Non-infective occupational risk factors for hepatocellular carcinoma: A review (Review)

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Abstract. Liver cancer is the second leading worldwide cause of cancer-associated mortalities. Hepatocellular carcinoma, which accounts for the majority of liver tumors, ranks fifth among types of human cancer. Well-established risk factors for liver cancer include the hepatitis B and C viruses, aflatoxins, alcohol consumption, and oral contraceptives. Tobacco smoking, androgenic steroids, and diabetes mellitus are suspected risk factors. Current knowledge regarding non-infective occupational risk factors for liver cancer is inconclusive. The relevance of liver disorders to occupational medicine lies in the fact that the majority of chemicals are metabolized in the liver, and toxic metabolites generated via metabolism are the predominant cause of liver damage. However, their non-specific clinical manifestations that are similar in a number of liver diseases make diagnosis difficult. Furthermore, concomitant conditions, such as viral hepatitis and alcohol or drug abuse, may mask liver disorders that result from occupational hepatotoxic agents and block the demonstration of an occupational cause. The identification of environmental agents that result in human cancer is a long and often difficult process. The purpose of the present review is to summarize current knowledge regarding the association of non-infective occupational risk exposure and HCC, to encourage further research and draw attention to this global occupational public health problem.

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1. Introduction

Liver cancer is the second leading cause of cancer-associated mortality worldwide; in 2012 it was responsible for ~746,000 mortalities (1). Hepatocellular carcinoma (HCC), which accounts for the majority of liver tumors, ranks fifth among human cancers, with ~750,000 new cases arising worldwide each year (2).

The widely variable geographic distribution and occurrence of liver cancer in immigrant populations demonstrate that the predominant factors involved are environmental (3). Liver cancer is most common in less developed countries, as demonstrated by the fact that in 2012 as many as 83% of the estimated 782,000 new cases worldwide occurred in such areas.

Well-established risk factors for liver cancer include hepatitis B virus (HBV), hepatitis C virus (HCV) (4-7),

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aflatoxins (4-7), alcohol consumption (5,6), and oral contraceptives (8). Tobacco smoking, androgenic steroids, and diabetes mellitus are suspected risk factors (5,6).

Current knowledge regarding non-infective occupational risk factors and liver cancer is inconclusive, except for the well-established association between vinyl chloride monomer (VCM) and angiosarcoma of the liver (ASL) (9).

High liver cancer mortality has been reported among heavy construction equipment operators (10), chimney sweepers (11), chemical workers (12), seamen (13) and painters (14). A meta-analysis by Chen and Seaton (15) found a standardized mortality ratio (SMR) of 1.20 [95% confidence interval (CI), 1.04-1.37] for solvent exposure (15). A previous study of biliary duct and liver cancer investigating occupational exposure to methylene chloride in a factory producing cellulose fibers observed an SMR of 0.81 (95% CI, 0.02-4.49) for high exposure and an SMR of 0.75 (95% CI, 0.02-4.20) for low exposure (men only) (16). A census-linkage study conducted in Shanghai, China, found modest excesses among men operating textile machinery [standardized incidence ratio (SIR), 1.64; P<0.01], bleachers, dyers, and textile workers (SIR=1.52; P<0.01) (17). Data from multiple population-based case-control studies suggest an association between occupational exposure and primary liver cancer. In a case-control study from Texas, USA, male textile workers, whose job was not specified, were demonstrated to be at higher risk of liver cancer mortality (18). An international multicenter case-control study indicated an increased HCC risk among female chemical industry workers (19). However, these studies have often failed to identify a single agent responsible for the increased HCC risk.

Investigations into the role of occupational exposure in inducing liver cancer are rare. A number of factors, predominantly including small sample size, inconsistent case definition, and incomplete adjustment for confounders, have precluded drawing firm conclusions. Furthermore, occupation classification has often relied on crude, surrogate, exposure-associated measures based on the industry's characteristics, job or task, and exposure duration (20). The purpose of this review is to summarize current knowledge regarding the association of non-infective occupational risk exposure and HCC, to promote further research and draw attention to this global occupational and public health problem.

2. Methods

Research publications on the incidence and mechanisms of HCC development due to occupational exposure to non-infective risk factors of the past 45 years were searched for in three databases: Medline (www.ncbi.nlm.nih.gov/pubmed), Scopus (www.scopus.com/) and Cumulative Index to Nursing and Allied Health Literature (www.ebscohost.com/nursing/products/cinahl-databases/the-cinahl-database).

The MeSH term Unique ID D006528 was used to identify the pathology with the following entry terms: Carcinomas, hepatocellular; hepatocellular carcinomas; liver cell carcinoma, adult; liver cancer, adult; adult liver cancer; adult liver cancers; cancer, adult liver; cancers, adult liver; liver cancers, adult; liver cell carcinoma; carcinoma, liver cell; carcinomas, liver cell; cell carcinoma, liver; cell carcinomas, liver; liver cell carcinomas; hepatocellular carcinoma; hepatoma; and hepatomas; together with occupational, work and occupational disease. Only published data for humans was considered and studies with imprecise descriptions of exposure or diagnosis were rejected. Toxicological studies, particularly studies of biochemical pathways, were not included.

Languages other than English were not an exclusion criterion. HCC cases not directly linked to occupational or environmental exposure were excluded.

3. Results

A wide range of occupational activities may involve worker exposure to a variety of chemical agents. The liver is the predominant organ involved in metabolism in the toxicokinetics of a xenobiotic (21). However, it is frequently also a target organ, due to the characteristics of its blood supply and its role in numerous metabolic and excretory processes. 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, including VCM, organic solvents, chlorinated pesticides, and arsenic exert adverse effects on the liver (22), some of these are presented in Tables I and II.

Inorganic risk factors

Arsenic (As). As [Chemical Abstracts Service (CAS) no. 7440-38-2] is a naturally occurring element that is widespread in the Earth's crust. In the environment, it combines with oxygen, chlorine, and sulfur to form inorganic As compounds. The primary route of exposure is groundwater contamination with inorganic As (96).

Inorganic As compounds are predominantly used to preserve wood, for example, copper chromated arsenic (CCA) is used to make pressure-treated lumber. Organic As compounds are employed as pesticides, primarily to treat cotton plants (97). The most heavily exposed workers are currently those from industries using As-containing compounds, including carpentry involving CCA pressure-treated lumber and copper or lead smelting (97). As is also used in the pharmaceutical industry, to treat certain types of neoplasms (98), in the glass industry, in the manufacture of alloys, sheep dips, leather preservatives, a number of pigments, antifouling paints and poison baits and, increasingly rarely, in the production of agrochemicals, particularly for use in orchards and vineyards. As compounds are employed in limited quantities in the microelectronics and optical industries (99-102). High air As levels can be found in the working environment, as well as in the general environment around non-ferrous metal smelters, where As trioxide may be formed, and in the vicinity of certain coal-fired power plants, particularly those using low-grade brown coal (96,97).

As is absorbed from the gastrointestinal tract and first reaches the liver, where arsenate is reduced to arsenite (103,104). The liver is rich in glutathione, thus, it is a major site for As detoxification, either with glutathione acting as an antioxidant or by glutathione-arsenic conjugation for cellular efflux and biliary excretion (104,105). The liver is also the major site of As methylation, which is catalyzed by arsenic methyltransferase with S-adenosylmethionine as the substrate (106).

Table I. Metal agents, occupational exposure and IARC classification.

First author, year	CAS no.	Agent	IARC classification	Occupational exposure	Refs.
IARC, 2011; McElvenny, 2014; Bolognesi, , 2014; de Vocht, 2007; Jönsson, 2009; Iavicoli, 2006	7440-38-2	Arsenic	Group 1	Coal-fired power plants; As extraction industry; timber manufacturing; glass industry; pesticides use; lead processing; pharmaceutical industry; leather preservatives; antifouling paints; agrochemicals production; microelectronics and optical industries; non-ferrous metal smelters	(23-28)
Baccarelli, 2002; NIOSH, 2015; Tijet, 2006; Walker, 2005	7440-43-9	Cadmium	Group 1	Ni-Cd battery manufacturing, Cd alloy production; Cd mining; manufacturing of Cd-containing ores and products	(29-32)

IARC, International Agency for Research on Cancer; CAS, Chemical Abstracts Service; NIOSH, National Institute of Occupational Safety and Health.

As is an International Agency for Research on Cancer (IARC) Group 1 carcinogen. Chronic exposure to As is associated with cancer of the skin, lungs, bladder, liver, kidneys, and prostate in humans (107-109). Epidemiological findings, supported by data from case reports and from rodent and cell model systems, indicate that the liver is a target of As carcinogenesis. Epidemiology studies have also demonstrated an association between chronic As exposure and pre-neoplastic lesions, abnormal liver function, hepatomegaly, hepatoportal sclerosis, liver fibrosis, cirrhosis, and ASL (104,110).

It is important to differentiate between exposure to inorganic and organic As, as only inorganic compounds have been associated with cancer (111). Monomethylarsonic acid and dimethylarsinic acid are the active ingredients of certain herbicides and are inorganic As metabolites. On the basis of sufficient evidence of cancer in experimental animals, and as monomethylarsonic acid is extensively metabolized to dimethylarsinic acid, the two compounds are classified as possibly carcinogenic to humans (IARC Group 2B). Organic As is predominantly found in food (for example, seafood), while inorganic As is predominantly present in drinking water (96,97). In the latest IARC monograph, As was considered limited in the induction of liver cancer in experimental animals (108). However, more recent laboratory data from rodents and cell model systems have indicated that the liver is a major target for carcinogenesis from inorganic As (104,111-115).

The exact mode of action (MOA) of As carcinogenicity, including hepatocarcinogenesis, require further elucidation. Various potential mechanisms have been suggested including epigenetic and genetic mechanisms, including oxidative DNA damage (105), alteration of apoptosis (116), increased cell proliferation (117), irregular DNA methylation (118), genome instability (119), and abnormal estrogen signaling (120).

In occupationally exposed subjects, urinary As may be used to assess the level of occupational exposure (101).

Cadmium (Cd). Cd (CAS no. 7440-43-9) is a silver-white, metal or grayish-white powder. It occurs in the environment as isotopes, 8 of which are stable and 2 radioactive. Cd was identified in Germany in 1817 and used as a pigment due to its ability to produce brilliant yellow, orange, and red colors. It subsequently became an important material in the manufacturing of rechargeable nickel-Cd (Ni-Cd) batteries and as a corrosion-protection coating for iron and steel.

Workplace exposure to Cd and Cd compounds predominantly involves exposure to airborne dusts and fumes. It occurs chiefly during mining and work with Cd-containing ores, during manufacture and formulation of Cd-containing products, such as paints and pigments, and during activities, including soldering, welding, painting, metal machining, mechanical plating, and zinc smelting (120). Cd pigment manufacture and formulation, Cd alloy production, Cd production and refining, Ni-Cd battery manufacture, mechanical plating, soldering, zinc smelting and polyvinyl chloride (PVC) compounding are associated with the highest potential exposures (121). Current industrial uses of Cd are in batteries, alloys, coatings (electroplating), solar cells, plastic stabilizers, and pigments. Cd is also used in nuclear reactors as a neutron absorber. Workers involved in landfill operations, and the recycling of electronic parts or of plastics may be exposed to Cd. Compost workers and waste collectors are also potentially exposed to dust that may contain Cd and the incineration of municipal waste is a further source of Cd exposure (120,122). Increased investment in solar power is expected to increase Cd use in the future.

Cd found in food and cigarette smoke accumulates in the liver, kidney, and pancreas. Liver concentrations increase with age, peaking at 40-60 years (123,124). Long-term inhalation or oral exposure typically leads to build-up in the kidneys and the liver, where it has the potential to induce disease (120-125). In workplaces, chronic inhalation and oral exposure results in lung damage, including bronchiolitis and emphysema (120,122,125). In animals, long-term inhalation or oral exposure exerts adverse effects on the kidneys, lungs, bones, liver, immune system, nervous systems and blood (126).

Table II. Chemical and organic agents, occupational exposure and IARC classification.

First author, year	CAS no.	Agent	IARC classification	Occupational exposure	Refs.
Manne, 2014; Lin, 2013; Desai, 2003	75-01-4	VCM	Group 1	Food packaging industry, house framing, plastics, plumbing, cabling, waterproof clothing, medical devices and food	(33,34,51)
DCC, 2007; Levy, 2011 Lopez, 2013	79-01-6	TCE	Group 1	Aircraft/aerospace, electronics and printing industry; metal degreasing; dry cleaning; shoe manufacturing; production of chlorinated chemical compounds; paint stripping	(52-54)
DCC, 2007; Lewis, 2003	127-18-4	PCE	Group 2A	Textile processing; dry cleaning; metal degreasing	(52,55)
Trivers, 1995; Mastrangelo, 2004; Weihrach, 2001	50-29-3	DDT	Group 2B	Farming industry	(56-58)
Ward, 2001; Wong, 2002; Wong, 2003; Gennaro, 2003; Scott, 2006; Gennaro, 2008 Pirastu, 2003	35576-91-1	N-Nitrosamines	Group 1	Plastic, rubber and pharmacological manufacturing; metalworking; components production and use; farming industry; electrical gasoline and lubricant additives, production and use	(59-65)
Manne, 2014; Campos-Outcalt, 1992 IARC, 1986	1746-01-6	TCDD	Group 1	Waste management; paper mill; timber manufacturing; iron and steel manufacturing; electric power industry	(33,66,67)
Manne, 2014; Campos-Outcalt, 1992 Porru, 2001; Zhou, 1998	57117-31-4	PeCDF	Group 1	Cement and metalworking industry; chemical manufacturing	(33,66,68,69)
Manne, 2014, Lynge, 1990 Sano, 2009; Pogribny, 2008 Chiu, 2011; Budke, 2013; Jiang, 2014	1336-36-3	PCB	Group 1[a]	Maintenance/repair technicians of PCB devices; electrical industry, plastic and chemical industry	(33,70-75)
Lynge, 1990; EPA, 2012; CDC, 2013; Costa, 2013 Freire, 2015		PBB	Group 2A	Electronics recycling industry; maintenance/repair technicians of PBB devices	(70,76-79)
Levy, 2011; Cordier, 1993; Anwar, 2008; Soliman, 2010	75-87-6	Chloral	Group 2A	Insecticides and herbicide production; polyurethane foam production and use	(53,80-82)
DCC, 2007; Cordier, 1993	302-17-0	Chloral hydrate	Group 2A	Pharmaceutical producing; water disinfection by chlorination; health care workers; laboratory research	(52,80)
Manne, 2014; Rossi, 1997; Tomatis, 1972; Turusov, 1972; Yang, 2008; van den Berg, 2011	95-53-4	Ortho-toluidine	Group 1	Clinical laboratories; herbicide and pharmaceutical production; rubber industry; dyes production and use	(33,83-87)
Manne, 2014; Rossi, 1977;	101-14-4	MOCA	Group 1	Rubber and polyurethane industry	(33,83,88-90)

Table II. Continued.

First author, year	CAS no.	Agent	IARC classification	Occupational exposure	Refs.
Rogan, 2005; Smith, 2001; WHO, 1979					
Manne, 2014; Rossi, 1977; Figà-Talamanca, 1993; McGlynn, 2006; Zhou, 2011	92-67-1	4-ABP	Group 1	Dyes production; rubber industry	(33,83,91-94)
Cocco, 2000					
Manne, 2014; Ross, 1977; IARC, 1978	92-87-5	Bzd and dyes metabolized to Bzd	Group 1	Dyes production and use; clinical laboratories	(33,83,95)
Manne, 2014; Long, 2013; Hu, 2014; Liu, 2012; Bressac, 1991; Hsu, 1991; Villar, 2012; Kirk, 2005		Aflatoxins	Group 1[a]	Feed industries; food industries; processing of flours	(33,35-41)

[a]Not all of them are to be referred to group 1. IARC, International Agency for Research on Cancer; VCM, vinyl chloride monomer; TCE, trichloroethylene; PCE, tetrachloroethylene; DDT, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)-ethane; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; PCB, polychlorinated biphenyls; PBB, polybrominated biphenyls; MOCA, 4,4'-methylene bis (2-chlorobenzenamine); 4-ABP, 4-aminobiphenyl; Bzd, benzidine; DCC, Dow Chemical Company (Midland, MI, USA); EPA, Environmental Protection Agency; CDC, Center for Disease Control.

Review and evaluation of epidemiological findings and other relevant information on Cd exposures resulted in the IARC conclusion that Cd is carcinogenic to humans (125).

The hepatocarcinogenic potential of Cd has attracted little attention, despite an association between dietary intake, predominantly of plant origin, and HCC mortality being observed two decades ago in a large and comprehensive cross-sectional study conducted in China (127).

A standard two-year bioassay was used to evaluate the carcinogenic potential of Cd in two mouse strains, DBA/2NCr (DBA) and NFS/NCr (128). Cd resulted in liver cancer, sarcoma, lung cancer and testicular cancer in male NFS mice, and lymphoma in male DBA mice; carcinogenicity was demonstrated to vary with dose, animal strain, and route of exposure (124). HCC development was markedly enhanced in male Wistar rats treated with the hepatocarcinogen dimethylnitrosamine and Cd (129). In another previous study, Cd inoculation (dose level, 1.0 μM) led to 10-fold increases in the expression of oncogenes c-myc and c-jun, as well as increases in the DNA-binding activity of transcription factors activator protein-1 and nuclear factor-κB in nude mice. Oncogene overexpression and loss of growth control appeared to be critical in carcinogenicity due to low-level Cd exposure (124), whereas higher exposure enhanced oxidative stress (130). These data have identified proto-oncogene activation via DNA hypomethylation as a novel epigenetic mechanism underlying the development of cancer cells, induced by prolonged exposure to low-level Cd (124). The carcinogenic potential of Cd was studied *in vitro* using the TRL1215 rat liver epithelial cell line (131). Cd concentrations from 0-2.5 μM led TRL1215 cells to undergo malignant transformation following exposure for 10 weeks (131). Cd-exposed TRL1215 cells exhibited phenotypic characteristics of transformed cells, including hyperproliferation, increased invasiveness, and decreased serum dependence. Furthermore, DNA methyltransferase and DNA methylation activity increased, providing, for the first time, suggestive evidence of an epigenetic effect of Cd. Cd has been demonstrated to induce expression of the metal-binding protein metallothionein (MT) in the liver. Liver MT induction results in Cd sequestration, which underpins its long biological half-life (132). Sabolić *et al* (133) have reported that MT binds Cd and enters Kupffer cells. Internalization of protein-bound Cd by these cells may induce release of various pro-inflammatory cytokines, including interleukin-6 (IL-6). IL-6 produced by Kupffer cells has been implicated in HCC development in a mouse model (134).

In a review of Cd carcinogenicity, Huff *et al* (121) demonstrated that Cd-induced biochemical changes may be important in all stages of carcinogenicity, including induction of oxidative stress together with decreased DNA repair, aberrant gene expression and signaling combined with inhibition of DNA methylation, which induces proto-oncogenes, and E-cadherin dysfunction breaks cell adhesion.

A multiplicity of effects on the liver due to long-term Cd exposure, increased cancer mortality in men, and evidence of liver carcinogenicity in mice suggests urgent human case-control studies are required, these should compare individuals with cirrhosis and/or HCC with different Cd body burden, perhaps as indicated by urinary Cd. Currently,

biological monitoring of exposed workers involves determination of Cd level in blood or urine.

Organic risk factors

VCM and PVC. VCM (CAS no. 75-01-4) is an aliphatic hydrocarbon, also known as chloroethene, whose polymerization produces a synthetic resin known as polyvinyl chloride (PVC). VCM is typically a sweet-smelling, colorless gas that is insoluble in water. It is predominantly used to produce PVC (CAS no. 9002-86-2), which is extensively used in the plastics industry and as a raw material in organic synthesis (135,136). PVC is found in a wide range of products, including water pipes, substitutes for painted wood (window frames, sills, flooring), electrical cable insulation, inflatable products, waterproof clothing (coats, skiing equipment, shoes), medical devices and similar products (tubing, catheters, containers), food packaging, dental appliances, and vinyl records. VCM is also extensively used as a coolant in plastic manufacturing and as an intermediate in organic synthesis. PVC is harmless in its polymeric form, thus, workers handling the finished goods are not at risk of exposure. However, the at-risk phase is manual descaling of the autoclaves used for polymerization, where workers may come into contact with the material in its monomeric state (54).

VCM does not occur naturally and is therefore found almost exclusively in factories making PVC. Small quantities of VCM are found in finished plastic products, the highest concentration being contained in vinyl records. It is also found in cigarette smoke at concentrations that depend on the chloride concentration of the tobacco (137). VCM has been produced in the USA for >70 years, ~6.2 million tons were produced in 2001 (9). In 2005, ~35 million tons were produced worldwide (52). Approximately 40,000 workers in Europe and 80,000 in the USA have been potentially exposed to VCM prior to 1997 (137). Prior to the adoption of environmental regulations, exposure levels were as high as 13,000 ppm (138). In developed countries, where strict controls are now in place, current levels of occupational exposure are <1 ppm (139).

Detailed reports of VCM toxicity first appeared in the 1970s. VCM is causally associated with a form of non-cirrhotic portal hypertension associated with sinusoidal endothelial damage and ASL. VCM and PVC production involve the use of various chemicals, a number of which are carcinogenic, such as ethylene dichloride (140). More recently it has been suggested that VCM also results in HCC (9).

VCM is rapidly absorbed following inhalation and is primarily metabolized by the liver (141), resulting in generation of chloro-ethylene oxide. This is a reactive intermediate metabolite detoxified by conjugation with glutathione or via aldehyde dehydrogenase, which can also form mutagenic DNA adducts (142). VCM vapor induces DNA strand breaks, sister chromatid exchanges (SCE), micronucleus (MN) formation, and other chromosomal aberrations. VCM has been demonstrated to be mutagenic in a number of different *in vitro* assays (9).

A wide range of experimental and epidemiological studies have demonstrated the carcinogenicity of VCM in animal models and humans (142), resulting in its classification by the IARC as a Group 1 carcinogen (135,136). There is considerable evidence for the association of occupational VCM exposure and liver cancer (143,144), as well as tumors of the brain (55), lung (145), and hemo-lymphopoietic system (146). VCM results in the development of ASL, but it may also have a toxic impact on the liver, leading to cirrhosis and HCC (57). It has a direct negative effect on the liver (134) in combination with other toxic agents (57,147). In addition, in VCM-exposed workers with HCC, a high prevalence of Kirsten rat sarcoma viral oncogene homolog (KRAS)2 mutations (58) and a characteristic p53 mutation pattern (58) have been identified. In ASL, a distinctive GGC to GAC mutation is observed in the KRAS2 gene at codon 13, or less often at codon 12, where it is also G to A (148,149). The p53 gene mutations that are observed in VCM-induced ASL occur at multiple positions on the p53 gene and do not appear to be characteristic of VCM exposure (56,150). In an *in vivo* study HCC was induced in rats by VCM inhalation or oral feeding (151-155), however, HCC was not induced when exposure was via subcutaneous or intraperitoneal injection (149,156-159). Feron *et al* (160,161) and Til *et al* (159) also described dose-response associations between VCM exposure and HCC development.

An association between VCM exposure and HCC or cirrhosis mortality has also been reported in a cohort of workers at one of the plants that was surveyed in a previous study (141). Wong *et al* (60,61) examined mortality rates in 3,293 PVC factory male workers, and observed an increased SMR for malignant neoplasms of the liver (SMR, 1.78, 95% CI, 1.15-2.62). A meta-analysis of studies of occupational exposure to VCM and its association with cancer mortality (143) also observed that workers were at an increased risk of HCC. Overall, epidemiological and experimental studies have reported sufficient data for an association between exposure to inhaled VCM and HCC (62,63,65,140). Thiodiglycolic acid is the predominant VCM metabolite detected in the urine of occupationally exposed subjects.

Organic solvents (OS). OS are a group of volatile compounds or mixtures that are carbon-based solvents. Common OS include halogenated, cyclic, aromatic or aliphatic hydrocarbons, ketones, amines, esters, alcohols, aldehydes, and ethers. Numerous OS are found as mixtures of chemical compounds (162-165).

OS are used to extract, dissolve, or suspend substances, such as waxes, fats and resins, which are usually water insoluble. Solvents are used in paints, glues, adhesives, degreasing/cleaning agents, coatings and in the production of dyes, textiles, agricultural products polymers, plastics, and pharmaceuticals (162,163). Tens of millions of workers in the USA and Europe are estimated to be exposed to organic solvents (15).

A high risk of mortality from biliary duct and liver cancer has been observed among painters and workers exposed to OS in a meta-analysis of cohort investigations (15,166), even though in numerous studies the solvent-specific risk may not be easily estimated due to concurrent exposure to various xenobiotics (68). However, few studies have addressed the association between exposure to OS and the risk of liver cancer, with the exception of perchloroethylene (PCE) and trichloroethylene (TCE).

TCE (CAS no. 79-01-6) is widely used in dry cleaning and paint stripping, in industrial applications as an OS for metal

degreasing, and in the manufacturing of chlorinated chemical compounds (69). Workers employed in a range of industries, including aircraft/aerospace maintenance or manufacture, shoe manufacturing, electronics, printing, painting, dry cleaning, metal degreasing, and chemical industries are at risk of TCE exposure (167,168). TCE is a common, persistent environmental pollutant that has been detected in over one third of hazardous waste sites and in 10% of groundwater sources (66). Although exposure has been associated with a variety of adverse health effects, it is particularly toxic for the kidneys and the liver (169). Experimental research has documented high risks of liver, lung, kidney, and hematopoietic neoplasms in TCE-exposed animals (67,170). In particular, chronic exposure has been demonstrated to induce renal cell carcinoma and HCC in rats and mice, respectively (171). In 2012, IARC, based on evidence of TCE exposure and kidney cancer, recognized TCE as a definite human carcinogen (Group 1) (172,173). A recent study has also reported a markedly higher rate of liver cancer in TCE-exposed workers compared with non-exposed individuals (174).

The carcinogenic MOA of TCE remains to be elucidated (175). A mutagenic MOA has been suggested for TCE-induced kidney tumors, possibly associated with the genotoxic TCE metabolites that form via glutathione conjugation in the kidney (176). Despite reports of liver carcinogenicity in experimental animals and in human epidemiological studies (171,174,177), the exact underlying molecular mechanism(s) involved in TCE-induced hepatocarcinogenesis require further elucidation. Biotransformation occurs in the liver predominantly via the cytochrome P450 (CYP) enzymes. Its major metabolite is tricarboxylic acid (TCA) (176,177). However, neither TCE nor TCA have been confirmed to be mutagenic (177), thus, a role for non-genotoxic mechanisms in TCE hepatocarcinogenesis has recently been suggested (72).

Non-genotoxic carcinogens induce cancer via a variety of mechanisms, including alteration of cell proliferation and apoptosis, peroxisome proliferation, and epigenetic changes. An altered balance between proliferation and apoptosis is a characteristic of tumorigenesis, and abnormal liver regeneration may be a common mechanism for hepatocarcinogenesis, independent of etiology (73,74). Hyperactivation of peroxisome proliferator activated receptor (PPAR)α has been suggested to contribute to liver cancer development in rodents (176).

Jiang *et al* (75) described the dysregulation of a number of genes involved in PPAR, proliferation, and apoptosis signaling pathways in the liver of mice exposed to 1,000 mg/kg TCE. Notably, liver expression of marker of proliferation Ki67, a cell proliferation-associated nuclear marker, increased in a dose-dependent manner. TCA is a ligand for PPAR, and peroxisome proliferation has been reported in mouse liver following TCE exposure (71,178). Hepatocyte hyperplasia and increased liver-to-body weight ratio have also been frequently described in TCE-exposed mouse liver (71,179).

TCE has been demonstrated to induce mRNA overexpression of three homologous recombination (HR)-associated genes, Rad51, Rad51b, and Rad51ap1, in a dose-dependent manner. HR catalyzed by Rad51 is a key mechanism in the elimination of DNA double-strand breaks, and HR dysfunction results in inappropriate recombination and genomic instability (180). It has recently been reported that TCE exposure may affect the expression of HR-associated genes in mouse liver, which may lead to HR hyperactivity, genome fragility, and tumorigenesis (75).

HCC is currently recognized as a genetic and an epigenetic disease. Mounting experimental evidence indicates that epigenetic regulation of gene expression by DNA methylation, histone modifications and microRNAs are key at all stages of liver carcinogenesis (181).

Jiang *et al* (75) also found that TCE induced marked changes in the expression of genes involved in key signaling pathways, including regulation of DNA methylation, and that it may result in hypo- and hypermethylation in the promoter regions of single-copy genes, contributing to aberrant transcriptional changes. TCE may also induce DNA hypomethylation and mRNA overexpression of c-jun and c-myc, two oncogenes that are critical promoters of cellular proliferation in the mouse liver (182). Dysregulated expression and activation of the two genes is often detected in cancer (183,184).

PCE, also known as tetrachloroethylene (CAS no. 127-18-4), occurs in a number of occupational settings where organic solvents are used, particularly the dry cleaning industry and textile processing, as a chemical intermediate, and for vapor degreasing in metal cleaning operations (185). Exposure in the dry cleaning industry is primarily via inhalation and dermal contact, and is highest during machinery operation (186). A previous study of dry cleaning workers exposed to PCE have indicated there are associations with multiple types of cancer, particularly bladder cancer, non-Hodgkins lymphoma, and multiple myeloma. There is also limited evidence suggesting associations with esophageal, kidney, cervical, and breast cancer (177). An increased risk of liver cancer has been reported among workers and experimental animals exposed to PCE (70,187,188).

Animal studies have demonstrated an increased incidence of liver tumors in mice following PCE inhalation and gavage, and of kidney and mononuclear cell leukemia in rats following inhalation exposure (76,172,189).

PCE has been classified by the US Environmental Protection Agency (EPA) as likely to be carcinogenic to humans by all routes of exposure, based on suggestive evidence from epidemiological studies and on conclusive evidence demonstrated in rats developing mononuclear cell leukemia and mice indicating increased incidence of liver tumors. it has also been designated as probably carcinogenic to humans (Group 2A) in industry dry cleaners by the IARC (167,172).

A previous study (68) conducted on workers in Northern Italy assessed the association between occupation and risk of liver cancer and observed a slightly increased HCC risk in workers exposed to toluene and xylene. Results indicated that occupational exposure exerted a limited effect in liver carcinogenesis and that prolonged exposure to OS, such as toluene and xylene, may increase the risk. The biological indicator of occupational exposure to TCE is urinary trichloroacetic acid.

1,1,1-Trichloro-2,2-bis(p-chlorophenyl)-ethane (DDT) and other pesticides. Investigations into occupational exposure to pesticides have predominantly focused on agriculture, particularly product distributors, mixers and loaders, applicators,

bystanders, and workers re-entering the fields shortly following treatment.

Approximately 500,000 tons of active pesticide ingredients are used annually and >20,000 pesticide products are currently sold in the US (77). According to EPA estimates, 10,000-20,000 physician-diagnosed pesticide poisonings occur each year among the ~2 million agricultural workers in the US (77). Agricultural workers, groundskeepers, pet groomers, fumigators, and a variety of other jobs are at risk of exposure to a multiple products, including fungicides, herbicides, insecticides, rodenticides, and sanitizers. Toxicity depends on the compound family, and is generally greater for the older compounds. In humans, pesticides are responsible for acute poisonings, as well as long-term health effects, including cancer and adverse effects on reproduction (78,79,190).

A number of epidemiological studies have suggested that pesticides may be important in HCC development among workers employed in the farming industry (80-82). Various pesticides, such as chlordane, dieldrin, lindane, heptachlor and pyrethrins (139,191,192) are established as liver carcinogenic in animal models. However, few investigations have addressed the association between exposure to pesticides and the risk of liver cancer, except for DDT (CAS no. 50-29-3) (137,193).

DDT has been implicated in liver damage and hepatocarcinogenesis in animals (83-85,194). Based on animal studies, DDT and its most persistent metabolite, 1,1-dich loro-2,2-bis(p-chlorophenyl)-ethylene (DDE), have been classified by the IARC as possibly carcinogenic to humans (Group 2B) (195), and DDT has been defined as a reasonably anticipated human carcinogen by the US National Toxicology Program (NTP) (196,197).

DDT is an insecticide that was largely used in the past, however, in the 70s, numerous developed countries banned it due to its toxic effects and environmental persistence (196). China banned it in 1983, but production is still permitted; annual production is 4,000-6,000 metric tons, employed to make dicofol (86) and for uses in agriculture and the control of malaria, leishmaniasis and termites in numerous African and Asian countries (87). WHO recommendations and guidelines allow using DDT to control disease vectors until suitable alternatives become available (198). The general population is exposed to DDT primarily via food ingestion, while occupational exposure is predominantly due to inhalation and dermal contact (88,89). Although DDT is preferentially stored in adipose tissue, the majority of DDT-associated compounds in blood are bound to proteins (90). The half-life of DDT in humans is ~7 years, whereas the half-life of DDE is notably longer (193). DDT and DDE induce a wide range of adverse health effects in humans, including reproductive, neurological, carcinogenic, and developmental disorders (88). Like a number of other chlorinated compounds, DDT leads to liver cancer in laboratory animals (83-85,90,194,199,200). A risk of liver cancer has also been described in workers exposed to DDT (91).

Previously, three studies on human patients have addressed the association between DDT and/or DDE and the risk of developing HCC (92,93,193). A notable correlation has been observed between quantity of DDE in adipose tissue and liver cancer mortality (94). The risk of liver cancer was higher among Chinese men with higher DDT blood levels (92). Current epidemiological studies indicate that DDT may be a risk factor for HCC (92). However, data interpretation must be considered as consistency among various studies is rare, particularly with regards to their methodological limitations (88,93,201,202). The association between DDT and HCC may also be associated with the endocrine disruption properties of the compound. DDT exerts estrogenic effects, whereas p,p'-DDE has anti-androgenic effects (193). A previous study of endocrine-disrupting chemicals in male mice demonstrated that DDT had an upregulating effect on a number of genes including CYP3A11, one of the hepatic CYP family members involved in inflammatory responses in the liver (203). DDT and DDE have been demonstrated to affect the immune response (204). It is difficult to interpret the role of serum DDT and DDE levels in HCC development in a population with a high prevalence of chronic HBV infection (193). According to Zhao *et al* (93), HBV infection and DDT exert a synergistic effect, promoting the development of HCC.

DDT promotes aflatoxin B1 (AFB1)-induced hepatocarcinogenesis in rats (205). This effect may be particularly important in areas with high HCC risk, such as China and Africa, where AFB1 has strongly been associated with HCC. AFB1 is a known hepatocarcinogen in certain areas of China, and combined with DDT has been reported to exert a synergistic effect on HCC development (93).

Health surveillance involves biological monitoring of exposed workers by search for specific exposure indicators, in this case serum concentration of DDT (p,p'-DDT) and DDE (p,p'-DDE).

N-Nitrosamines. *N*-Nitrosamines are chemical compounds in which the key feature of *N*-nitroso compounds is the N-N=O structure. R_1 and R_2 groups attached to the amine nitrogen may range from a single hydrogen atom to more complex chemical substituents, including ring structures that incorporate the nitrogen atom (206). *N*-Nitrosamines include: *N*-Methyl-*N*'-nitro-*N*-nitrosoguanidine (CAS no. 70-25-7); *N*-nitrosodi-*n*-butylamine (CAS no. 924-16-3); *N*-nitrosodiethanolamine (CAS no. 1116-54-7); *N*-nitrosodiethylamine (CAS no. 55-18-5); *N*-nitrosodimethylamine (CAS no. 62-75-9); *N*-nitrosodi-*n*-propylamine (CAS no. 621-64-7); *N*-nitroso-*N*-ethylurea (CAS no. 759-73-9); 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (CAS no. 64091-91-4); *N*-nitroso-*N*-methylurea (CAS no. 684-93-5); *N*-nitrosomethylvinylamine (CAS no. 4549-40-0); *N*-nitrosomorpholine (CAS no. 59-89-2); *N*-nitrosonornicotine (CAS no. 16543-55-8); *N*-nitrosopiperidine (CAS no. 100-75-4); *N*-nitrosopyrrolidine (CAS no. 930-55-2); and *N*-nitrososarcosine (CAS no. 13256-22-9).

From 1981 to 1991, the US NTP conducted a number of investigations to characterize and assess the toxicological potential and carcinogenic activity of *N*-nitrosamines in laboratory animals (rats and mice) (206). Experimental results indicated that all *N*-nitrosamines were reasonably anticipated to be human carcinogens on the basis of ample evidence of carcinogenicity from animal studies. In fact, all had the capacity to result in tumors 'in several species of experimental animals, at several different tissue sites, and by several different routes of exposure' (206,207). Tumors were

predominantly observed in the liver, kidneys, respiratory and upper digestive tracts (95,206,208). HCC was induced by all *N*-nitrosamine compounds, however, data extension to other species and quantitative risk analyses for humans require broader investigation.

Human exposure to nitrosamines can result from formation of *N*-nitroso compounds in food during storage, preparation, cooking, or else *in vivo*, usually in the stomach (209). Nitrosamines, or their precursors, are commonly found in agricultural chemicals, detergents, tobacco, rust inhibitors, cutting fluids, plastics, tanned leather goods, solvents, pharmaceuticals, textiles, rubber additives, and cosmetics (201-214). Usually, they form from constituents of the foods or products that are naturally present, such as protein amines; less commonly, they are added to food during production, like nitrates or nitrites added to meat as preservatives.

Nitrosamines are also produced in research laboratories, in rubber and tire manufacturing processes, and they may be found as contaminants in the final rubber product (24). Certain nitrosamines have been observed to be effective for a variety of purposes, including antimicrobial (*N*-nitrosomorpholine) or chemotherapeutic agents (*N*-nitrosodimethylamine and N-nitroso-N-methylurea) in conjunction with other agents; herbicides (*N*-nitrosodimethylamine and N-nitrosodi-n-propylamine); additives to soluble and synthetic metalworking fluids (N-nitrosodiethanolamine); solvents or gasoline and lubricant additives (*N*-nitrosodiethylamine); antioxidants, stabilizers in plastics, fiber industry solvents, and copolymer softeners, and to increase dielectric constants in condensers (95,206,208).

Occupational exposure may occur via inhalation or dermal contact where *N*-nitrosamines are produced or used in manufacturing, or are employed as herbicides, in research, and in clinical testing for use as chemotherapeutics. Healthcare workers may be exposed during therapeutic agent preparation, administration or cleanup (95,206). Occupational exposure to *N*-nitrosodiethylamine has been suggested in laboratory, chemical research, copolymer, and lubricant workers (95,208).

A review of large body of evidence from epidemiological studies of workers employed in the rubber manufacturing industry observed a marked excess cancer risk at a variety of sites (25). The IARC has recently classified occupational exposures in the rubber-manufacturing industry as carcinogenic to humans (Group 1) (24,135). According to exposure assessment studies such workers may be exposed to different airborne carcinogenic and/or genotoxic chemicals, including certain aromatic amines, polycyclic aromatic hydrocarbons, and *N*-nitrosamines, although current data do not support a causal association of particular substances/classes of chemicals or occupations with cancer or genotoxic risk. In environmental surveys of a number of European rubber factories De Vocht *et al* (26) and Jönsson *et al* (27) found average *N*-nitrosamine levels well below current regulatory limits, although exposure has not completely been eliminated and accidental high exposures still occur. High urinary levels of *N*-nitrosamines have been detected in exposed workers (28). Recent studies have reported a strong correlation between *N*-nitrosamine exposure and telomere shortening among workers in the rubber industry. Telomeres are critical to maintain chromosome integrity, and telomere length abnormalities are associated with carcinogenesis (215,216).

Health surveillance envisages biological monitoring of exposed workers via the search for specific exposure markers, in this case urinary N-nitrosamines.

Dioxin-like compounds (DLC). DLC are byproducts of a variety of industrial processes that include polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF), or furans and dioxin-like polychlorinated biphenyls (217).

PCDD are formed inadvertently, sometimes in combination with PCDF, as contaminants during production of chlorophenols and chlorophenoxyherbicides (218). PCDD and PCDF may also be produced in thermal processes, including incineration and metal-processing (135).

PCDD are everywhere in the environment. Occupational exposures to PCDD have occurred since the 1940s following the production and use of chlorophenols and chlorophenoxy herbicides, and higher exposures have sometimes occurred following accidents in these industries (29).

The most toxic and best investigated member of the dibenzo-p-dioxin family of isomers is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (219).

TCDD (CAS no. 1746-01-6) is a Group 1 IARC carcinogen, thus, is classified as carcinogenic to humans (135,218). IARC recently classified 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (CAS no. 57117-31-4) and 3,3',4,4',5-pentachlorobiphenyl (PCB 126; CAS no. 57465-28-8) as carcinogenic to humans (Group 1). There is limited or no evidence of carcinogenicity in experimental animals for numerous other dibenzo-p-dioxins, including PCDD and 2, 7-DCDD (218).

TCDD is a contaminant of materials that include 2,4,5-trichlorophenol (TCP), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2-(2,4,5-trichlorophenoxy) propionic acid (Silvex). Occupational exposure may take place following contact with materials used or from past workplace contamination (135,220).

PCDF are commercially manufactured exclusively for scientific purposes. Their release into the environment is predominantly from combustion. Based on congener-specific profiles, all combustion sources produce 2,3,7,8-substituted PCDD and PCDF, including PeCDF. The latter substance is the major congener emitted from cement kilns burning hazardous waste (~20% of total congener emission). Furthermore, major sources of PeCDF are metal manufacturing, chemical processing [production of chlorophenols, polychlorinated biphenyls (PCB), and vinyl chloride]; and pulp bleaching (218,221,222). PCB mixtures, including PCB 126, were produced for use as dielectric insulating fluids for transformers and capacitors for the electrical industry between 1929 and 1977 (135). Inhalation and dermal contact are the major routes of occupational exposure (220).

The major sources of TCCD environmental contamination are municipal incinerators, production and use of pentachlorophenol as a wood preservative, and use of chlorine for bleaching in pulp and paper mills (223). Additional sources include emissions from iron and steel manufactures, burning of various fuel types (for example, wood, diesel and heating

oil), backyard burning of household waste, electric power generation, and tobacco smoking (223,224). Natural sources include forest fires and volcanoes (225).

TCDD usually persists as a pollutant in TCP in small, variable quantities (0.07-6.2 mg/kg) (226). TCP has chiefly been used to produce phenoxy herbicides 2,4,5-T and Silvex. However, occupational TCDD exposure may occur during TCP production, in the treatment of contaminated sites, from waste materials (such as reclaimed oil), or from cleanup following fires in transformers containing polychlorinated aromatics.

In animal studies, a wide range of exposure concentrations has been demonstrated to induce various systemic effects, such as carcinogenesis, immunological alteration, and teratogenesis. In humans exposed to TCDD-contaminated materials, the compound has been reported to result in chloracne and metabolic disorders (219). The carcinogenic and hepatotoxic effects of TCDD appear to be gender-dependent, as female rats proved to be more susceptible than male rats (223). A two-year cancer bioassay by the US NTP, evaluating the hepatotoxic and carcinogenic properties of TCDD in female rats (32,220,227), indicated that chronic exposure (100 ng/kg/day) for 104 weeks induced a notable increase in the incidence and range of non-neoplastic and neoplastic liver lesions (220,227). Non-neoplastic lesions included hepatocyte hypertrophy, pigmentation, bile duct hyperplasia, oval cell hyperplasia, diffuse fatty changes, necrosis, inflammation, cholangiofibrosis and numerous others. Neoplastic lesions included HCC.

In *in vivo* studies, oral PeCDF administration induced a marked proportional rise of cholangiocarcinoma (CLC) and hepatocellular adenoma (HCA) (32,227), whereas subcutaneous injection increased the number of focal liver damage sites in female rats (228), and the multiplicity of HCC and liver hyperplastic nodules in male rats (229). Oral administration of PCB 126 resulted in a notably higher incidence of HCA and CLC (32,226). The most important epidemiological studies of TCDD carcinogenicity were cohort studies of herbicide producers and users in the US, the Netherlands and Germany, and of the residents of a contaminated area at Seveso, Italy (218,230-233). All found an increased risk for lung cancer, soft tissue sarcoma and non-Hodgkin lymphoma, primarily in the more heavily exposed sub-groups (135,218).

The majority of the effects of TCDD are mediated by aryl hydrocarbon receptor (AhR) (234). In a previous study of AhR knockout mice, acute TCDD toxicity was demonstrated to depend on AhR functionality. This suggests that the hepatotoxic effects of TCDD and similar DLC are mediated by AhR, and that gene expression changes resulting from its activation are likely to be important for toxicity (219). Upon binding to its ligands, cytoplasmic AhR, which is bound to multiple chaperone proteins (235,236), undergoes a conformational change that results in its dissociation from chaperone proteins and ins translocation into the nucleus, where it dimerizes with its partner AhR receptor nuclear translocator (237). Binding of the heterodimer to xenobiotic-responsive elements in target gene promoters results in upregulation of these genes. TCDD is well known to upregulate the genes encoding the enzymes involved in xenobiotic metabolism, such as CYP1A1 (238). However, increasing data indicates that AhR controls the expression of a variety of genes not associated with xenobiotic metabolism (239,233). In human lymphocytes, TCDD, a potent AhR agonist, markedly increased the frequency of SCEs (234). AhR knockdown has resulted in decreased proliferation and/or invasion and migration of liver cancer cell lines. A previous *in vivo* study demonstrated that mice overexpressing constitutively active AhR exhibited more liver cancer, suggesting a pro-oncogenic role for AhR (235).

The receptor-mediated MOA for human TCDD-associated carcinogenesis is suggested to include 2,3,4,7,8-PeCDF and PCB 126 as leading to cancer in humans. The predominant mechanism is promotion of carcinogenesis via activation of cell replication and cellular senescence, and apoptosis alteration via the AhR. These congeners, through activation of an array of metabolic enzymes, increase the risk of oxidative stress as an indirect starter of tumorigenesis, which makes these congeners carcinogenic. Preservation of the AhR and associated signaling pathways across species strongly support this MOA in humans (135).

The health surveillance for TCDD, PeCDF and PCB involves biological monitoring of exposed workers using assessment of blood concentrations of TDCC, PeCDF, and PCB, respectively.

Polychlorinated biphenyls (PCB). PCB (CAS no. 1336-36-3) comprise a class of synthetic chlorinated aromatic hydrocarbons. They generally have a biphenyl molecule with ≥1 or up to 10 chlorine atoms ($C_{12}H_{10-x}Cl_x$). PCB are mixtures of 209 congeners, which differ in the number and position of chlorines on the biphenyl rings (236). However, only 130 have been described in marketable PCB mixtures (237). Due to their chemical stability, PCB are ubiquitous environmental and human contaminants.

PCB were extensively produced in the USA from 1929 to 1977. Their stability, dielectric properties, oxidation resistance, and incombustibility prompted their use in electrical insulation, heat exchange, and lubricating fluids. PCB were also blended with other chemicals, such as plasticizers and fire retardants, and used in a variety of products, including caulks, adhesives, plastics, and carbonless copy paper (137). Production peaked in the 1970s and steadily declined thereafter, as numerous countries worldwide banned their use or restricted production (238,239).

Occupational exposure is predominantly via inhalation and dermal contact. Commercial PCB mixtures vary from colorless to dark brown oils, and from viscous liquids to sticky, resinous semisolids. Although PCB evaporate slowly at room temperature, their volatility markedly increases with minimum rises in temperature. Equipment that contains PCB can overheat and vaporize notable quantities of these compounds, creating an inhalation hazard that can be amplified by poor ventilation (240,241).

As PCB-containing products are no longer manufactured, occupational exposure is no longer relevant except in relation to maintenance or repair of old PCB-containing material, such as old industrial equipment (welding equipment), medical equipment (x-ray machines), household appliances (refrigerators, microwaves and TV sets) (237,242,243), accidents involving such equipment (240,244), waste-site cleanup or disposal activities (242,245), and repair or removal of old construction materials, including plaster, paint, and caulk.

PCBs accumulate in adipose tissue, thus potentially causing long-term effects (137). Animal studies by the US NTP and other investigators have documented that PCB is important in the development of liver disease (226,246-249) and that the liver is their main target organ (137).

In vivo data indicates that PCB induces pre-neoplastic lesions and HCC in a dose-and-time-dependent manner, however, its MOA is unknown (138). A previous study has associated PCB exposure with high levels of human alanine transaminase as well as increased hepatic expression of genes involved in apoptosis, inflammation, and oxidative stress (247).

The 209 PCB congeners greatly vary in their propensity for metabolic attack, the first line of which is mono-oxygenation by members of the CYP superfamily. This can theoretically produce >837 possible monohydroxylated products (250). It has been hypothesized that enzyme hydroxylation may occur via a 'direct insertion' mechanism or via the intermediacy of an arene oxide (251-255). The autoxidation/enzymatic oxidation of a PCB hydroquinone may produce reactive oxygen species (ROS), such as oxygen ions and peroxides (256,257). ROS are considered to be important in PCB-associated genotoxicity (258). A number of higher chlorinated PCB congeners are effective inducers of xenobiotic metabolizing enzymes (259), a change that may alter the metabolism of endogenous or exogenous compounds. For instance, PCB induce CYP in the liver, which may change the metabolism of endogenous estrogen to more dangerous estrogen catechol derivatives (260) or ROS producing estrogen quinones (261). In a previous study, PCB 153, 138, 101, and 118 induced MN in fish cells *in vitro* (262) and PCB-contaminated soil from industrial or irrigation sites induced MN in plant species (263,264). Para-quinone induced MN predominantly by chromosome breaks. However, monohydroxylated products and, to a lesser extent, other metabolites, induced MN largely by chromosome loss, pointing at different genotoxicity mechanisms. The highly reactive quinone may interact with DNA directly, or with DNA maintenance proteins like topoisomerase, leading to chromosome breaks. The other compounds may react with the cytoskeleton or with other proteins involved in chromosome distribution. Numerous PCB congeners and PCB3 p-quinone induce telomere shortening, the former likely by reducing telomerase activity, the latter likely via ROS generation (265-267). Chromosome breaks and rearrangements have been described in human lymphocytes exposed to PCB77 or PCB153 (268,269) In *in vivo* studies in rats (270), lower chlorinated PCB were able to initiate hepatocarcinogenesis.

By contrast, there is little data regarding PCB in human liver disease. Over a 24-year follow-up subsequent to the Yu-Cheng accident (Taiwan), a number of people exposed to cooking oil contaminated with PCB developed cirrhosis and other chronic liver disorders (271,272). Epidemiological investigations reported a higher mortality from HCC in subjects with heavy PCB exposure (273). Previous studies on PCB-exposed workers, including cohorts of electrical capacitor and transformer manufacturing workers, have observed a notable association between doses of PCB exposure and liver cancer mortality; however, the role of PCB in human hepatocarcinogenesis is still debated (274-277).

PCB were earlier classified as IARC Group 2A as probable human carcinogens based on evidence of carcinogenicity in animals and limited evidence from human studies (278). The subsequent classification of PCB 126 as a human carcinogen (135) prompted a reassessment of all PCB in 2013 (236,279). Epidemiological studies associating PCB exposure with melanoma, and animal studies reporting exposure-associated tumors in the lung, liver and oral mucosa, were judged to be sufficient evidence for carcinogenicity in humans and experimental animals, leading to the classification of PCB as IARC Group 1 (279,280). Health surveillance requires biological monitoring of exposed workers by assessment of plasma PCB.

Polybrominated biphenyls (PBB). PBB are a class of biphenyl compounds where one to 10 hydrogen atoms are replaced by bromine. Hexabromobiphenyl ($C_{12}H_4Br_6$, CAS no. 6355-01-8), is the predominant component of the commercial PBB mixtures tested in animal carcinogenicity studies, including FireMaster FF-1 (281). The NTP has characterized and tested the toxic potential and carcinogenic activity of PBB in laboratory rats and mice. PBB have been defined as reasonably anticipated human carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals. Oral exposure to PBB resulted in liver tumors in mice and rats. Administration of FireMaster FF-1 by stomach tube led to HCC in mice and rats of both genders, and CLC in rats of both genders (281).

No epidemiological studies have evaluated the association between human cancer and specific exposure to PBB. The IARC reviewed the available evidence in 1986 and concluded that there were no informative studies. Since then, a case-control study of participants in a PBB exposure registry in Michigan observed a marked exposure level-associated increases, based on serum PBB, in lymphoma and digestive system cancer (282). Other studies, however, are uninformative.

Two PBB isomers, hexaoctabromobiphenyl (CAS no. 61288-13-9), and decabromobiphenyl (CAS no. 13654-09-6), were formally commercially produced. In 2009, decabromobiphenyl was produced in China and Europe and was available on the US market (283). No suppliers for either hexabromobiphenyl or octabromobiphenyl are currently found worldwide (283). PBB have largely been replaced by polybrominateddiphenyl ethers (PBDE) as fire retardants in textiles, electronic equipment, and plastics (284). However, PBB have been detected as impurities in PBDE.

Residues remaining in and around facilities that formerly manufactured, processed, or produced PBB-containing goods are current sources of exposure. Workers at companies that manufactured PBB may have been exposed by skin contact, inhalation or unintentional ingestion.

The conclusions of the IARC meeting on PBB are summarized in a Lancet Oncology report (279). The full report will be issued as volume 107 of the IARC monograph series. There was 'inadequate' epidemiological evidence for PBB carcinogenicity, however, 'sufficient' evidence in experimental animals, as well as data indicating that their toxic effects and carcinogenic potential involve a number of the same pathways as PCB, resulted in their classification as 'probably carcinogenic to humans' (Group 2A) (280).

Health surveillance requires biological monitoring of exposed workers by determination of PPB serum concentration.

Chloral and chloral hydrate. Chloral (CAS no. 75-87-6) is produced by chlorinating acetaldehyde or ethanol in acidic solution (278). It has predominantly been used to produce DDT and other insecticides, namely methoxychlor, naled, trichlorfon, dichlorvos and the herbicide TCA (285). Chloral has also been used to produce rigid polyurethane foam (167,209) and to induce swelling of starch granules at room temperature (286).

Chloral hydrate (CAS no. 302-17-0) has been used since the 1870s as a hypnotic, chiefly for the short-term treatment of insomnia, to alleviate anxiety, and to induce sedation. It is also an ingredient in Hoyer's solution, which is used in microscopy to mount organisms, such as bryophytes, ferns, seeds, and arthropods (172).

Chloral has been detected during spraying and casting of polyurethane foam (287), has been identified as a TCE autoxidation product during vegetable oil extraction, and observed in the output of etching chambers in semiconductor processing (288). Even though chloral is employed as an intermediate in the production of insecticides and herbicides, chloral hydrate is found in swimming pools as part of a mixture of by-products resulting from water disinfection by chlorination. There is no epidemiological evidence of cancer risks associated specifically with these by-products (289).

An *in vivo* study on mice, oral administration of chloral in water induced liver nodules, hyperplastic nodules and HCC after 92 weeks (290). Significant increases in HCC incidence have been observed in treated mice surviving 104 weeks (291,292).

The association between numbers of chloral hydrate prescriptions and overall cancer has been examined in a case-control study, but no notable patterns have been observed (172).

Strong evidence suggests that chloral hydrate is genotoxic in mammals and other species *in vivo* and *in vitro,* inducing mutations, chromosomal aberrations, and MN formation. One study observed a marked increase in MN formation in peripheral blood lymphocytes in infants exposed to oral chloral hydrate (172). Adverse health effects have been reported for the liver, kidney, and central nervous system (CNS), suggesting that these organs are potential targets for the chemical (171).

The MOA remains unknown, however, multiple genotoxicity mechanisms have been hypothesized, such as an increase in cell proliferation, induction of peroxisome proliferation response, and disruption of gap-junction intercellular communication. Evidence for non-genotoxic mechanisms in liver cancer is poor (172). Chloral hydrate is used as sedative for humans and veterinary application. CNS is a target tissue, however, the relevance of neurotoxicity to cancer is unknown (172).

Human adverse effects resulting from chloral hydrate depend on inter-individual variability. The major metabolic enzymes alcohol dehydrogenase and aldehyde dehydrogenase are linked to their common polymorphisms that result in differences in alcohol metabolism. The consumption of alcoholic beverages may also be a susceptibility factor, as the enzymes are also involved in the biotransformation of chloral hydrate. With regards to chloral and chloral hydrate, IARC reported inadequate evidence for the carcinogenicity of humans, but sufficient evidence in animals. The two compounds are likely Group 2A carcinogens.

The biological indicator of occupational exposure to both chemicals is chloral hydrate in the blood and urine.

ortho-Toluidine (o-toluidine). o-Toluidine (CAS no. 95-53-4) is used for the production of herbicides, such as metolachlor and acetochlor, dyes and pigments, including azo pigment dyes, triarylmethane dyes, sulfur dyes, and indigo compounds, and for synthesis of rubber, pharmaceuticals and other chemicals (135). In diagnostic laboratories it is used as reagent for glucose analysis and for tissue staining (293,294).

Occupational exposure may occur during manufacturing/production of dyes, pigments and in rubber chemicals via inhalation or skin contact. Laboratory and medical staff may be exposed when using it for staining tissues (295,296). Other possible exposure may result from the use of certain hair dyes, the local anesthetic prilocaine and tobacco smoke (297,298).

Sorahan *et al* (299,300) reported an excess of bladder-cancer risk in UK workers exposed to o-toluidine. Epidemiological studies indicate significant associations between o-toluidine exposure and bladder cancer (135).

Oral administration to male and female rats has been reported to cause an increased HCC incidence (301). There is sufficient evidence for its carcinogenicity in humans and animals (IARC Group 1). The biological indicator of occupational exposure is urinary o-toluidine concentrations in post-shift samples.

4, 4'-Methylene bis (2-chlorobenzenamine) (MOCA). MOCA (CAS no. 101-14-4) is used for polyurethane pre-polymers in the manufacture of castable urethane rubber products. In addition, it is used as a model compound to study carcinogens (295,302,303). Occupational exposure can occur during its production and with its use in the polyurethane industry. The common occupational exposure mode is by dermal absorption following contact with contaminated surfaces, whereas inhalation and ingestion are minor pathways (304). Few epidemiological studies have been available to the IARC to evaluate its association with the risk of bladder cancer.

In vivo studies have indicated an increased incidence of HCC, lung and mammary gland adenocarcinoma (305,306). MOCA is an IARC Group 1 agent, its genotoxicity is clearly documented (135). Its toxicological MOA is similar to that of *o*-toluidine, MOCA interacts with DNA and hemoglobin to form adducts, SCE and MN in urothelial cells and lymphocytes of exposed workers (135). MOCA concentrations in blood and urine are monitored in MOCA-exposed workers.

4-Aminobiphenyl (4-ABP). 4-ABP (CAS no. 92-67-1) was formerly used in rubber and dye industry. It is classified as a Group 1 carcinogen to humans (135). It is now used as a carcinogenic agent in mutagenicity studies and cancer research (135,302,303). Major non-occupational sources of exposure to 4-ABP are tobacco smoke and hair dyes (307).

Historically, occupational exposure was mainly during its production and use as a rubber antioxidant and dye intermediate, however, no exposure measurements are available for these situations (295). Occupational exposure can occur during work

with 4-ABP-contaminated products, or during the exposure to benzidine (Bzd) and Bzd-based dyes (295). Epidemiological surveys in US chemical plants indicate a high incidence of bladder cancer among workers exposed to 4-ABP (308,309). Oral 4-ABP administration has been reported to result in an increased incidence of angiosarcoma in mice of both genders; bladder carcinoma and HCC in male and female mice, respectively (310,311); and bladder carcinoma in dogs of both genders (312,313). Subcutaneous (314) or intraperitoneal injection (315,316) have been demonstrated to increase HCC incidence in male mice.

4-ABP is metabolized by hepatic CYP1A2 to yield *N*-hydroxy ABP, a direct-acting mutagen capable of inducing tumors at the site of application (317,318). Animal studies have demonstrated that administration to dogs results in formation of *N*-(deoxyguanonsin-8-yl)-4-ABP (dG-C8-ABP) as the major DNA adduct (~70% of total adducts) in hepatocytes and bladder cells (319,320). In BALB/c mice, a linear association has been described between dG-C8-ABP levels in liver DNA and liver tumor incidence (312). In human liver tissue, higher 4-ABP-DNA levels were observed in HCC cases compared with controls (321-323). Despite observation of a dose-associated increase in 4-ABP DNA, tested using number of cigarettes smoked/day, and an association with mutant p53 protein expression in bladder cancers (324), there are currently no reports of p53 or other specific gene mutations that result from exposure to polycyclic aromatic hydrocarbons or 4-ABP in HCC (307).

Carcinogenicity of 4-ABP in humans operates by a genotoxic MOA that involves formation of DNA adducts, and induction of mutagenic and clastogenic effects. Metabolic activation to DNA-reactive intermediates occurs by multiple pathways, including *N*-oxidation in liver, *O*-acetylation in bladder, and peroxidative activation in the mammary glands and other organs (135). Ac4ABP is the predominant 4-ABP metabolite detected in urine of occupationally exposed subjects.

Bzd and dyes metabolized to Bzd. Bzd (CAS no. 92-87-5) and dyes metabolized to Bzd, including Direct Black 38 (CAS no. 1937-37-7), Direct Blue 6 (CAS no. 2602-46-2), and Direct Brown 95 (CAS no. 16071-86-6) are Group 1 carcinogens (135).

Bzd has been used as reagent base for dye production, which are used primarily to color textiles, leather, and paper products and also in the petroleum, rubber, plastics, wood, soap, fur, and hair-dye industries.

Direct Black 38, Blue 6 and Brown 95 were used for textiles and leather products. They were also used in aqueous printing inks, in hair dyes and as biological stains (Black 38 and Blue 6); in plastic (Black 38 and Brown 95); in paper (Blue 6 and Brown 95); and in wood stains and wood floor (Black 38) (135).

In the 1970s, USA manufacturers replaced them with other dyes (325). In 2002, the EU Directive (76/769/EEC) banned azo-dyes in compounds that may come into contact with the oral cavity or human skin (such as clothing and gloves) (326).

Workers were usually exposed to Bzd-based dyes during their production and use. The primary routes of potential exposure include inhalation, accidental ingestion, and dermal absorption.

The potential for exposure has declined since the late 1970s, when they were replaced with other dye types. Since 1980, use of Bzd-containing mixtures at concentrations ≥0.1% is permitted exclusively in closed systems and workers are required to observe special precautions to reduce exposure. Strict transport procedures have also been adopted (327).

The general population can be exposed to Bzd through contact with articles containing its based dyes, such as leather (326), clothes and toys (328). Traces of Bzd were reported in food colorants, such as tartrazine and sunset yellow FCF (329).

Epidemiological surveys have not clarified the association between Bzd exposure and human cancer. *In vivo* studies on male and female rats demonstrated that following 13 weeks oral administration of Direct Black 38, Blue 6, and Brown 95, there was a significant increase in HCC in males and of neoplastic liver nodules in both genders (330,331).

Monoacetylbenzidine (MoAcBzd) is the predominant Bzd metabolite in the urine of occupationally exposed subjects.

Aflatoxins. Aflatoxin is a mycotoxin produced by fungi of the *Aspergillus* species, which grow rapidly on foods, such as corn and peanuts, stored in warm, damp conditions. Optimum conditions for mycotoxin production are a temperature range of 25-32°C, a moisture content range of 12-16%, and a relative humidity of 85% (332,333).

Aflatoxins (AFB1, aflatoxin B2, aflatoxin G1, and aflatoxin G2) are known to be carcinogenic to humans and animals, AFB1 is considered a more potent hepatotoxic and hepatocarcinogenic agent (334,335). The IARC has classified 'naturally occurring aflatoxin' as a Group 1 human carcinogen (135). Two forms of aflatoxin poisoning are recognized, acute severe intoxication, which results in direct liver damage followed by illness and mortality, and chronic symptomatic exposure (332).

AFB1 is genotoxic and a potent hepatocarcinogen (336-338). It is bioactivated by cytochrome P450 (CYP), a group of enzymes found abundantly in the liver that are associated with the bioactivation and metabolism of multiple xenobiotics and endogenous compounds (339). In particular, CYP enzymes bioactivate AFB1 to an unstable metabolite (AFB1-8, 9-epoxide) that can react with cellular macromolecules, such as DNA and proteins to form covalent adducts causing genotoxicity and cytotoxicity (337,340-342). AFB1 is converted to AFB1-8, 9-exo-epoxide, which in turn is converted to the 8, 9-dihydroxy-8-(N7)guanyl-9-hydroxy AFB1 adduct (334). To date, all animal models that have been exposed to AFB1 have developed HCC (334). Numerous studies have demonstrated a dose-response association between AFB1 adduct levels, HCC risk, and years of AFB1 exposure (34,35,343). These data are consistent with reports of an association between airway AFB1 exposure and serum AFB1 adducts, which may correlate with an increased risk of AFB1-associated HCC (335,344).

Whereas a strong association between dietary AFB1 exposure and HCC risk has been established (334), an association to AFB1 airway exposure has been hypothesized. Of the 550,000-600,000 new HCC cases worldwide each year, 25,200-155,000 may be attributable to aflatoxin exposure (335). Approximately 40% of those affected live in

sub-Saharan Africa (332). The latency period for the development of AFB1-induced HCC remains unknown (334).

AFB1-induced adducts may be fixed as mutations consequent to an HBV-associated increase in hepatocyte turnover. An arginine to serine (G to T) mutation at codon 249 of the p53 tumor suppressor gene (R249S; Ser249 mutation) is specific for exposure to aflatoxin and is detected in as many as 64% of HCC patients (135,38-40,345). The mutation accounts for 90% of p53 mutations in AFB1-associated HCC cases (346), suggesting that it confers a selective advantage during hepatocarcinogenesis. In addition, Ser249 is observed in tumor tissue from up to 75% of Chinese patients (39) and 56% of Mozambican Shangaans with HCC (38). The mutation is also detected in 44% of HCC patients who have no evidence of cirrhosis, supporting a direct, in addition to an indirect, hepatocarcinogenic effect of AFB1 (40). The simultaneous presence of the Ser249 mutation and chronic HBV infection is associated to an odds ratio of developing HCC of 399 (95% CI, 486-3270) (41). AFB1 and chronic HBV infection co-exist in the countries with the highest HCC incidence, raising the possibility of a synergistic hepatocarcinogenic interaction (41).

Workers exposed to aflatoxins by inhalation, particularly in the form of airborne dust, are prone to ingestion, transmucosal absorption, and inhalation of AFB1 released during storage, loading, handling, or milling of contaminated materials, such as grain, waste, feed, corn and other substances (340,42-46). Dermal absorption is particularly severe in workplaces where short clothes are allowed and large skin areas are exposed to particulate matter deposition (47,48).

A recent study conducted in a paper mill and sugar factory demonstrated that AFB1 airway exposure may result in serum AFB1 adducts and HCC risk (50). Poultry production and rice mill workers who are in direct contact with grain dust are often exposed to AFB1 (46,49-50,338,340). Other types of AFB1 exposure include, workers employed in waste management or swine production (338), agri-food industry (347) and wheat handling (348). Textile workers may also be occupationally exposed during pre-spinning, spinning, and weaving (349). Textile workers account for a large proportion of the workforce in Egypt (349), where a significant correlation has been observed between tumor markers and urinary AFB1 in workers and controls who tested positive for *Aspergillus niger* (349).

4. Risk prevention in the workplace

Workplace risk prevention and safety rely predominantly on eliminating the risk itself known as primary prevention. However, where this is not technically feasible, technical, organizational, and procedural measures have to be enacted to reduce risk of exposure to a minimum (350).

When chemical agents are involved, primary prevention entails replacing a toxic agent with a non-toxic one. However, certain mutagenic/carcinogenic agents can be produced in synthetic processes as intermediates or as waste products (351).

When risk assessment determines the existence of a healthy risk, adequate risk control systems must be implemented. These systems are divided into general and personal protection devices (PPD). The former includes adoption of technical and procedural measures, for instance the reduction of environmental pollutants, whereas PPD largely consist of devices worn by workers (such as masks and gloves), preventing direct contact with vapors, fumes and/or potentially contaminated material.

In workplaces where risks are documented, safety procedures must be instituted in accordance with national guidelines. In case of flaws or deficiencies in such guidelines, those in charge of workplace safety are required to refer to the guidelines of internationally recognized organizations, such as the American Conference of Industrial Hygienists or National Institute for Occupational Safety and Health.

The employer and occupational physician have key roles in preventing occupational risk and diseases. The occupational physician, in addition to conducting biological monitoring and health surveillance (known as secondary prevention), is responsible for promoting workplace health (350-356).

With regards to specific HCC prevention, all exposed workers should have HBV vaccination. In addition, campaigns against smoking and drinking alcohol should be organized, providing explicit warning that these factors may be important in liver cancer development (82).

5. Conclusion

Hepatic disorders are common in conditions worldwide. They are important in occupational medicine as the majority of chemicals are metabolized in the liver, and toxic metabolites generated during metabolism are the predominant cause of liver damage. However, numerous liver diseases are difficult to diagnose due to non-specific clinical manifestations. Furthermore, given the high incidence of liver diseases like alcoholic or viral hepatitis, it is difficult to demonstrate an occupational cause. Concomitant conditions, such as viral hepatitis and alcohol or drug abuse, may mask liver disorders resulting from occupational hepatotoxic agents (357).

Epidemiological studies have demonstrated a causal association between tobacco exposure, alcohol consumption, HBV and HCV infection, and HCC, and the occupational origin of certain types of human cancer is well established. The identification of the environmental causes of human cancers has been a long and difficult process. The role of specific dietary components and the interaction of different risk factors in the etiology of human cancer remains to be determined. Despite the progress achieved in understanding the cancer process, and the impact of this knowledge on treatment, primary prevention remains the most effective approach to reduce cancer mortality in developed and developing countries (358).

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