Safe S**, Lee SO, Jin UH. Role of the aryl hydrocarbon receptor in carcinogenesis and potential as a drug target. *Toxicol Sci* 2013; **135**: 1-16 [PMID: 23771949 DOI: 10.1093/toxsci/kft128]

185 **Ludewig G**, Robertson LW. Polychlorinated biphenyls (PCBs) as initiating agents in hepatocellular carcinoma. *Cancer Lett* 2013; **334**: 46-55 [PMID: 23211541 DOI: 10.1016/j.canlet.2012.11.041]

186 **Crinnion WJ**. Polychlorinated biphenyls: persistent pollutants with immunological, neurological, and endocrinological consequences. *Altern Med Rev* 2011; **16**: 5-13 [PMID: 21438643]

187 **Holler J**. The emergency response program at the Agency for Toxic Substances and Disease Registry. *J Environ Health* 2013; **76**: 46-47 [PMID: 24288850]

188 **Erickson MD**, Kaley RG. Applications of polychlorinated biphenyls. *Environ Sci Pollut Res Int* 2011; **18**: 135-151 [PMID: 20848233 DOI: 10.1007/s11356-010-0392-1]

189 **Wolff MS**, Schecter A. Use of PCB blood levels to assess potential exposure following an electrical transformer explosion. *J Occup Med* 1992; **34**: 1079-1083 [PMID: 1432297]

190 **Schecter A**, Stanley J, Boggess K, Masuda Y, Mes J, Wolff M, Fürst P, Fürst C, Wilson-Yang K, Chisholm B. Polychlorinated biphenyl levels in the tissues of exposed and nonexposed humans. *Environ Health Perspect* 1994; **102** Suppl 1: 149-158 [PMID: 8187704]

191 **National Toxicology Program (NTP).** NTP technical report on the toxicology and carcinogenesis studies of 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) (CAS No. 35065-27-1) in female Harlan Sprague-Dawley rats (Gavage studies). *Natl Toxicol Program Tech Rep Ser* 2006; **529**: 4-168 [PMID: 16835634]

192 **Hennig B**, Reiterer G, Toborek M, Matveev SV, Daugherty A, Smart E, Robertson LW. Dietary fat interacts with PCBs to induce changes in lipid metabolism in mice deficient in low-density lipoprotein receptor. *Environ Health Perspect* 2005; **113**: 83-87 [PMID: 15626652]

193 **Zani C**, Toninelli G, Filisetti B, Donato F. Polychlorinated biphenyls and cancer: an epidemiological assessment. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2013; **31**: 99-144 [PMID: 23672403 DOI: 10.1080/10590501.2013.782174]

194 **Rayne S**, Forest K. pK(a) values of the monohydroxylated polychlorinated biphenyls (OH-PCBs), polybrominated biphenyls (OH-PBBs), polychlorinated diphenyl ethers (OH-PCDEs), and polybrominated diphenyl ethers (OH-PBDEs). *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2010; **45**: 1322-1346 [PMID: 20658412 DOI: 10.1080/10934529.2010.500885]

195 **Tampal N**, Lehmler HJ, Espandiari P, Malmberg T, Robertson LW. Glucuronidation of hydroxylated polychlorinated biphenyls (PCBs). *Chem Res Toxicol* 2002; **15**: 1259-1266 [PMID: 12387623]

196 **Klaunig JE**, Wang Z, Pu X, Zhou S. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicol Appl Pharmacol* 2011; **254**: 86-99 [PMID: 21296097 DOI: 10.1016/j.taap.2009.11.028]

197 **Ho PW**, Garner CE, Ho JW, Leung KC, Chu AC, Kwok KH, Kung MH, Burka LT, Ramsden DB, Ho SL. Estrogenic phenol and catechol metabolites of PCBs modulate catechol-O-methyltransferase expression via the estrogen receptor: potential contribution to cancer risk. *Curr Drug Metab* 2008; **9**: 304-309 [PMID: 18473748]

198 **Brown JF**, Mayes BA, Silkworth JB, Hamilton SB. Polychlorinated biphenyls modulated tumorigenesis in Sprague Dawley rats: correlation with mixed function oxidase activities and superoxide (O2\* ) formation potentials and implied mode of action. *Toxicol Sci* 2007; **98**: 375-394 [PMID: 17510085]

199 **Marabini L**, Calò R, Fucile S. Genotoxic effects of polychlorinated biphenyls (PCB 153, 138, 101, 118) in a fish cell line (RTG-2). *Toxicol In Vitro* 2011; **25**: 1045-1052 [PMID: 21504788 DOI: 10.1016/j.tiv.2011.04.004]

200 **Senthilkumar PK**, Klingelhutz AJ, Jacobus JA, Lehmler H, Robertson LW, Ludewig G. Airborne polychlorinated biphenyls (PCBs) reduce telomerase activity and shorten telomere length in immortal human skin keratinocytes (HaCat). *Toxicol Lett* 2011; **204**: 64-70 [PMID: 21530622 DOI: 10.1016/j.toxlet.2011.04.012]

201 **Senthilkumar PK**, Robertson LW, Ludewig G. PCB153 reduces telomerase activity and telomere length in immortalized human skin keratinocytes (HaCaT) but not in human foreskin keratinocytes (NFK). *Toxicol Appl Pharmacol* 2012; **259**: 115-123 [PMID: 22210444 DOI: 10.1016/j.taap.2011.12.015]

202 **Espandiari P**, Glauert HP, Lehmler HJ, Lee EY, Srinivasan C, Robertson LW. Polychlorinated biphenyls as initiators in liver carcinogenesis: resistant hepatocyte model. *Toxicol Appl Pharmacol* 2003; **186**: 55-62 [PMID: 12583993]

203 **Bencko V**, Rames J, Ondrusova M, Plesko I, Jurickova L, Trnovec T. Human exposure to polyhalogenated hydrocarbons and incidence of selected malignancies -central European experience. *Neoplasma* 2009; **56**: 353-357 [PMID: 19469657]

204 **Zhao G**, Wang Z, Zhou H, Zhao Q. Burdens of PBBs, PBDEs, and PCBs in tissues of the cancer patients in the e-waste disassembly sites in Zhejiang, China. *Sci Total Environ* 2009; **407**: 4831-4837 [PMID: 19539352 DOI: 10.1016/j.scitotenv.2009.05.031]

205 **Mallin K**, McCann K, D'Aloisio A, Freels S, Piorkowski J, Dimos J, Persky V. Cohort mortality study of capacitor manufacturing workers, 1944-2000. *J Occup Environ Med* 2004; **46**: 565-576 [PMID: 15213519]

206 **Lauby-Secretan B**, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. *Lancet Oncol* 2013; **14**: 287-288 [PMID: 23499544 DOI: 10.1016/S1470-2045(13)70104-9]

207 **International Agency for Research on Cancer (IARC)**. Polychlorinated Biphenyls and Polybrominated Biphenyls. IARC Monogr Vol. 107. Lyon: France, 2014. Available from: URL: http://monographs.iarc.fr/ENG/Monographs/PDFs/

208 **National Toxicology Program (NTP)**. Polybrominated biphenyls. *Rep Carcinog* 2011; **12**: 347-349 [PMID: 21863083]

209 **Hoque A**, Sigurdson AJ, Burau KD, Humphrey HE, Hess KR, Sweeney AM. Cancer among a Michigan cohort exposed to polybrominated biphenyls in 1973. *Epidemiology* 1998; **9**: 373-378 [PMID: 9647899]

210 **International Agency for Research on Cancer (IARC)**. Some chemicals used in plastics and elastomers. IARC Working Group. Lyon, 11-18 June 1985. *IARC Monogr Eval Carcinog Risk Chem Hum* 1986; **39**: 7-378 [PMID: 3465697]

211 **Hanari N**, Kannan K, Miyake Y, Okazawa T, Kodavanti PR, Aldous KM, Yamashita N. Occurrence of polybrominated biphenyls, polybrominated dibenzo-p-dioxins, and polybrominated dibenzofurans as impurities in commercial polybrominated diphenyl ether mixtures. *Environ Sci Technol* 2006; **40**: 4400-4405 [PMID: 16903277]

212 **Sjödin A**, Carlsson H, Thuresson K, Sjölin S, Bergman A, Ostman C. Flame retardants in indoor air at an electronics recycling plant and at other work environments. *Environ Sci Technol* 2001; **35**: 448-454 [PMID: 11351713]

213 **Jira R**, Kopp E, Blaine C, McKusick BC, Röderer G Chloroacetaldehydes. In: Ullmann’s Encyclopedia of Industrial Chemistry, 2007 [DOI: 10.1002/14356007.a06\_527]

214 **Boĭtsov AN**, Rotenberg IuS, Mulenkova VG. [Toxicologic assessment of chloral in the process of its liberation during filling and pouring of foam polyurethanes]. *Gig Tr Prof Zabol* 1970; **14**: 26-29 [PMID: 5433673]

215 **Delinsky AD**, Bruckner JV, Bartlett MG. A review of analytical methods for the determination of trichloroethylene and its major metabolites chloral hydrate, trichloroacetic acid and dichloroacetic acid. *Biomed Chromatogr* 2005; **19**: 617-639 [PMID: 15828053]

216 **International Agency for Research on Cancer (IARC)**. Some chemicals present in industrial and consumer products, food and drinking-water. *IARC Monogr Eval Carcinog Risks Hum* 2013; **101**: 9-549 [PMID: 24772663]

217 **Leakey JE**, Seng JE, Latendresse JR, Hussain N, Allen LJ, Allaben WT. Dietary controlled carcinogenicity study of chloral hydrate in male B6C3F1 mice. *Toxicol Appl Pharmacol* 2003; **193**: 266-280 [PMID: 14644627]

218 **National Toxicology Program (NTP)**. Toxicology and carcinogenesis study of chloral hydrate (ad libitum and dietary controlled) (CAS no. 302-17-0) in male B6C3F1 mice (gavage study). *Natl Toxicol Program Tech Rep Ser* 2002; **503**: 1-218 [PMID: 12533745]

219 **Merdink JL**, Robison LM, Stevens DK, Hu M, Parker JC, Bull RJ. Kinetics of chloral hydrate and its metabolites in male human volunteers. *Toxicology* 2008; **245**: 130-140 [PMID: 18243465 DOI: 10.1016/j.tox.2007.12.018]

220 **International Agency for Research on Cancer (IARC)**. Some aromatic amines, organic dyes, and related exposures. *IARC Monogr Eval Carcinog Risks Hum* 2010; **99**: 1-658 [PMID: 21528837]

221 **National Toxicology Program (NTP)**. o-Toluidine and o-toluidine hydrochloride. *Rep Carcinog* 2004; **11**: III258-III259 [PMID: 21089974]

222 **Kauppinen T**, Pukkala E, Saalo A, Sasco AJ. Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. *Am J Ind Med* 2003; **44**: 343-350 [PMID: 14502761]

223 **Akyüz M**, Ata S. Determination of aromatic amines in hair dye and henna samples by ion-pair extraction and gas chromatography-mass spectrometry. *J Pharm Biomed Anal* 2008; **47**: 68-80 [PMID: 18280687 DOI: 10.1016/j.jpba.2007.12.011]

224 **Johansson GM**, Jönsson BA, Axmon A, Lindh CH, Lind ML, Gustavsson M, Broberg K, Boman A, Meding B, Lidén C, Albin M. Exposure of hairdressers to ortho- and meta-toluidine in hair dyes. *Occup Environ Med* 2015; **72**: 57-63 [PMID: 24912758 DOI: 10.1136/oemed-2013-101960]

225 **Condorelli DF**, Kaczmarek L, Nicoletti F, Arcidiacono A, Dell'Albani P, Ingrao F, Magrì G, Malaguarnera L, Avola R, Messina A. Induction of protooncogene fos by extracellular signals in primary glial cell cultures. *J Neurosci Res* 1989; **23**: 234-239 [PMID: 2547086]

226 **Riedel K**, Scherer G, Engl J, Hagedorn HW, Tricker AR. Determination of three carcinogenic aromatic amines in urine of smokers and nonsmokers. *J Anal Toxicol* 2006; **30**: 187-195 [PMID: 16803653]

227 **Sorahan T**, Hamilton L, Jackson JR. A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-beta-naphthylamine and o-toluidine. *Occup Environ Med* 2000; **57**: 106-115 [PMID: 10711278]

228 **Sorahan T**. Bladder cancer risks in workers manufacturing chemicals for the rubber industry. *Occup Med* (Lond) 2008; **58**: 496-501 [PMID: 18725381 DOI: 10.1093/occmed/kqn104]

229 **National Toxicology Program (NTP)**. Bioassay of o-toluidine hydrochloride for possible carcinogenicity. *Natl Cancer Inst Carcinog Tech Rep Ser* 1979; **153**: 1-147 [PMID: 12799709]

230 **National Toxicology Program (NTP)**. NTP 11th Report on Carcinogens. *Rep Carcinog* 2004; **11**: 1-A32 [PMID: 19826456]

231 **Venitt S**, Searle CE. Mutagenicity and possible carcinogenicity of hair colourants and constituents. *IARC Sci Publ* 1976; **(13)**: 263-271 [PMID: 793979]

232 **International Agency for Research on Cancer (IARC)**. Occupational exposures of hairdressers and barbers and personal use of hair colourants. *IARC Monogr Eval Carcinog Risks Hum* 1993; **57**: 43-118 [PMID: 8207865]

233 **Butler MA**, Guengerich FP, Kadlubar FF. Metabolic oxidation of the carcinogens 4-aminobiphenyl and 4,4'-methylene-bis(2-chloroaniline) by human hepatic microsomes and by purified rat hepatic cytochrome P-450 monooxygenases. *Cancer Res* 1989; **49**: 25-31 [PMID: 2908851]

234 **Zhang YJ**. Interactions of chemical carcinogens and genetic variation in hepatocellular carcinoma. *World J Hepatol* 2010; **2**: 94-102 [PMID: 21160980 DOI: 10.4254/wjh.v2.i3.94]

235 **Beyerbach A**, Rothman N, Bhatnagar VK, Kashyap R, Sabbioni G. Hemoglobin adducts in workers exposed to benzidine and azo dyes. *Carcinogenesis* 2006; **27**: 1600-1606 [PMID: 16497705]

236 **Collins JJ**, Strauss ME, Levinskas GJ, Conner PR. The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a trichlorophenol process accident. *Epidemiology* 1993; **4**: 7-13 [PMID: 8420584]

237 **Collins JJ**, Strauss ME, Riordan SG. Mortalities of workers at the Nitro plant with exposure to 2-mercaptobenzothialzole. *Occup Environ Med* 1999; **56**: 667-671 [PMID: 10658544]

238 **Melick WF**, Naryka JJ, Kelly RE. Bladder cancer due to exposure to para-aminobiphenyl: a 17-year followup. *J Urol* 1971; **106**: 220-226 [PMID: 5099312]

239 **Parsons BL**, Beland FA, Von Tungeln LS, Delongchamp RR, Fu PP, Heflich RH. Levels of 4-aminobiphenyl-induced somatic H-ras mutation in mouse liver DNA correlate with potential for liver tumor development. *Mol Carcinog* 2005; **42**: 193-201 [PMID: 15761837]

240 **Lee HW**, Wang HT, Weng MW, Hu Y, Chen WS, Chou D, Liu Y, Donin N, Huang WC, Lepor H, Wu XR, Wang H, Beland FA, Tang MS. Acrolein- and 4-Aminobiphenyl-DNA adducts in human bladder mucosa and tumor tissue and their mutagenicity in human urothelial cells. *Oncotarget* 2014; **5**: 3526-3540 [PMID: 24939871]

241 **Huan LC**, Wu JC, Chiou BH, Chen CH, Ma N, Chang CY, Tsen YK, Chen SC. MicroRNA regulation of DNA repair gene expression in 4-aminobiphenyl-treated HepG2 cells. *Toxicology* 2014; **322**: 69-77 [PMID: 24857880 DOI: 10.1016/j.tox.2014.05.003]

242 **Tao L**, Day BW, Hu B, Xiang YB, Wang R, Stern MC, Gago-Dominguez M, Cortessis VK, Conti DV, Van Den Berg D, Pike MC, Gao YT, Yu MC, Yuan JM. Elevated 4-aminobiphenyl and 2,6-dimethylaniline hemoglobin adducts and increased risk of bladder cancer among lifelong nonsmokers--The Shanghai Bladder Cancer Study. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 937-945 [PMID: 23539508 DOI: 10.1158/1055-9965.EPI-12-1447]

243 **Wang S**, Sugamori KS, Brenneman D, Hsu I, Calce A, Grant DM. Influence of arylamine N-acetyltransferase, sex, and age on 4-aminobiphenyl-induced in vivo mutant frequencies and spectra in mouse liver. *Environ Mol Mutagen* 2012; **53**: 350-357 [PMID: 22508569 DOI: 10.1002/em.21695]

244 **Nauwelaers G**, Bessette EE, Gu D, Tang Y, Rageul J, Fessard V, Yuan JM, Yu MC, Langouët S, Turesky RJ. DNA adduct formation of 4-aminobiphenyl and heterocyclic aromatic amines in human hepatocytes. *Chem Res Toxicol* 2011; **24**: 913-925 [PMID: 21456541 DOI: 10.1021/tx200091y]

245 **NIOSH**. Special Occupational Hazard Review for Benzidine-Based Dyes. NIOSH Criteria Documents. DHHS (NIOSH) Publication No. 80–109. U.S. Department of Health, Education and Welfare, Public Health Services, Center for Disease Control, 1980: 60. Available from: URL: http://www.ncbi.nlm.nih.gov/books/NBK304402/

246 **Ahlström LH**, Sparr Eskilsson C, Björklund E. Determination of banned azo dyes in consumer goods. *Trends in Analytical Chemistry* 2005; **24**: 49-56 [DOI: 10.1016/j.trac.2004.09.004]

247 **International Agency for Research on Cancer (IARC)**. Some industrial chemicals and dyestuffs. *IARC Monogr Eval Carcinog Risk Chem Hum* 1982; **29**: 1-398 [PMID: 6957379]

248 **Garrigós MC**, Reche F, Marín ML, Jiménez A. Determination of aromatic amines formed from azo colorants in toy products. *J Chromatogr A* 2002; **976**: 309-317 [PMID: 12462623]

249 **National Toxicology Program**. Dyes metabolized to 3,3'-dimethylbenzidine (3,3'-dimethylbenzidine dye class). *Rep Carcinog* 2011; **12**: 170-171 [PMID: 21852830]

250 **National Toxicology Program**. 3,3'-Dimethylbenzidine and dyes metabolized to 3,3'-dimethylbenzidine: 3,3'-dimethylbenzidine. *Rep Carcinog* 2011; **12**: 168-170 [PMID: 21852829]

251 **National Toxicology Program**. Benzidine and dyes metabolized to benzidine: dyes metabolized to benzidine (benzidine dye class). *Rep Carcinog* 2011; **12**: 64-66 [PMID: 21850110]

252 **National Toxicology Program**. Benzidine and dyes metabolized to benzidine: benzidine. *Rep Carcinog* 2011; **12**: 62-64 [PMID: 21850109]

253 **World Health Organization (WHO)**. Preventing disease through healthy environments exposure to arsenic: a major public health concern, 2010. Available from: URL: http://www.who.int/ipcs/features/10chemicals\_en.pdf

254 **Perlman GD**, Berman L, Leann K, Bing L. Agency for Toxic Substances and Disease Registry Brownfields/ land-reuse site tool. *J Environ Health* 2012; **75**: 30-34 [PMID: 23270111]

255 **Cataudella E**, Malaguarnera G, Gagliano C, Condorelli G, Antic T, Rampello L, Erdogan Ö, Rampello L, Malaguarnera M. Pesticides exposure and the management of acute hepatic injury. *Acta Medica Mediterranea* 2012; **28**: 245

256 **Amadori S**, Fenaux P, Ludwig H, O'dwyer M, Sanz M. Use of arsenic trioxide in haematological malignancies: insight into the clinical development of a novel agent. *Curr Med Res Opin* 2005; **21**: 403-411 [PMID: 15811209]

257 **Frazzetto PM**, Malaguarnera G, Gagliano C, Lucca F, Giordano M, Rampello L, Rampello L, Malaguarnera M. Biohumoral Tests in Chronic Pesticide Exposure. *Acta Medica Mediterranea* 2012; **28**: 237

258 **Xi S**, Zheng Q, Zhang Q, Sun G. Metabolic profile and assessment of occupational arsenic exposure in copper- and steel-smelting workers in China. *Int Arch Occup Environ Health* 2011; **84**: 347-353 [PMID: 21132326 DOI: 10.1007/s00420-010-0574-7]

259 **Liu J**, Waalkes MP. Liver is a target of arsenic carcinogenesis. *Toxicol Sci* 2008; **105**: 24-32 [PMID: 18566022 DOI: 10.1093/toxsci/kfn120]

260 **Thomas DJ**. Molecular processes in cellular arsenic metabolism. *Toxicol Appl Pharmacol* 2007; **222**: 365-373 [PMID: 17397889]

261 **Tchounwou PB**, Patlolla AK, Centeno JA. Carcinogenic and systemic health effects associated with arsenic exposure--a critical review. *Toxicol Pathol* 2003; **31**: 575-588 [PMID: 14585726]

262 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans**. Some drinking-water disinfectants and contaminants, including arsenic. Monographs on chloramine, chloral and chloral hydrate, dichloroacetic acid, trichloroacetic acid and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone. *IARC Monogr Eval Carcinog Risks Hum* 2004; **84**: 269-477 [PMID: 15645578]

263 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans**. Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum* 2012; **100**: 11-465 [PMID: 23189751]

264 **Mazumder DN**. Effect of chronic intake of arsenic-contaminated water on liver. *Toxicol Appl Pharmacol* 2005; **206**: 169-175 [PMID: 15967205]

265 **Chen Y**, Ahsan H. Cancer burden from arsenic in drinking water in Bangladesh. *Am J Public Health* 2004; **94**: 741-744 [PMID: 15117692]

266 **Abernathy CO**, Thomas DJ, Calderon RL. Health effects and risk assessment of arsenic. *J Nutr* 2003; **133**: 1536S-1538S [PMID: 12730460]

267 **Reichard JF**, Schnekenburger M, Puga A. Long term low-dose arsenic exposure induces loss of DNA methylation. *Biochem Biophys Res Commun* 2007; **352**: 188-192 [PMID: 17107663]

268 **Tokar EJ**, Benbrahim-Tallaa L, Ward JM, Lunn R, Sams RL, Waalkes MP. Cancer in experimental animals exposed to arsenic and arsenic compounds. *Crit Rev Toxicol* 2010; **40**: 912-927 [PMID: 20812815 DOI: 10.3109/10408444.2010.506641]

269 **Wanibuchi H**, Salim EI, Kinoshita A, Shen J, Wei M, Morimura K, Yoshida K, Kuroda K, Endo G, Fukushima S. Understanding arsenic carcinogenicity by the use of animal models. *Toxicol Appl Pharmacol* 2004; **198**: 366-376 [PMID: 15276416]

270 **Waalkes MP**, Liu J, Diwan BA. Transplacental arsenic carcinogenesis in mice. *Toxicol Appl Pharmacol* 2007; **222**: 271-280 [PMID: 17306315]

271 **Qu W**, Bortner CD, Sakurai T, Hobson MJ, Waalkes MP. Acquisition of apoptotic resistance in arsenic-induced malignant transformation: role of the JNK signal transduction pathway. *Carcinogenesis* 2002; **23**: 151-159 [PMID: 11756236]

272 **Waalkes MP**, Keefer LK, Diwan BA. Induction of proliferative lesions of the uterus, testes, and liver in swiss mice given repeated injections of sodium arsenate: possible estrogenic mode of action. *Toxicol Appl Pharmacol* 2000; **166**: 24-35 [PMID: 10873715]

273 **Rossman TG**. Mechanism of arsenic carcinogenesis: an integrated approach. *Mutat Res* 2003; **533**: 37-65 [PMID: 14643412]

274 **Waalkes MP**, Ward JM, Diwan BA. Induction of tumors of the liver, lung, ovary and adrenal in adult mice after brief maternal gestational exposure to inorganic arsenic: promotional effects of postnatal phorbol ester exposure on hepatic and pulmonary, but not dermal cancers. *Carcinogenesis* 2004; **25**: 133-141 [PMID: 14514661]

275 NTP 12th Report on Carcinogens. *Rep Carcinog* 2011; **12**: iii-499 [PMID: 21822324]

276 **Mannino DM**, Holguin F, Greves HM, Savage-Brown A, Stock AL, Jones RL. Urinary cadmium levels predict lower lung function in current and former smokers: data from the Third National Health and Nutrition Examination Survey. *Thorax* 2004; **59**: 194-198 [PMID: 14985551]

277 **Huff J**, Cirvello J, Haseman J, Bucher J. Chemicals associated with site-specific neoplasia in 1394 long-term carcinogenesis experiments in laboratory rodents. *Environ Health Perspect* 1991; **93**: 247-270 [PMID: 1773796]

278 **Malaguarnera M**, Drago F, Malaguarnera G, Li Volti G, Salomone S, Caraci F, Galvano F, Vacante M, Bucolo C, Malaguarnera M. Metal fume fever. *Lancet* 2013; **381**: 2298 [PMID: 23809563 DOI: 10.1016/S0140-6736(13)60689-3]

279 **Satarug S**, Garrett SH, Sens MA, Sens DA. Cadmium, environmental exposure, and health outcomes. *Environ Health Perspect* 2010; **118**: 182-190 [PMID: 20123617 DOI: 10.1289/ehp.0901234]

280 **Satarug S**. Long-term exposure to cadmium in food and cigarette smoke, liver effects and hepatocellular carcinoma. *Curr Drug Metab* 2012; **13**: 257-271 [PMID: 22455552]

281 **Rani A**, Kumar A, Lal A, Pant M. Cellular mechanisms of cadmium-induced toxicity: a review. *Int J Environ Health Res* 2014; **24**: 378-399 [PMID: 24117228 DOI: 10.1080/09603123.2013.835032]

282 **Alessandria I**, Pennisi M, Cataudella E, Frazzetto P.M., Malaguarnera M, Rampello L, Rampello L. Neurotoxicity in cadmium-exposed workers. *Acta medica mediterranea* 2012; **28**: 253

283 **Liu F**, Li H, Chang H, Wang J, Lu J. Identification of hepatocellular carcinoma-associated hub genes and pathways by integrated microarray analysis. *Tumori* 2015; **101**: 206-214 [PMID: 25768320 DOI: 10.5301/tj.5000241]

284 **Hassan MM**, Spitz MR, Thomas MB, El-Deeb AS, Glover KY, Nguyen NT, Chan W, Kaseb A, Curley SA, Vauthey JN, Ellis LM, Abdalla E, Lozano RD, Patt YZ, Brown TD, Abbruzzese JL, Li D. Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer* 2008; **123**: 1883-1891 [PMID: 18688864 DOI: 10.1002/ijc.23730]

285 **Polosa R**, Russo C, Caponnetto P, Bertino G, Sarvà M, Antic T, Mancuso S, Al-Delaimy WK. Greater severity of new onset asthma in allergic subjects who smoke: a 10-year longitudinal study. *Respir Res* 2011; **12**: 16 [PMID: 21261960 DOI: 10.1186/1465-9921-12-16]

286 **Takiguchi M**, Achanzar WE, Qu W, Li G, Waalkes MP. Effects of cadmium on DNA-(Cytosine-5) methyltransferase activity and DNA methylation status during cadmium-induced cellular transformation. *Exp Cell Res* 2003; **286**: 355-365 [PMID: 12749863]

287 **Sabolić I**, Breljak D, Skarica M, Herak-Kramberger CM. Role of metallothionein in cadmium traffic and toxicity in kidneys and other mammalian organs. *Biometals* 2010; **23**: 897-926 [PMID: 20549307 DOI: 10.1007/s10534-010-9351-z]

288 **Naugler WE**, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, Karin M. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007; **317**: 121-124 [PMID: 17615358]

289 **Tellez-Plaza M**, Navas-Acien A, Crainiceanu CM, Sharrett AR, Guallar E. Cadmium and peripheral arterial disease: gender differences in the 1999-2004 US National Health and Nutrition Examination Survey. *Am J Epidemiol* 2010; **172**: 671-681 [PMID: 20693268 DOI: 10.1093/aje/kwq172]

290 **Gallagher CM**, Meliker JR. Blood and urine cadmium, blood pressure, and hypertension: a systematic review and meta-analysis. *Environ Health Perspect* 2010; **118**: 1676-1684 [PMID: 20716508 DOI: 10.1289/ehp.1002077]

291 **Rapisarda V**, Valentino M, Bolognini S, Fenga C. [Noise-related occupational risk aboard fishing vessels: considerations on prevention and the protection of exposed workers]. *G Ital Med Lav Ergon* 2004; **26**: 191-196 [PMID: 15551949]

292 **Rapisarda V**, Ledda C, Castaing M, Proietti L, Ferrante M. [Potential exposure to carcinogens in low-melting alloys processing]. *G Ital Med Lav Ergon* 2013; **35**: 73-76 [PMID: 23914599]

293 **Rapisarda V**, Valentino M, Ravalli P, Fenga C, Duscio D. [Occupational brucellosis in slaughtering of sheep and goats: study of five cases from a municipal abattoir in south-eastern Sicily]. *Med Lav* 2005; **96**: 134-141 [PMID: 16001513]

294 **Valentino M**, Rapisarda V, Scalise L, Paone N, Santarelli L, Fenga C, Rossi GL. A new method for the experimental assessment of finger haemodynamic effects induced by a hydraulic breaker in operative conditions. *J Occup Health* 2004; **46**: 253-259 [PMID: 15308823]

295 **Rapisarda V**, Bracci M, Nunnari G, Ferrante M, Ledda C. Tetanus immunity in construction workers in Italy. *Occup Med* (Lond) 2014; **64**: 217-219 [PMID: 24706467 DOI: 10.1093/occmed/kqu019]

296 **Valentino M**, Rapisarda V. Tetanus in a central Italian region: scope for more effective prevention among unvaccinated agricultural workers. *Occup Med* (Lond) 2001; **51**: 114-117 [PMID: 11307686]

297 **Malaguarnera G**, Giordano M, Cappellani A, Berretta M, Malaguarnera M, Perrotta RE. Skin cancers in elderly patients. *Anticancer Agents Med Chem* 2013; **13**: 1406-1411 [PMID: 24102278]

298 **Mangia A**, Cenderello G, Orlandini A, Piazzolla V, Picciotto A, Zuin M, Ciancio A, Brancaccio G, Forte P, Carretta V, Zignego AL, Minerva N, Brindicci G, Marignani M, Baroni GS, Bertino G, Cuccorese G, Mottola L, Ripoli M, Pirisi M. Individualized treatment of genotype 1 naïve patients: an Italian multicenter field practice experience. *PLoS One* 2014; **9**: e110284 [PMID: 25340799 DOI: 10.1371/journal.pone.0110284]

299 **Herceg Z**, Lambert MP, van Veldhoven K, Demetriou C, Vineis P, Smith MT, Straif K, Wild CP. Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation. *Carcinogenesis* 2013; **34**: 1955-1967 [PMID: 23749751 DOI: 10.1093/carcin/bgt212]

300 **Malaguarnera G**, Gagliano C, Giordano M, Salomone S, Vacante M, Bucolo C, Caraci F, Reibaldi M, Drago F, Avitabile T, Motta M. Homocysteine serum levels in diabetic patients with non proliferative, proliferative and without retinopathy. *Biomed Res Int* 2014; **2014**: 191497 [PMID: 24877066 DOI: 10.1155/2014/191497]

301 **Cardin R**, Piciocchi M, Bortolami M, Kotsafti A, Barzon L, Lavezzo E, Sinigaglia A, Rodriguez-Castro KI, Rugge M, Farinati F. Oxidative damage in the progression of chronic liver disease to hepatocellular carcinoma: an intricate pathway. *World J Gastroenterol* 2014; **20**: 3078-3086 [PMID: 24696595 DOI: 10.3748/wjg.v20.i12.3078]

302 **Hernandez-Gea V**, Toffanin S, Friedman SL, Llovet JM. Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. *Gastroenterology* 2013; **144**: 512-527 [PMID: 23313965 DOI: 10.1053/j.gastro.2013.01.002]

303 **Lee S**, Kim JS. Mitophagy: therapeutic potentials for liver disease and beyond. *Toxicol Res* 2014; **30**: 243-250 [PMID: 25584143]

304 **Cui J**, Gong Z, Shen HM. The role of autophagy in liver cancer: molecular mechanisms and potential therapeutic targets. *Biochim Biophys Acta* 2013; **1836**: 15-26 [PMID: 23428608 DOI: 10.1016/j.bbcan.2013.02.003]

305 **Czaja MJ**, Ding WX, Donohue TM, Friedman SL, Kim JS, Komatsu M, Lemasters JJ, Lemoine A, Lin JD, Ou JH, Perlmutter DH, Randall G, Ray RB, Tsung A, Yin XM. Functions of autophagy in normal and diseased liver. *Autophagy* 2013; **9**: 1131-1158 [PMID: 23774882 DOI: 10.4161/auto.25063]

306 **Kudchodkar SB**, Levine B. Viruses and autophagy. *Rev Med Virol* 2009; **19**: 359-378 [PMID: 19750559 DOI: 10.1002/rmv.630]

307 **Tang H**, Da L, Mao Y, Li Y, Li D, Xu Z, Li F, Wang Y, Tiollais P, Li T, Zhao M. Hepatitis B virus X protein sensitizes cells to starvation-induced autophagy via up-regulation of beclin 1 expression. *Hepatology* 2009; **49**: 60-71 [PMID: 19065679 DOI: 10.1002/hep.22581]

308 **Dreux M**, Gastaminza P, Wieland SF, Chisari FV. The autophagy machinery is required to initiate hepatitis C virus replication. *Proc Natl Acad Sci U S A* 2009; **106**: 14046-14051 [PMID: 19666601 DOI: 10.1073/pnas.0907344106]

309 **Wang K**. Autophagy and apoptosis in liver injury. *Cell Cycle* 2015; **14**: 1631-1642 [PMID: 25927598 DOI: 10.1080/15384101.2015.1038685]

**P-Reviewer:** Tomizawa M **S-Editor:** Ji FF **L-Editor: E-Editor:**

**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%2C3%2C7%2C8-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.