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Hepatocellular Carcinoma: Epidemiology and Etiology

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1. Introduction

Hepatocellular carcinoma (HCC) is a major public health problem, accounting for about 600,000 deaths in the world in 2004 (WHO, 2008). HCC is the sixth most common cancer worldwide with about 500,000 new cases annually, representing the third largest cause of cancer-related death (Parkin, 2005; Ferlay et al., 2010). A slight decrease in the HCC incidence has been reported in high-rate areas, such as China and Japan (McGlynn et al., 2001). However, a steadily increasing trend has been reported in historically low-rate countries, particularly the United States and some European countries, such as Italy, France, UK and Germany (IARC, 2008a; El-Seragh et al., 2007). In particular, HCC incidence rates doubled in the United States in the period 1985-2002, an earlier age of onset has been observed (with a shift towards 45-60 years old), and HCC has become the fastest growing cause of cancer-related death in men (El-Seragh et al., 2004). Interestingly, it has been reported that in the United States 15-50% of HCC patients had no established risk factors, such as viral hepatitis infections, heavy alcohol consumption or aflatoxin B1 exposure (El-Seragh et al., 2007). Moreover, approximately 10% of all HCC cases in the USA occur in patients with non-cirrhotic livers (Shaw & Shah, 2011). In Europe an analysis of mortality rates from HCC trends in the last 20 years has shown increasing rates for men in 11 countries and for women in 6 countries out of 17 whose data were considered (Bosetti et al., 2008).

The observed increase in the incidence rates of HCC has been concomitant with the obesity epidemic observed in the last 30 years in western countries. Obesity is one of the clinical

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manifestations of metabolic syndrome and, in the last decade, epidemiological and experimental studies have shown that metabolic syndrome and high fat diets are associated with an increased risk of HCC incidence/mortality (Bugianesi 2007; Starley et al., 2010; Welzel et al., 2011). However, other causes may be involved in the increased incidence of HCC and chemical-induced liver carcinogenesis appears to be a less considered etiology. In this chapter, we will review recent acquisitions in epidemiology and experimental studies on HCC and will focus on chemical risk factors and possible new mechanisms of liver carcinogenesis, in particular those concerning metabolic disruption.

2. Chemical risk agents of hepatocellular carcinoma

Most human HCC occurs following viral hepatitis (mainly HBV or HCV) infections or aflatoxin B1 exposure caused by ingestion of contaminated food (IARC 2008a). However, the epidemiological evidence shows that the human liver is susceptible to chemical-induced carcinogenesis (Blonski et al., 2010; Degli Esposti et al., 2009) and the increased incidence of HCC in patients not having established risk factors (El-Seragh et al., 2007) suggests that some underestimated or new but still not recognized risk factors exist (Blonski et al., 2010). In particular, many natural and artificial agents have been shown by experimental or epidemiological studies to induce HCC (Table 1). In this section we will review the chemical risk factors of HCC as emerging from the epidemiological and experimental data.

2.1 Human hepatocarcinogens

Various classes of chemicals are reported to induce HCC in humans: drugs or hormonal therapies (azathioprine, tamoxifen and estrogen-progesteron oral contraceptives) (IARC, 2011); radioisotopes or heavy metals (Plutonium-239, Radium-224, Thorium-232; arsenic in drinking water) (IARC, 2001; IARC, 2004b); complex mixtures of polyaromatic hydrocarbons (PAH) and combustion products (soots and tobacco smoking)(IARC, 1987; IARC, 2004a); organochlorines such as vinyl chloride monomer (VCM) or 2,3,7,8 tetrachloride-dibenzo-para-dioxin (TCDD) (IARC, 2008b, IARC, 1997); and plant derivatives (betel or *Areca catechu*) (IARC, 2004c). Recently, some psychoactive substances, like cannabinoids, have been reported to worsen liver steatosis and fibrosis, in particular in the presence of HCV infections (Hézode et al., 2008, Parfieniuk & Flisiak, 2008). However, no evidence of carcinogenicity has been shown for delta 9-tetrahydrocannabinol (the principal psychoactive ingredient in marijuana) in rats and mice (Chan et al., 1996). More research is warranted to assess the long-term carcinogenic or co-carcinogenic effects of cannabinoids, particularly in the liver, as assumption of them during cannabis smoking may result in cannabinoid exposure for a large population. Finally, recent reviews have focused on a possible underestimation of non-viral causes of HCC (Blonski et al., 2010; Degli Esposti et al., 2009). In particular, metabolic disorders (Non-Alcoholic Fatty Liver Disease (NAFLD), obesity and diabetes), hormonal drugs (oral contraception, tamoxifen), organochlorine compounds, polycyclic aromatic hydrocarbons, tobacco smoking, betel quid chewing and dietary exposures (in particular arsenic in drinking water and aflatoxin B1, a well known hepatocarcinogen) are indicated as important contributing factors for HCC (Blonski et al., 2010; Degli Esposti et al., 2009).

| Agents | | Human exposure | Evidence of carcinogenicity | | References |
|----------|----------------------------|--|-----------------------------|----------------------|---|
| Category | Type | | Humans | Experimental animals | |
| Natural | 1. Aflatoxins | food contaminant (rice, peanuts, etc.) | + | + | Wogan and Newbern 1967; Wogan et al. 1974; Yeh et al. 1985; Olsen et al. 1988; IARC 1993; Soffritti et al. 1988 |
| | 2. Alcohol | lifestyle dependent | + | | Hakulinen et al. 1974; Adelstein and White 1976; Hirayama 1981; IARC 1988 |
| | 3. Hepatitis B virus | blood transfusion | + | + | Snyder et al. 1982; Buendia 1992 |
| | 4. Sterigmatocystin | food contaminant (grain, legumes) | | + | Purchase and van der Watt 1970 |
| | 5. Luteoschirina | food contaminant rice | | + | Uraguchi et al. 1972 |
| | 6. Cyclochlorotina | food contaminant rice | | + | IARC 1976 |
| | 7. Pyrazolidinic Alkaloids | plants contaminant | | + | Swoboda and Reddy 1972 |
| | 8. Cycasin | alimentary exposure | | + | Laquer et al. 1963 |
| | 9. Safrole | flavouring substance | | + | Long et al. 1963; Hagan et al. 1965 |

+ = strong evidence; (+) = limited evidence

Table 1. Agents inducing Hepatocellular Carcinoma based on experimental/epidemiological evidence (Part I)

| Agents | | Human exposure | Evidence of carcinogenicity | | References |
|------------|-----------------------------------|----------------------------|-----------------------------|----------------------|--|
| Category | Type | | Humans | Experimental animals | |
| Artificial | 1. Thorotrast | iatrogenic | (+) | + | Guimares et al. 1955; Commission of European Communities (CEC) 1984 |
| | 2. Radioactive colloidal gold | iatrogenic | | + | Upton et al. 1956 |
| | 3. Gamma radiation | occupational or accidental | | | Upton et al. 1968 |
| | 4. Vinyl Chloride | occupational | (+) | + | Gokel et al. 1976; Koischwitz et al. 1981; Evans et al. 1983; Maltoni et al. 1984; Dietz et al. 1985, Pirastu et al. 1990 |
| | 5. Benzidine | occupational | | + | IARC 1982 |
| | 6. 2-Acetyl-amino-fluorene | occupational | | + | Wilson et al. 1941; Teebor and Becker 1971 |
| | 7. 4-Diethylamino-azobenzene | occupational | | + | Kinosita 1936 Terayama 1967 |
| | 8. Dimethyl-nitrosamina | occupational | | + | Magee and Barnes 1956 |
| | 9. Diethylnitrosamina | occupational | | + | Schmal et al. 1960 |
| | 10. Steroidal oral contraceptives | iatrogenic | (+) | (+) | Klatskin 1977; Jick and Hermann 1978; IARC 1979 |
| | 11. Androgen steroids | iatrogenic | (+) | | Johnson et al. 1972 |

+ = strong evidence; (+) = limited evidence

Table 1. Agents inducing Hepatocellular Carcinoma based on experimental/epidemiological evidence (Part II)

The diversity of chemical agents that induce liver tumors in humans may be at least partially explained by the multiplicity of molecular pathways that have been found altered both in human and animal hepatic tumors (Degli Esposti et al., 2009; Saffroy et al., 2007).

Hormonal-induced liver tumors, such those observed after estrogen-progesteron oral contraceptives and tamoxifen administration, have been in part explained by promotion of the epithelium proliferation and the generation of reactive oxygen species (ROS) caused by estrogen reactive metabolites (Russo & Russo, 2006) and ER-dependent liver responses, such as hepatocyte mitogenesis (Vickers et al., 1991). Liver carcinogenicity of alpha-particle emitters, in particular Plutonium-239, Radium-224, Thorium-232, and heavy metals such as arsenic may be explained by their ability to induce direct or indirect genotoxic damage (Lehnert et al., 1997; IARC, 2004b). The carcinogenicity of VCM has been linked to the capacity of its two active metabolites (chloroethylene oxide and chloroacetaldehyde) to react with nucleic acid bases to form adducts (IARC, 2008b) and to induce p53 mutations both in humans and in rats (Barbin et al., 1997). It is worth noting that 10-40% of HCC are characterized by global genomic instability as shown by microsatellite analyses and that the exact mechanisms behind this instability still need to be assessed (Salvucci et al., 1999, Chiappini et al., 2004).

Gene polymorphisms and gene-environment interactions may also be risk factors for HCC, particularly concerning gene coding for metabolizing enzymes (glutathione-S-transferase, epoxide hydrolase, cytochrome p4502E1) or DNA repairing enzymes (XRCC1, UDP-glucuronosyltransferase1A7)(Wong et al., 2000, Borentain, 2007). However, until now, these studies have reported contrasting results. Meta-analysis and additional studies with larger samples should be performed in order clarify the role of genetic polymorphisms in the onset of HCC (El-Seragh, 2007; White et al., 2008).

Overall, these data clearly indicate that the human liver is sensitive to chemical-induced carcinogenesis and that xenobiotic exposure could play an underestimated role in inducing hepatocellular carcinomas, alone or associated with already known etiologies.

2.2 Long-term carcinogenicity bioassays as a tool to identify potential hepatocarcinogens

Long-term carcinogenicity bioassays, mainly using rats and mice, have become a consolidated tool for identifying potentially carcinogenic chemical or physical agents (Huff, 2002; Maronpot et al., 2004; Soffritti et al., 2002). The two most extensive bioassay programs in the world are those of the American National Toxicology Program (NTP) and of the Italian Ramazzini Institute (Bucher, 2002; Huff, 2002; Soffritti et al., 2002). Although differences in the etiology exist between rodent and human HCC, there are also significant similarities in the genetic alterations leading to liver cancer in mice, rats and humans (Hoenerhoff et al., 2011; Feo et al., 2009). A recent study performed a global gene profiling of spontaneous (naturally occurring) HCC in B6C3F1 mice used in the NTP two-year bioassay (Hoenerhoff et al., 2011). The authors identified the dysregulation of genes similarly altered in human HCC, namely re-expression of fetal oncogenes, upregulation of protooncogenes, downregulation of tumor suppressor genes, and abnormal expression of cell cycle mediators, growth factors, apoptosis regulators, angiogenesis and extracellular matrix remodeling factors (Hoenerhoff et al., 2011). The use of a pathway-centered approach has lead to the identification of important targets that may be relevant to human HCC and, despite differences in etiology and pathogenesis from human HCC, the molecular readout has proved very similar, thus providing further support for applying this animal model to the study of HCC (Hoenerhoff et al., 2011). Importantly, the results from the two-year

carcinogenicity bioassays conducted by the NTP show that 188 out of 577 tested agents induced liver tumors in Fischer 344 rats or B6C3F1 mice (Table 2). Interestingly, 76% of these agents (145 out of 188) induced cancer in other sites than the liver (NTP, 2011). In particular, concerning the use of B6C3F1 mice, it has been suggested that this model might be a very sensitive system to detect chemicals that are likely to cause molecular events leading to cancer (Hoenerhoff et al., 2011). Results from the long term carcinogenicity bioassay program performed by the *Cesare Maltoni* Cancer Research Center of the Ramazzini Institute reveal that, among the studies already concluded and published, 52 agents showed clear evidence of carcinogenicity and 5 of them induced liver tumors in Sprague-Dawley rats or Swiss mice (Table 3). Interestingly, all these agents also induced cancer in other sites than the liver. These results confirm the finding that different strains of rats and mice present a different susceptibility to the development of HCC (Feo et al., 2009; Maronpot 2009). It should be noted that recent studies on genetic susceptibility and epigenetic regulation of the signaling pathways involved in hepatocarcinogenesis in rats have shown that most alterations responsible for a resistant or susceptible phenotype in rats also have a similar contribution to the prognosis of human HCC (Feo et al., 2009). In conclusion, the results of both long-term carcinogenicity studies and of genetic investigation of HCC from rodent models may provide important insights into the mechanisms of hepatocarcinogenesis, helping to identify some critical initiating events that lead to carcinogenesis, as well as progression markers and therapeutic targets (Feo et al., 2009; Hoenerhoff et al., 2011).

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | | Carcinogenicity in other site | Human exposure |
|----|----------------------------------|-------------------|--|----|------|----|-------------------------------|--------------------------------------|
| | | | Rats | | Mice | | | |
| | | | M | F | M | F | | |
| 1 | Acetonitrile | Inhalation | E | NE | NE | NE | No | chemical industry |
| 2 | Aldrin | Dosed-feed | E | E | CE | NE | Yes | pesticide |
| 3 | 2-Aminoanthraquinone | Dosed-feed | CE | IS | CE | CE | Yes | dye industry |
| 4 | 1-Amino-2,4-dibromoanthraquinone | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |
| 5 | 3-Amino-9-ethylcarbazole HCl | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |
| 6 | 11-Aminoundecanoic acid | Dosed-feed | CE | NE | E | NE | Yes | car industry; food packaging |
| 7 | Androstenedione | Gavage | E | E | CE | CE | Yes | hormonal treatment |
| 8 | Anthraquinone | Dosed-feed | SE | CE | CE | CE | Yes | dye industry |
| 9 | Aroclor 1254 | Dosed-feed | E | E | | | Yes | insulator for current transformers |
| 10 | Benzofuran | Gavage | NE | SE | CE | CE | Yes | painting industry; food packaging |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | | Carcino- genicity in other site | Human exposure |
|----|---|----------------------|---|----|------|----|---------------------------------------|--|
| | | | Rats | | Mice | | | |
| 11 | Benzophenone | Dosed-feed | SE | E | SE | SE | Yes | printing industry |
| 12 | Benzyl acetate | Gavage | E | NE | SE | SE | Yes | cosmetic industry |
| 13 | 2-Chloro-1- methylethyl ether | Gavage | | | CE | CE | Yes | dye industry; pharmaceutics |
| 14 | Bromodi- chloromethane | Gavage | CE | CE | CE | CE | Yes | water contaminant |
| 15 | 1,3 Butadiene | Inhalation | | | CE | CE | Yes | chemical industry; plastic and rubber |
| 16 | 2-Butoxyethanol | Inhalation | NE | E | SE | SE | Yes | painting industry |
| 17 | Chloral hydrate | Gavage | | | SE | | No | drugs treatment |
| 18 | Chloramben | Dosed-feed | NE | NE | E | CE | No | herbicide |
| 19 | Chlordane | Dosed-feed | NE | NE | CE | CE | No | pesticide |
| 20 | Chlordecone | Dosed-feed | CE | CE | CE | CE | No | insecticide, fungicide |
| 21 | Chlorendic acid | Dosed-feed | CE | CE | CE | NE | Yes | plastic industry |
| 22 | Chlorinated paraffins: C12 60% chlorine | Gavage | CE | CE | CE | CE | Yes | combustion products; oils |
| 23 | Chlorinated paraffins: C23 43% chlorine | Gavage | NE | E | CE | E | Yes | combustion products; oils |
| 24 | p-Chloroaniline hydrochloride | Gavage | CE | E | SE | NE | Yes | dye industry |
| 25 | Chlorobenzene | Gavage | E | NE | NE | NE | No | chemical industry; solvents |
| 26 | Chlorobenzilate | Dosed-feed | E | E | CE | CE | Yes | insecticide |
| 27 | Chlorodi- bromomethane | Gavage | NE | NE | E | SE | No | water contaminant |
| 28 | Chloroethane | Inhalation | E | E | IS | CE | Yes | chemical industry; anaesthetic |
| 29 | Chloroform | Gavage | CE | NE | CE | CE | Yes | chemical industry; anaesthetic |
| 30 | 4-Chloro-m phenylenediamide | Dosed-feed | CE | NE | NE | CE | Yes | dye industry |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | | Carcinogenicity in other site | Human exposure |
|----|------------------------------------|---------------------|--|----|------|----|-------------------------------|---------------------------------------|
| | | | Rats | | Mice | | | |
| 31 | 4-Chloro-o phenylenediamide | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |
| 32 | Chloroprene | Inhalation | CE | CE | CE | CE | Yes | chemical industry |
| 33 | 5-Chloro-o-toluidine | Dosed-feed | NE | NE | CE | CE | Yes | dye industry |
| 34 | C.I. Acid red 114 | Dosed-water | CE | CE | | | Yes | dye industry |
| 35 | C.I. Direct blue 15 | Dosed-water | CE | CE | | | Yes | dye industry |
| 36 | C.I. Direct blue 218 | Dosed-feed | SE | NE | CE | CE | Yes | dye industry |
| 37 | C.I. Disperse blue 1 | Dosed-feed | CE | CE | E | NE | Yes | hair colouring |
| 38 | C.I. Disperse yellow 3 | Dosed-feed | CE | NE | NE | CE | Yes | dye for clothes |
| 39 | C.I. Pigment red 3 | Dosed-feed | SE | SE | SE | NE | Yes | dye industry |
| 40 | C.I. Basic red 9 monohydrochloride | Dosed-feed | CE | CE | CE | CE | Yes | dye industry; clothes, paper, leather |
| 41 | Cinnamyl anthranilate | Dosed-feed | CE | NE | CE | CE | Yes | synthetic flavour |
| 42 | C.I. solvent yellow 14 | Dosed-feed | CE | CE | NE | NE | Yes | dye industry |
| 43 | Coconut oil acid diethanolamine | Topical application | NE | E | CE | CE | Yes | cosmetic industry |
| 44 | Coumarin | Gavage | SE | E | SE | CE | Yes | pharmaceutical use |
| 45 | p-Cresidine | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |
| 46 | Cumene | Inhalation | CE | SE | CE | CE | Yes | chemical industry |
| 47 | Cupferron | Dosed-feed | CE | CE | CE | CE | Yes | chemical industry |
| 48 | Daminozide | Dosed-feed | NE | CE | E | NE | Yes | plants growing regulator |
| 49 | D & C red 9 | Dosed-feed | CE | E | NE | NE | Yes | cosmetic industry |
| 50 | D & C yellow 11 | Dosed-feed | SE | SE | | | Yes | cosmetic industry |
| 51 | Decabromodiphenyl oxide | Dosed-feed | Se | SE | E | NE | Yes | plastic industry |
| 52 | Decalin | Inhalation | CE | NE | NE | E | Yes | industrial solvent |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | Carcino- genicity in other site | Human exposure | |
|----|---|------------------------|---|------|----|---------------------------------------|----------------|--|
| | | | Rats | Mice | | | | |
| 53 | 2,4 Diaminotoluene | Dosed-feed | CE | CE | NE | CE | Yes | dye industry |
| 54 | 1,2 Dibromoethane | Gavage | CE | CE | CE | CE | Yes | gasoline additive; pesticide |
| 55 | 2,3 Dibromo-1- propanol | Topical application | CE | CE | CE | CE | Yes | pesticide |
| 56 | 1,4 Dichlorobenzene | Gavage | CE | NE | CE | CE | Yes | moth killer; deodorant |
| 57 | 2,7 Dichlorodibenzo dioxin- | Dosed-feed | NE | NE | E | NE | Yes | pesticides contaminant |
| 58 | p,p'-Dichlorodiphenyl dichloroethylene | Dosed-feed | NE | NE | CE | CE | No | insecticide |
| 59 | 2,6- Dichloro-p- phenylenediamine | Dosed-feed | NE | NE | CE | CE | No | chemical industry |
| 60 | 1,2- Dichloropropane | Gavage | NE | E | SE | SE | Yes | chemical industry |
| 61 | 1,3-Dichloropropene | Gavage | CE | SE | IS | CE | Yes | pesticide |
| 62 | Dicofol | Dosed-feed | NE | NE | CE | NE | No | miticide |
| 63 | Dieldrin | Dosed-feed | NE | NE | E | NE | No | insecticide |
| 64 | Diethanolamine | Topical application | NE | NE | CE | CE | Yes | chemical industry |
| 65 | Di(2-ethylhexyl) adipate | Dosed-feed | NE | NE | CE | CE | No | polivynil plastic |
| 66 | Di(2-ethylhexyl) phthalate | Dosed-feed | CE | CE | CE | CE | No | polivynil plastic |
| 67 | Di(p-ethylphenyl) dichloroethane | Dosed-feed | NE | NE | NE | E | No | insecticide |
| 68 | Diethyl phthalate | Topical application | NE | NE | E | E | No | plastic industry |
| 69 | 3,4-Dihydrocoumarin | Gavage | SE | NE | NE | SE | Yes | pharmaceutical use |
| 70 | 3,3'- Dimetoxybenzidine dihydrochloride | Dosed- water | CE | CE | | | Yes | dye industry |
| 71 | 1,4 Dioxane | Dosed- water | CE | CE | CE | CE | Yes | dye, cosmetic and plastic industry |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | Carcino- genicity in other site | | Human exposure |
|----|--|----------------------|---|------|----|---------------------------------------|-----|--------------------------------------|
| | | | Rats | Mice | | | | |
| 72 | 5,5-Diphenylhydantoin | Dosed-feed | E | NE | NE | CE | No | pharmaceutical use |
| 73 | 2,5-Dithiobiurea | Dosed-feed | NE | NE | NE | E | No | film material |
| 74 | Elmiron | Gavage | NE | NE | SE | SE | Yes | pharmaceutical use |
| 75 | Ethylbenzene | Inhalation | CE | SE | SE | SE | Yes | chemical industry |
| 76 | Ethylene thiourea | Dosed-feed | CE | CE | CE | CE | Yes | rubber industry |
| 77 | Eugenol | Dosed-feed | NE | NE | E | E | No | flavouring compound |
| 78 | Fluometuron | Dosed-feed | NE | NE | E | NE | No | herbicide |
| 79 | Formamide | Gavage | NE | NE | CE | E | No | pharmaceutical use |
| 80 | Fumonisin B1 | Dosed-feed | CE | NE | NE | CE | Yes | toxin |
| 81 | Furan | Gavage | CE | CE | CE | CE | Yes | polymers industry |
| 82 | Furfural | Gavage | SE | NE | CE | SE | Yes | food additive |
| 83 | Glycidol | Gavage | CE | CE | CE | CE | Yes | plastic industry |
| 84 | Goldenseal root powder | Dosed-feed | CE | CE | SE | NE | No | homeopathic use |
| 85 | HC blue 1 | Dosed-feed | E | SE | CE | CE | Yes | hair colouring |
| 86 | HC red 3 | Gavage | NE | NE | E | IS | No | hair colouring |
| 87 | Heptachlor | Dosed-feed | NE | E | CE | CE | Yes | insecticide |
| 88 | 1,2,3,6,7,8- Hexachloro dibenzo-p-dioxin | Gavage | E | CE | CE | CE | No | pesticides contaminant |
| 89 | Hexachloroethane | Gavage | NE | NE | CE | CE | No | chemical industry; veterinary use |
| 90 | Hydrazobenzene | Dosed-feed | CE | CE | NE | CE | Yes | dye industry |
| 91 | Hydrochlorothiazide | Dosed-feed | NE | NE | E | NE | No | pharmaceutical use |
| 92 | Hydroquinone | Gavage | SE | SE | NE | SE | Yes | rubber and film industry |
| 93 | 5-(Hydroxymethyl)-2- -furfural | Gavage | NE | NE | NE | SE | No | food additive |

| N. | Agents | Route of exposure | Evidence of carcinogenicity ^b | | Carcinogenicity in other site | Human exposure | | |
|-----|--|---------------------|--|------|-------------------------------|----------------|---------------------|---------------------|
| | Type | | Rats | Mice | | | | |
| 94 | Indium phosphide | Inhalation | CE | CE | CE | Yes | electronic industry | |
| 95 | Isoeugenol | Gavage | E | NE | CE | E | Yes | flavouring compound |
| 96 | Isophorone | Gavage | SE | NE | E | NE | Yes | solvent |
| 97 | Lauric acid diethanolamine condensate | Topical application | NE | NE | NE | SE | No | pharmaceutical use |
| 98 | Leucomalachite green | Dosed-feed | E | E | | SE | Yes | dye industry |
| 99 | Malachite green | Dosed-feed | | E | | NE | Yes | dye industry |
| 100 | 2-Mercaptobenzo thiazole | Gavage | SE | SE | NE | E | Yes | rubber industry |
| 101 | Methyl carbamate | Gavage | CE | CE | NE | NE | No | textil industry |
| 102 | 4,4'-Methylenebis (N,N-dimethyl) benzenamine | Dosed-feed | CE | CE | E | CE | Yes | dye industry |
| 103 | Methylene chloride | Inhalation | SE | CE | CE | CE | Yes | chemical industry |
| 104 | 4,4' - Methylene dianiline dihydrochloride | Dosed-water | CE | CE | CE | CE | Yes | chemical industry |
| 105 | Methyleugenol | Gavage | CE | CE | CE | CE | Yes | flavouring industry |
| 106 | 2-Methylimidazole | Dosed-feed | SE | CE | SE | SE | Yes | chemical industry |
| 107 | Methyl isobutyl ketone | Inhalation | SE | E | SE | SE | Yes | solvent |
| 108 | 2-Methyl-1-nitro anthraquinone | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |
| 109 | N-Methylolacrylamide | Gavage | NE | NE | CE | CE | Yes | adhesive industry |
| 110 | Methylphenidate hydrochloride | Dosed-feed | NE | NE | SE | SE | No | pharmaceutical use |
| 111 | alpha-Methylstyrene | Inhalation | SE | NE | E | CE | Yes | plastic industry |
| 112 | Michler's Ketone | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | | Carcino- genicity in other site | Human exposure |
|-----|------------------------------------|----------------------|---|-------|------|----|---------------------------------------|-------------------------|
| | | | Rats | | Mice | | | |
| 113 | Mirex | Dosed-feed | CE | CE | | | Yes | insecticide |
| 114 | Monuron | Dosed-feed | CE | NE | NE | NE | Yes | herbicide |
| 115 | beta-Myrcene | Gavage | CE | E | CE | E | Yes | cosmetic industry |
| 116 | 1,5-Naphthalene diamine | Dosed-feed | NE | CE | CE | CE | Yes | chemical industry |
| 117 | Nithiazide | Dosed-feed | NE | CE | CE | E | Yes | veterinary use |
| 118 | 5-Nitroacenaphthene | Dosed-feed | CE | CE | NE | CE | Yes | dye industry |
| 119 | 3-nitro-p- acetophenetide | Dosed-feed | NE | NE | CE | NE | No | pharmaceutical use |
| 120 | 5-nitro-o-aniside | Dosed-feed | CE | CE | E | CE | Yes | dye industry |
| 121 | o-Nitroanisole | Dosed-feed | CE | CE | CE | SE | Yes | chemical industry |
| 122 | 6-Nitrobenzimidazole | Dosed-feed | NE | NE | CE | CE | No | film industry |
| 123 | Nitrofen | Dosed-feed | IS/NE | CE/NE | CE | CE | Yes/N o | pesticide |
| 124 | Nitromethane | Inhalation | NE | CE | CE | CE | Yes | engine fuel |
| 125 | 2-Nitro-p-phenyl enediamine | Dosed-feed | NE | NE | NE | CE | No | hair colouring |
| 126 | 3 Nitropropionic acid | Gavage | E | NE | NE | NE | Yes | chemical industry |
| 127 | p-Nitrosodiphenyl- amine | Dosed-feed | CE | NE | CE | NE | No | rubber industry |
| 128 | o-Nitrotoluene | Dosed-feed | CE | CE | CE | CE | Yes | dye industry |
| 129 | 5-Nitro-o-toluidine | Dosed-feed | NE | NE | CE | CE | Yes | dye industry |
| 130 | Oxazepam | Dosed-feed | | | CE | CE | Yes | pharmaceutical use |
| 131 | 4,4' Oxydianiline | Dosed-feed | CE | CE | CE | CE | Yes | metallurgic industry |
| 132 | Oxymetholone | Gavage | E | CE | | | Yes | pharmaceutical use |
| 133 | Petachloroethane | Gavage | E | NE | CE | CE | Yes | chemical industry |
| 134 | Pentachlorophenol Dowicide EC-7 | Dosed-feed | | | CE | CE | Yes | insecticide |
| 135 | Pentachlorophenol technical | Dosed-feed | | | CE | SE | Yes | insecticide |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | Carcino- genicity in other site | Human exposure | |
|-----|---|-----------------------------|---|------|----|---------------------------------------|----------------|--------------------|
| | | | Rats | Mice | | | | |
| 136 | Phenazopyridine hydrochloride | Dosed-feed | CE | CE | NE | CE | Yes | pharmaceutical use |
| 137 | Phenylbutazone | Gavage | E | SE | SE | NE | Yes | pharmaceutical use |
| 138 | Picloram | Dosed-feed | NE | E | NE | NE | No | herbicide |
| 139 | Piperonyl sulfoxide | Dosed-feed | NE | NE | CE | NE | No | insecticide |
| 140 | Polibrominated biphenyl mixture (Firemaster FF-1) | Dosed-feed and Gavage | CE | CE | CE | CE | No | engine fuel |
| 141 | Primidone | Dosed-feed | E | NE | CE | CE | Yes | pharmaceutical use |
| 142 | Probenecid | Gavage | NE | NE | NE | SE | No | pharmaceutical use |
| 143 | Proflavin hydrochloride | Dosed-feed | E | NE | E | E | Yes | pharmaceutical use |
| 144 | Propylene glycol mono-t-butyl ether | Inhalation | E | NE | CE | CE | Yes | solvent |
| 145 | Pulegone | Gavage | NE | SE | CE | CE | Yes | cosmetic use |
| 146 | Pyridine | Dosed- water | SE | E | CE | CE | Yes | chemical industry |
| 147 | Riddelliine | Gavage | CE | CE | CE | CE | Yes | food contaminant |
| 148 | Salicylazosulfa- pyridine | Gavage | SE | SE | CE | CE | Yes | pharmaceutical use |
| 149 | Selenium sulfide | Gavage | CE | CE | NE | CE | Yes | cosmetic use |
| 150 | Stoddard solvent (type 11C) | Inhalation | SE | NE | NE | E | Yes | solvent |
| 151 | Binary mixture PCB 126/153 (TEF evaluation) | Gavage | | CE | | | Yes | chemical industry |
| 152 | PECDF (TEF evaluation) | Gavage | | SE | | | Yes | chemical industry |
| 153 | PCB 118 (TEF evaluation) | Gavage | | CE | | | Yes | chemical industry |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | Carcino- genicity in other site | Human exposure | |
|-----|--|----------------------|---|------|---------------------------------------|-------------------|---------------------------------|
| | | | Rats | Mice | | | |
| 154 | PCB mixture PCB 126/118 (TEF evaluation) | Gavage | | CE | Yes | chemical industry | |
| 155 | TCDD (TEF evaluation) | Gavage | | CE | Yes | chemical industry | |
| 156 | 3,3',4,4' Tetrachloro azobenzene | Gavage | CE | CE | CE | CE | Yes pesticide contaminant |
| 157 | 2,3,7,8 Tetrachloro Dibenzo-p-dioxin | Gavage | CE | CE | CE | CE | Yes herbicide contaminant |
| 158 | 1,1,1,2 Tetrachloroethane | Gavage | E | NE | CE | CE | No solvent |
| 159 | 1,1,2,2 Tetrachloroethane | Gavage | E | NE | CE | CE | No solvent |
| 160 | Tetrachloroethylene | Gavage | IS | IS | CE | CE | No stain remover |
| | | Inhalation | CE | SE | CE | CE | Yes |
| 161 | Tetrachlorvinphos | Dosed-feed | NE | CE | CE | CE | Yes insecticide |
| 162 | Tetrafluoroethylene | Inhalation | CE | CE | CE | CE | Yes chemical industry |
| 163 | Tetrahydrofuran | Inhalation | SE | NE | NE | CE | Yes chemical industry |
| 164 | Tetralin | Inhalation | SE | SE | NE | E | Yes chemical industry |
| 165 | 4,4'-Thiodianiline | Dosed-feed | CE | CE | CE | CE | Yes dye industry |
| 166 | 2,4-& 2,6- Toluene diisocyanate | Gavage | CE | CE | NE | CE | Yes chemical industry |
| 167 | o-Toluidine hydrochloride | Dosed-feed | CE | CE | CE | CE | Yes dye industry |
| 168 | Toxaphene | Dosed-feed | E | E | CE | CE | Yes insecticide |
| 169 | Dioxin mixture (TEF evaluation) | Gavage | | CE | | | Yes chemical industry |
| 170 | PCB 153 (TEF evaluation) | Gavage | | E | | | No chemical industry |
| 171 | PCB 126 (TEF evaluation) | Gavage | | CE | | | Yes chemical industry |

| N. | Agents Type | Route of exposure | Evidence of carcinogenicity ^b | | | Carcino- genicity in other site | Human exposure | |
|-----|-----------------------------------|------------------------|---|------|----|---------------------------------------|----------------|-------------------------------|
| | | | Rats | Mice | | | | |
| 172 | Triamterene | Dosed-feed | E | NE | SE | SE | No | pharmaceutical use |
| 173 | 1,1,2-Trichloroethane | Gavage | NE | NE | CE | CE | Yes | chemical industry |
| 174 | Trichloroethylene | Gavage | NE/IS | NE | CE | CE | No | solvent |
| 175 | 2,4,6-Trichlorophenol | Dosed-feed | CE | NE | CE | CE | Yes | insecticide |
| 176 | 1,2,3-Trichloropropane | Gavage | CE | CE | CE | CE | Yes | solvent |
| 177 | Triethanolamine | Topical application | | | E | SE | No | chemical industry |
| 178 | Trifluralin | Dosed-feed | NE | NE | NE | CE | Yes | pesticide |
| 179 | 2,4,5-Trimethylaniline | Dosed-feed | CE | CE | E | CE | Yes | dye industry |
| 180 | tris(2,3-Dibromopropyl) phosphate | Dosed-feed | CE | CE | CE | CE | Yes | engine fuel |
| 181 | tris(2-Ethylhexyl) phosphate | Gavage | E | NE | NE | SE | Yes | engine fuel |
| 182 | Turmeric, oleoresin (curcumin) | Dosed-feed | NE | E | E | E | Yes | pharmaceutical use |
| 183 | Urethane | Dosed-water | | | CE | CE | Yes | chemical industry |
| 184 | Bromochloroacetic acid | Dosed-water | CE | CE | CE | CE | Yes | water disinfection byproducts |
| 185 | Dibromoacetic acid | Dosed-water | SE | SE | CE | CE | Yes | water disinfection byproducts |
| 186 | Dibromoacetonitrile | Dosed-water | CE | SE | CE | CE | Yes | water disinfection byproducts |
| 187 | 2,6 -Xylidine | Dosed-feed | CE | CE | | | Yes | dye industry |
| 188 | Zearalenone | Dosed-feed | NE | NE | CE | CE | Yes | micotoxin |

^a Data from: <http://ntp.niehs.nih.gov/>

^b CE= clear evidence; SE= some evidence; E= equivocal evidence; NE= no evidence; IS= inadequate experiment

Table 2. Chemicals industrial agents associated with tumor induction in liver based on long term carcinogenicity bioassays performed in Fischer 344 rats and B6C3F1 mice males and females by the *National Toxicology Program (NTP) USA*^a

| Agents | | Route of exposure | Evidence of carcinogenicity | | | | References |
|--------|-------------------|-------------------|-----------------------------|-----|------|----|-----------------------|
| N. | Type | | Rats | | Mice | | |
| | | | M | F | M | F | |
| 1 | Vynil Chloride | Inhalation | + | + | - | - | Maltoni et al. 1984 |
| 2 | Trichloroethylene | Ingestion | - | - | NS | NS | Maltoni et al. 1986 |
| | | Inhalation | - | - | + | + | |
| 3 | Benzene | Inhalation | E | (+) | NS | NS | Maltoni et al. 1989 |
| 4 | Tamoxifen | Ingestion | E | E | - | - | Minardi et al. 1994 |
| | | Ingestion | + | + | NS | NS | |
| 5 | Aspartame | Ingestion | - | - | + | - | Soffritti et al. 2010 |

Table 3. Agents inducing Hepatocellular Carcinoma identified in the framework of the long term carcinogenicity bioassays program performed by the Cesare Maltoni Cancer Research Center of the Ramazzini Institute

3. New risk factors of hepatocellular carcinoma

The epidemic of obesity has been correlated to an increased risk of various types of cancer (Kaidar-Person et al., 2011). In the last few decades, experimental and epidemiological studies have shown a strong correlation between obesity or its related co-morbidities and HCC incidence or mortality. In this section we will review the data linking metabolic syndrome and HCC risk, as well as some recent results published in the literature suggesting novel paths to be explored in liver cancer etiology.

3.1 Metabolic syndrome and hepatocellular carcinoma: Experimental data

Although no long-term carcinogenic bioassays have been specifically performed to investigate the carcinogenic potential of a high-fat diet, some recent studies provide interesting clues, in particular concerning liver carcinogenesis. A 20-month study on C57BL/6J male mice fed with a high fat western style diet showed that treated animals developed NASH (non-alcoholic steatohepatitis) at 14 months while at 20 months primary liver dysplastic nodules were found (VanSaun et al., 2009). Similar results were found by another group which showed that a high fat diet induced NASH and HCC in C57BL/6J mice but not in A/J mice (Hill-Baskin et al., 2009). Interestingly, the switch from the high-fat to low-fat diet after 100 days of administration until the end of the experiment (400 days of life) in C57BL/6J males prevented the development of obesity by the end of study and reversed the progression of the disease (Hill-Baskin et al., 2009). Again, a study using a diethylnitrosamine-initiated hepatocarcinogenesis model on Sprague-Dawley rats showed

that animals fed with high-fat diets had an increased incidence of preneoplastic liver foci after 6 weeks compared to control animals (Wang et al., 2009).

These data may represent an early warning as to a possible liver cancer epidemic in coming decades. While obvious measures to contrast obesity have been undertaken in the last few years in many countries (WHO, 2006; Ministère de la Santé et de la Solidarité, 2006; White House Task Force on Childhood Obesity, 2010) and need to be strengthened, the impact of chemical indoor and outdoor pollution on obesity and HCC risk has been poorly studied and may play an underestimated and synergistic role. In this chapter, we will focus on chemical agents recognized as liver carcinogens and on novel mechanisms of hepatocarcinogenesis, in particular concerning metabolic and endocrine disruption.

3.2 Metabolic syndrome and hepatocellular carcinoma: The dimension

Metabolic syndrome and its characteristic manifestations, such as obesity (or central obesity), insulin resistance/type 2 diabetes, dyslipidemia or hypertension, are the most well-studied emerging risk factors of HCC (Bugianesi 2007; Starley et al., 2010; Welzel et al., 2011). In a recent US study, increase in Body Mass Index (BMI) results in a statistically significant increasing trend for HCC mortality both for women (highest calculated RR 1.68, CI 0.93-3.05, p for trend 0.04) and for men (highest calculated RR 4.52, CI 2.94-6.94, p for trend <0.001) (Calle et al., 2003). Other studies have shown that obesity is a risk factor for developing HCC, increasing the risk from 1.5 to 4 times (Møller et al., 1994; Wolk et al., 2001; Oh et al., 2005). Diabetes has been also shown to be an independent risk factor for HCC, with an increase in the risk ranging from 1.8 to 4 times in Swedish, Danish and Greek cohorts (Adami et al., 1996; Wideroff et al., 1997; Laggiou et al., 2000). Recently, metabolic syndrome has been reported to be more common in persons who developed HCC (37.1%) than in persons who did not (17.1%, $p < 0.0001$) and it was significantly associated with increased risk of HCC after multiple logistic regression analyses (OR=2.13; 95%CI=1.96-2.31, $p < 0.0001$) (Welzel et al., 2011). It is worth noting that a concurrent increase in the incidence and prevalence of NAFLD has been observed with the obesity epidemic (McCullough, 2004; Williams et al., 2011). NAFLD is a spectrum of liver disease ranging from simple steatosis to non-alcoholic steatohepatitis and cirrhosis (Bugianesi, 2007). The prevalence of NAFLD in the general population is estimated to range from 17 to 33% (McCullough, 2004). However, a recent prospective study on 328 persons (average age 54 years) reported that the prevalence of NAFLD was 46%, the global prevalence of NASH was 12.2% (Williams et al., 2011) and 2.7% of patients presented advanced NASH (fibrosis graded more than 2). The results of this study confirmed previous reports, as NAFLD and NASH were more frequently diagnosed in overweight/obese males, with a history of hypertension and diabetes (Williams et al., 2011); it suggests that NAFLD and its complications may be more widespread than previously reported. Importantly, some studies and several case reports have shown a direct relationship between NAFLD and HCC (Page and Harrison, 2009). In a Danish cohort study, the risk for primary liver cancer among NAFLD patients was elevated with a standardized incidence ratio of 4.4 (CI 1.2-11.4) (Sørensen et al., 2003). In a US single center case series, NAFLD accounted for 13% of the cases of HCC (Marrero et al., 2002). Moreover, at least 67 cases of HCC arising in a context of NASH have been reported and in 33% of cases HCC seems to have arisen in the absence of cirrhosis (Page and Harrison, 2009). In this context, it is of major concern that NAFLD is becoming the most common cause of liver disease in children and adolescents (Sundaram et al., 2009). A

large pediatric autopsy study found a NAFLD global prevalence of 9.6%, with 38% prevalence in obese children (Schwimmer et al., 2006). The prevalence of fatty liver increased with age from 0.7% in 2-4 year olds to 17.3% in 15-19 year olds (Schwimmer et al., 2006). Of even greater concern is the higher initial incidence of fibrosis or cirrhosis reported in pediatric cases than in adults: a study of obese children with liver steatosis and elevated aminotransferases found NASH in 88% and fibrosis in 71% of patients (Nadeau et al., 2003; Rashid & Roberts 2000).

3.3 Endocrine disruption: Linking metabolic disorder to cancer etiology in the liver?

Endocrine disruption is a term coined in the 1990s which refers to the hormone-like effects of various synthetic chemicals present in the environment (Wingspread consensus statement, 1992; Kavlock et al., 1996). Since then, most laboratory and epidemiological research conducted on endocrine disruptors (ED) has focused on reproductive system pathologies, such as decreased sperm quality, malformations of male genital tract (cryptorchidism or hypospadias), prostate and breast cancers, and on thyroid dysfunction (Soto & Sonnenschein, 2010). However, in the last decade, several ED, such as derivatives of alkylphenols (i.e. 4-nonylphenol), phthalates, polybrominated diphenyl ethers (PBDEs) or organotin compounds (i.e. tributyltin), have been shown to alter adipose tissue development and to promote fat accumulation in both adipose and liver tissues (Masumo et al., 2002; Grün et al., 2006; Grün & Blumberg 2009). Thus, some ED may also be addressed as “obesogens” and more generally considered as metabolic disruptors, suggesting that the various pathophysiological effects of ED may be due to pleiotropic effects on multiple metabolic pathways and that analyses of toxicological effects should not be limited to the endocrine system, but extended to all organs and tissues, with particular attention to adipose tissue and the liver (Grün & Blumberg, 2009; Casals-Casas & Desvergne, 2011).

Most data on the potential carcinogenic effects of ED derive from studies based on evidence of estrogen carcinogenicity. Estrogen carcinogenicity was experimentally demonstrated on the mouse mammary gland as early as the 1930s by Lacassagne (Lacassagne, 1936). In humans the most notorious case of estrogen carcinogenicity is diethylstilbestrol, a synthetic estrogen prescribed to pregnant women to prevent miscarriage in the 1940s-early 1970s. Diethylstilbestrol has been associated with an increased risk of developing clear-cell carcinoma of the vagina and breast cancer in daughters of exposed women (Herbst et al., 1971; Goodman et al., 2011; Palmer et al., 2006). Other ED, such as bisphenol A, tamoxifen or 2,3,7,8-tetrachlorodibenzodioxin, have been shown to alter mammary development and to induce precancerous and cancerous lesions in rodents (Vandenberg et al., 2008; Fenton et al., 2002; Soto & Sonnenschein, 2010). However, information on the potential carcinogenicity of ED for the liver is still elusive while the marshalling of epidemiological and experimental evidence for a potential carcinogenic effect by ED in the liver remains to be properly addressed. Interaction with nuclear receptors (NR) is one potential mechanism that may be involved in any pathological effects of ED on the liver. Indeed, many NR are signally expressed in the liver and have been reported to play an important role in liver diseases, such as steatosis and HCC (Wagner et al., 2011). Since many ED are small lipophilic compounds, their effects are thought to be mediated mostly by direct interaction with NR, modulating downstream gene expression (Casals-Casas & Desvergne, 2011). However, activation of various receptors, such as G protein-coupled membrane receptors, is also possible, as reported at least in the case of the well-established ED Bisphenol A (Chevalier et

al., 2011). The NR superfamily encompasses 48 members and ED are able to alter the signaling pathways mediated by many of them, including estrogen and androgen receptors, thyroid hormone receptor (TR), glucocorticoid receptor (GR), mineralcorticoid receptor (MR), retinoid X receptor (RXR), peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), farnesoid X receptor (FXR), constitutive androstane receptor (CAR), and pregnane X receptor (PXR) (Arrese & Karpen, 2010; Casals-Casas & Desvergne, 2011). The ability of ED to interact with various NR at nanomolar concentrations explains the diversity of induced metabolic perturbation and the increased effects observed particularly when fetal and neonatal exposures occur (Heindel, 2003; Soto & Sonnenschein, 2010; Casals-Casas & Desvergne, 2011). It is worth noting that in addition to sex steroid receptors, this receptor superfamily includes transcription factors playing a central role in integrating metabolic and developmental signaling pathways (Wagner et al., 2011). In particular, data from knockout mice showed that functional PPAR-alpha or FXR are essential in the regulation of hepatic lipid metabolism, as deletion or deficiency of them induces hepatic steatosis in mice. Moreover, PXR and CAR (NRs for which many xenobiotics are ligands) promote hepatic lipid storage by decreasing fatty acid beta-oxidation (Wagner et al., 2011). Importantly, FXR, CAR and PXR are also variously involved in HCC formation. FXR knockout mice suffer from chronic bile acid-induced chronic inflammation and are prone to develop HCC, while CAR and PXR are important in the liver proliferative response, although their exact role in liver tumor promotion is not clear (Yang et al., 2007; Wagner et al., 2011). These data suggest that important interactions exist between NR signaling, lipid metabolism and liver carcinogenesis. This hypothesis is supported by recent findings showing a direct implication of impaired lipid metabolism in the development of hepatocellular carcinoma in animal models. A recent study showed that mice double mutants (due to a growth hormone-activated signal transducer and activator of transcription (STAT5) and GR) developed liver steatosis that progressed to hepatocellular carcinomas (Mueller et al., 2011). Altered STAT5/GR signaling was associated with insulin resistance, high reactive oxygen species levels and increased liver and DNA injuries; that it function correctly was essential for maintenance of lipid homeostasis (Mueller et al., 2011). A second study showed that transgenic CAR $-/-$ mice fed with a NASH-inducing diet are protected from diethylnitrosamine-induced hepatocarcinogenesis (Takizawa et al., 2011). These results suggest that the nuclear receptor CAR might play an important role in promoting hepatocellular carcinomas against a background of NASH. Interestingly, human HCC have been associated with altered lipid metabolism, in particular choline and phospholipid metabolism with an increased synthesis in lysophosphatidic acid, which may provide a mitogenic and proliferative microenvironment through activation of G-protein-coupled receptors (Skill et al., 2011). Moreover, stimulation of lipid biosynthesis and perpetuating chronic hepatic metabolic disease by activation of the transactivator of stress proteins HSF1 promotes HCC development in mice (Jin et al., 2011). Finally, an interesting paper based on a microarray analysis of a hepatitis-induced HCC murine model showed that pro-inflammatory cytokines may promote HCC predominantly in males causing the loss of a gender-identifying hepatic molecular signature (Rogers et al., 2007), suggesting that HCC may be associated with liver-gender disruption in male mice and supporting the idea that endocrine disruption may have broader effects than those reported in reproductive and sexual organs.

Although the scientific data on ED and their effects on liver disease are mostly anecdotal, a few toxicological studies have shown that perinatal exposure to Bisphenol A (BPA) or organotin compounds alters not only adipogenesis in rodents, but also increases both the expression of

lipogenic genes and lipid accumulation in the liver of animals exposed (Somm et al., 2009; Grün et al., 2006). Ecotoxicological studies have shown that ED may bioaccumulate and induce altered gene expression in the liver of various animal species (Ter Veld et al., 2008). In particular, BPA, PCBs and PBDE were shown to bioaccumulate in fish livers caught in Italian seas or US lakes (Mita et al., 2011; Pérez-Fuenteaja et al., 2010) and nonylphenol (NP) was reported to induce the expression of female specific proteins in male lizard livers (Verderame et al., 2011). Although the relevance of NR stimulation to human liver cancer is still unclear, this is a well-known non-genotoxic mechanism of rodent liver cancer, in particular concerning PPAR-alpha activation (Ren et al., 2010). Interestingly, it has been shown that rodent carcinogens show higher *in vitro* potency for human NR than do non-carcinogens (Shah et al., 2011). NP was shown to activate human CAR *in vitro* and *in vivo* using transgenic mouse models (Hernandez et al., 2007). Moreover, CAR is involved in hepatic injury and in the development of HCC in a dietary model of NASH, probably by its cell proliferation promoting activity (Takizawa et al., 2011).

Available data on ED-induced hepatic alterations and on their potential action on systemic and hepatic lipid metabolism suggest that ED may have a role in the establishment and progression of some liver diseases, in particular NAFLD and HCC. However, systematic research aiming to investigate interactions between endocrine/metabolic disruption in liver disease/carcinogenesis is still lacking. We will report on some recent advances in the identification of common new subcellular targets in metabolic disease and liver carcinogenesis, with a particular focus on mitochondria and endoplasmic reticulum alterations and their cross-talks with NR signaling perturbation.

4. Molecular aspects of hepatocellular carcinoma

HCC is a cancer caused by a variety of etiologies, including HBV and HCV infection, alcohol over-consumption, aflatoxin B1 exposure and chemical agents. Thus, it is not surprising that a variety of HCC-associated molecular alterations have been detected and no universal molecular signature is definitively associated with all hepatic tumors, either in humans or in experimental animals (Degli Esposti et al., 2009; Pei et al., 2009). In particular, in humans HCC alterations are classically reported in four genetic pathways, namely p53, retinoblastoma (Rb), TGF-beta pathway and Wnt-beta-catenin pathways (Laurent-Puig, 2001; Saffroy et al., 2007). However, the carcinogenic process in the liver looks to be more complex, as a recent review on omics-based studies seems to suggest (Pei et al., 2009). In particular, comparative genomic hybridizations, high-throughput methods used to identify deletion or amplification in genomic DNA, have shown chromosomal aberrations in fourteen human chromosomes, not uniquely associated with viral infections (Pei et al., 2009). Various studies have also reported epigenetic alterations in HCC, in particular hypermethylation and subsequent silencing of some tumor suppressor genes (Pei et al., 2009). Microarray studies have been performed on both mRNA and microRNA (miRNA), but no consistent expression signatures seem to arise, due to alleged differences in technology and experimental design (Pei et al., 2009). All together, these data reinforce the view that the development of HCC, and probably all cancer types, involves multiple factors and interactions at a molecular level. While meta-analysis and integration of -omics data could prove a helpful approach for biomarker identification in cancer (Zender et al., 2006; Ludwig & Weinstein, 2005), it seems urgent we adopt a comprehensive framework

including pathophysiological and developmental aspects of the disease with consistent molecular, biochemical and biophysical interactions (Soto & Sonnenschein, 2004).

As we reported in the previous section, the case of endocrine and metabolic perturbation in liver disease and carcinogenesis offers a useful starting point for discussing newly identified or potential carcinogenic pathways and future directions to clarify the complex picture of hepatocellular carcinoma and, maybe more generally, of cancer.

4.1 New aspects of hepatocarcinogenesis: Metabolic disruption and altered cellular homeostasis

Alterations in the metabolism of cancerous tissues have been found since 1930s. Warburg (1930) described that, even in the presence of oxygen, cancer tissues had acquired an irreversible glycolytic metabolism. Increased glycolysis proves to allow the utilization of glycolytic intermediates into the various biosynthetic pathways, including nucleoside and amino acid synthesis, required by highly replicating cells (Potter, 1958, Vander Heiden et al., 2009). This feature is also described in rapidly dividing embryonic tissues, even though they are able to switch to oxidative metabolism as proliferation ceases and cells differentiate, suggesting that cancer development may be understood as altered embryonic development (Barger & Plas, 2010, Cooper, 2009, Soto & Sonnenschein, 2004). As a result of Warburg's observations, defects in mitochondrial function have been suspected as contributing to cancer development and progression (Chatterjee et al., 2011). Recently, not only mitochondria but also endoplasmic reticulum have been found to be implicated in controlling the lipid metabolism, in particular in the liver. Thus, since reprogramming of the energy metabolism has been rediscovered as a hallmark of cancer (Hanahan & Weinberg, 2011) while alteration of the lipid metabolism seems to be associated with HCC development, the role of mitochondria and endoplasmic reticulum in metabolic disruption during liver carcinogenesis forms a testable hypothesis in the context of liver carcinogenesis.

Mitochondria are key organelles both for energy (ATP) production (by oxidative phosphorylation of components of the tricarboxylic acid cycle and lipid beta-oxidation) and for integration of pro-survival/pro-death signaling in cells of every tissue and organ. These functions are essential in determining cellular and tissue homeostasis. In the last decade, a lot of research has focused on the role of mitochondria in liver diseases and mitochondrial dysfunctions have been described both in NAFLD and in HCC (Begriche et al., 2006; Chang et al., 2005; Sato, 2007; Rector et al., 2010). A recent study compared liver histology and function in the obese rodent model Otsuka Long-Evans Tokushima Fatty (OLETF) rat with its lean homolog LETO rat (Rector et al., 2010). The ultrastructure of hepatic mitochondria proved to be impaired and the total mitochondrial content decreased in OLETF rats. Moreover, mitochondrial and total fatty acid oxidation were already reduced as early as the fifth week of age in obese animals, before hepatic steatosis and insulin resistance were observed, suggesting that mitochondrial dysfunction may be a very early event in the natural history of NAFLD (Rector et al., 2010). Various mitochondrial alterations have been reported in patients with NASH. Megamitochondria with ultrastructure abnormalities have been found in NASH patients (Caldwell et al., 1999a; Sanyal et al., 2001). Severe depletion of mitochondrial DNA (mtDNA) has been also reported in patients with NASH or hepatic fibrosis (Caldwell et al., 1999b; Ducluzeau et al., 1999). mtDNA depletion may contribute to impairment of the respiratory chain, a common feature in drug-induced and primary NASH (Begriche et al., 2006). It should be noted that in primary NASH impairment of the

respiratory chain is concomitant with an increase in beta-oxidation flux (due to insulin resistance), leading to production of a high level of reactive oxygen species (ROS) (Begriche et al., 2006). Increased ROS generation by mitochondria has also been observed in genetically obese ob/ob mice (Yang et al., 2000) and in rat fed on a choline-deficient diet, a model of steatosis and NASH (Hensley et al., 2000). An increased production of ROS in fatty livers induces lipid peroxidation and subsequently reactive aldehyde formation (Begriche et al., 2006). ROS and aldehydes may further damage mitochondria, generating a vicious circle, and increase the expression of pro-inflammatory cytokines, such as TGF-beta, TNF-alpha, IL-8 or Fas ligand, worsening liver injury (Pessayre & Fromenty, 2005). Mitochondria are also involved in hepatocarcinogenesis. A decrease in mtDNA-dependent cytochromes with disturbed electron transfer has been reported in liver carcinomas, with a subsequent increase in ROS production that can induce nuclear gene mutation in carcinogenesis (Sato, 2007). Moreover, a higher frequency of somatic mutation in regulatory and coding regions of mtDNA has recently been reported in HCC compared to adjacent non-cancerous tissue (Yin et al., 2010). Interestingly, an experimental study showed that long-term administration of L-carnitine, a key molecule in fatty acid transport to mitochondria, decreases the occurrence of hepatic preneoplastic lesions in Long-Evans Cinnamon rats (Chang et al., 2005). These data reinforce the idea that mitochondrial dysfunction, and in particular its role in lipid catabolism, is involved in hepatocarcinogenesis. It is interesting to note that some chemicals with endocrine disruptive properties have been shown to target mitochondrion functionality in various tissues and organs, including the liver (Kovacic, 2010). In particular, five-month exposure to 10-50 ppm diethyl phthalate induced liver impairment, triglyceride accumulation and mitochondrial proliferation in Wistar rats (Pereira et al., 2006). Since phthalates are plasticizers present in plastics used for medical reasons, such as storage bags for blood conservation or instruments for dialysis, it is interesting to note that liver biopsies on dialyzed patients show peroxisome proliferation (Ganning et al., 1984) and that phthalate leakage from blood bags has been proposed as potentially pro-inflammatory (Rael et al., 2009). Furthermore, male mice treated perinatally with 160 or 480 mg/kg of BPA for 14 days showed an increase in cell death mediated by the mitochondrial apoptotic pathway in the testes (Wang et al., 2010). While the hepatic effects on the liver were not evaluated in this study, these results suggest that BPA may directly or indirectly target mitochondria. Other evidence of ED toxicity in mitochondria is provided by results showing that tamoxifen decreased ATP production in a model of isolated perfused rat liver (Marek et al., 2011) and that it impaired mitochondrial respiration, increased cytochrome c release, mitochondrial lipid peroxidation and mitochondrial protein nitration by stimulating mitochondrial nitric oxide synthase (Nazarewicz et al., 2007). Importantly, although epidemiological studies available in humans did not identify any increased risk of liver cancer in women who were administered tamoxifen for breast cancer, several experiments have shown that tamoxifen induces hepatocarcinomas in rats when administered at high doses (Maltoni et al., 1997; IARC, 2011). Another reported ED and human carcinogen, 2,3,7,8 TCDD, has been reported to induce cytotoxicity and mitochondrial dysfunction in isolated rat hepatocytes (Aly & Domènech, 2009) and to mediate tumor progression by activating signaling pathways similar to mtDNA depletion (Biswas et al., 2008). In this context, it would be helpful to consider the interactions between mitochondria, lipid metabolism and nuclear receptors in order to improve our understanding of liver disease and carcinogenesis. In point of fact, several members of the nuclear receptor superfamily are lipid-sensing factors that affect many aspects of lipid metabolism (Alaynick, 2008). PPARs, LXRs, interacting with their transcriptional coactivator PPARgamma Coactivator 1 alpha (PGC-1alpha) have been

shown to regulate insulin sensitivity and lipid metabolism (Alaynick, 2008). Interestingly, PGC-1 α is a known regulator of mitochondrial biogenesis and also able to modulate hepatic steatosis (Puigserver et al., 1998; Sonoda et al., 2007; Wu et al., 1999). Moreover, the mitochondrial protein ANT, a translocase that provides mitochondria with ADP allowing ATP synthesis, has recently been shown to be essential for the functioning of PGC-1 α (Kim et al., 2010) while another NR, the estrogen-related receptor α (ERR- α), important for adaptive energy metabolism (Villena & Kralli, 2008), has been shown to be an effector of PGC-1 α , regulating the expression of genes involved in oxidative phosphorylation and mitochondrial biogenesis (Schreiber et al., 2004). Thus, PGC-1 α may be a key molecule linking NR signaling to mitochondrial function and activity. Finally, it is important to note that ED and other NR ligands may also act independently on the receptor action and mitochondria can be a direct target of this mechanism, as proposed for PPAR agonists (Scatena et al., 2004). Hence, it has been suggested that characterization of reciprocal influences between mitochondria and PPAR physiology would be fundamental for a better understanding of cancer biology (Scatena et al., 2008).

Endoplasmic reticulum is an organelle responsible for protein synthesis, folding, maturation, quality control and trafficking, as well as for Ca²⁺ homeostasis. Every condition that stresses its folding ability, such as an excess of protein synthesis or alteration of energy availability, causes a physiological response called Unfolded Protein Response (UPR). UPR activation aims to increase the folding capacity of endoplasmic reticulum by inducing transcription of chaperons and by globally decreasing protein synthesis (Schroeder & Kaufman, 2005). In recent years, it has been shown that endoplasmic reticulum plays a central role in the multi-organ coordination of systemic metabolism through the integration of synthetic and catabolic pathways (Kammoun et al., 2009b, Hotamisligil, 2010). Obesity and diabetes have been shown to induce ER stress in both adipose tissue and the liver (Ozcan et al., 2004, Kammoun et al., 2009a). Puri et al., examined the role of endoplasmic reticulum stress in human NAFLD, showing UPR activation in liver biopsies from patients with NAFLD and NASH compared to subjects with the metabolic syndrome and normal liver histology (Puri et al., 2008). Moreover, free fatty acids (FFA) may be important mediators of cell dysfunction (lipotoxicity) not only through death receptors or the mitochondrial-lysosomal pathway, but also via endoplasmic reticulum stress (Alkhoury et al., 2009). Endoplasmic reticulum stress and activation of the UPR are also present in solid cancers, often characterized by hypoxia, nutrient starvation, oxidative stress and other metabolic deregulation, factors that cause endoplasmic reticulum impairment (Li et al., 2011). Depending on the duration and degree of ER stress, the UPR can provide either survival signals by activating adaptive and antiapoptotic pathways, or death signals by inducing cell death programs (Schroeder & Kaufman, 2005; Li et al., 2011). In hepatocellular carcinoma, higher accumulation of the Bip/GRP78 and nuclear localization of ATF6, characteristic of UPR activation, were found in moderately to poorly differentiated human HCC tissue samples (Shuda et al., 2003). Although direct demonstrations at a molecular level are still lacking, the cross-links between endoplasmic reticulum stress, NAFLD and HCC seem to be numerous and future research should address this potential new carcinogenic pathway. However, endoplasmic reticulum seems also to be a target of endocrine disruption. Recently, BPA has been shown, in a murine liver cell line, to increase the gene expression of various actors involved in endoplasmic reticulum stress, such as C/EBP homologous protein, caspase 12 and GRP78 (Asahi et al., 2010). This ties up interestingly with a microarray study in which activation of genetic networks involved in

endoplasmic reticulum stress was also detected in mouse testicular Sertoli cells treated with BPA at a concentration of 200 microM (Tabuchi et al., 2006). Furthermore, a number of ED, such as nonylphenol, octylphenol, bisphenol A, and butylated hydroxytoluene, have been shown to inhibit endoplasmic reticulum Ca^{2+} ATPase pumps in a low micromolar concentration (Hughes et al., 2000), suggesting that alterations in endoplasmic reticulum homeostasis may be a common action mechanism by BPA in various different organs. In this connection, some recent papers have highlighted a possible direct interaction between nuclear receptor signaling, lipid metabolism and endoplasmic reticulum stress. A protein deacetylase (SIRT1) has been shown to positively regulate the nuclear receptor PPAR alpha (Purushotham et al., 2009). In particular, hepatic-specific deletion of SIRT1 impairs PPAR alpha signaling and SIRT1 knockout mice develop hepatic steatosis, liver inflammation and endoplasmic reticulum stress (Purushotham et al., 2009). Moreover, the endoplasmic reticulum stress-induced transcription factor ATF6 has been shown to suppress insulin gene expression through the up-regulation of a transcriptional partner of nuclear receptors, SHP, in pancreatic beta-cells and in pancreatic islets of OLETF rats (Seo et al., 2008), suggesting that endoplasmic reticulum stress signaling may also act via NR signaling. As for mitochondria, while no extensive data are available, interactions between endoplasmic reticulum homeostasis and NR physiology have been shown and may play an important yet still under-explored role in the initiation and progression of liver steatosis and HCC. Perturbation of this network by ED is possible, although more research is needed to address the effects of environmental concentrations and to identify the biochemical pathways affected and any long-term pathophysiological consequences, in particular in liver carcinogenesis.

5. Conclusions

In this chapter, we have reviewed some recent acquisitions in HCC epidemiology, in particular regarding the association between obesity and metabolic syndrome and HCC incidence and mortality. We have also reviewed the evidence for liver susceptibility to chemical-induced carcinogenesis, in both rodents and humans, and have shown that long-term carcinogenicity bioassays are a useful tool for identifying potential hepatocarcinogens. In the last part of the chapter, we suggest that endocrine and metabolic disruption, a mechanism involved in the toxic effects of various chemicals, might be a plausible and testable hypothesis in the pathophysiology of NAFLD and its progression toward HCC, in particular concerning the alteration of mitochondria and endoplasmic reticulum in the liver and other tissues. We suggest that long-term carcinogenicity bioassays are a valuable approach to integrating pathological end-points, such as tumor induction, and the analysis of early chronic alteration in tissue and cellular homeostasis, such as mitochondrial and endoplasmic reticulum dysfunctions. This approach could provide important insights into chemical-induced carcinogenic mechanisms, in particular for non-genotoxic carcinogens such as most endocrine disruptors. Moreover, the comparison of experimental results with human biopsies of neoplastic and pre-neoplastic lesions, such as NASH, in well-characterized patients may help to develop specific early markers towards identifying the population at higher risk of HCC.

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7. References

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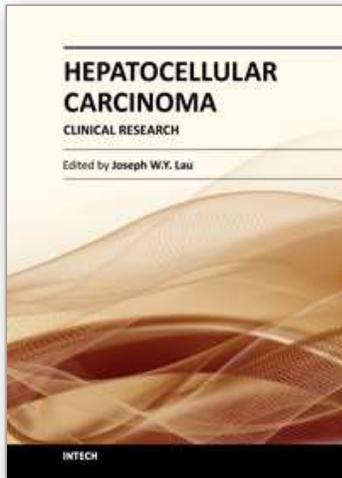
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This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

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