The multitude and diversity of environmental carcinogens

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Abstract

We have recently proposed that lifestyle-related factors, screening and aging cannot fully account for the present overall growing incidence of cancer. In order to propose the concept that in addition to lifestyle related factors, exogenous environmental factors may play a more important role in carcinogenesis than it is expected, and may therefore account for the growing incidence of cancer, we overview herein environmental factors, rated as certainly or potentially carcinogenic by the International Agency for Research on Cancer (IARC).

We thus analyze the carcinogenic effect of microorganisms (including viruses), radiations (including radioactivity, UV and pulsed electromagnetic fields) and xenochemicals. Chemicals related to environmental pollution appear to be of critical importance, since they can induce occupational cancers as well as other cancers. Of major concerns are: outdoor air pollution by carbon particles associated with polycyclic aromatic hydrocarbons; indoor air pollution by environmental tobacco smoke, formaldehyde and volatile organic compounds such as benzene and 1,3 butadiene, which may particularly affect children, and food pollution by food additives and by carcinogenic contaminants such as nitrates, pesticides, dioxins and other organochlorines. In addition, carcinogenic metals and metalloids, pharmaceutical medicines and cosmetics may be involved. Although the risk fraction attributable to environmental factors is still unknown, this long list of carcinogenic and especially mutagenic factors supports our working hypothesis according to which numerous cancers may in fact be caused by the recent modification of our environment.

Keywords: Air-pollution; Cancer dioxins; Environment; Food-additives; Food-contaminants; Nitrates; Pesticides; Radiations; Viruses

We have previously shown that improvement in screening detection and longer life expectancy cannot account alone for the recently observed growing incidence of cancer in high income countries (Belpomme et al., 2007). In addition, decrease of tobacco smoking and of alcohol consumption in some European countries and in North...
America allows us to consider that these factors cannot account for the overall growing incidence of cancer. Moreover, although changes in diet and hormone use are recognized cancer risk factors, they cannot be considered per se as cancer initiating factors, because they mainly act as promoters or cocarcinogens rather than as mutagens. This suggests that the formation of endogenous mutagens which are thought to be associated with lifestyle-related factors may in fact play a role far less important that it is usually speculated. By contrast, we defined environmental factors as physical, chemical and biological agents present in the surroundings of individuals. In order to explain the currently increasing cancer incidence and to justify the hypothesis according to which it could mainly be related to environmental factors, we examine environmental carcinogens, in particular mutagens and analyse their potential role in inducing cancer. In this paper, we intend to show that many cancer types are induced by multiple and diverse exogenous environmental carcinogens, so that in many cases, cancer may be considered not only as a lifestyle related-disease, but also as an environmental one. We analyse herein microorganisms, radiations and xenochemicals, which have been rated as certainly or potentially carcinogenic by national and international organizations.

1. Viruses and other microorganisms

It is estimated that oncogenic viruses are involved worldwide in about 16% of neoplasia (Pisani et al., 1997), while it would range from less than 10% in high-income countries to 25% in Africa (Parkin et al., 2001; Talbot and Crawford, 2004). However, because in Western countries, there are some cancer types for which a viral origin is suspected, although not yet proved, it is likely that the percentage of 5–10% is underestimated. Three groups of double-stranded DNA viruses and two groups of diploid RNA viruses have been shown to be associated with human cancers (Table 1). In Western developed countries, human papilloma virus (HPV) in particular HPV type 16 (HPV-16) and hepatitis-B virus (HBV) are the most frequent oncogenic DNA viruses. They have been recognized as being associated with cervical cancer and hepatocellular carcinoma (HCC), respectively (IARC, 1995a, 1997a). These two viruses contribute differently to carcinogenesis: HPV-16 is directly mutagenic by inducing the viral genes E6 and E7 (Song et al., 1999), while HBV is thought to be indirectly mutagenic by generating reactive oxygen species through chronic inflammation induction (Blumberg et al., 1975; Hagen et al., 1994; Jackson and Loeb, 2001). Epstein-Barr Virus (EBV) has been related to Hodgkin’s disease (HD) as well as to non-Hodgkin lymphoma (NHL) occurring in immunosuppressed patients (IARC, 1997a; Griffin, 2000). In non Western countries, in addition to the abovementioned cancers, Burkitt’s lymphoma (BL) and nasopharyngeal carcinoma have been shown to be caused by EBV, and Kaposi Sarcoma (KS), to be associated with HIV and the Human herpes virus type 8 (HHV-8) (De The, 1995; IARC 1996a, 1997a; Pagano et al., 2004). In Western countries, BL is an uncommon disease. This may be due to the fact that in endemic area, in addition to natural promoters such as extracts of a commonly used plant, Euphorbia tirucalli, malaria as well as arbovirus infections are mosquitoes- so climate-dependent cofactors (Brooks et al., 1999; Van Den Bosch, 2004).

RNA tumor viruses must also be considered. They include the Hepatitis C virus (HCV) and the unique retrovirus presently known to be oncogenic in humans, the human T-cell lymphotropic virus type 1 (HTLV-1) which is the causal agent of a very rare T-cell type leukemia (IARC, 1996a; Talbot and Crawford, 2004). Also, these two oncogenic viruses contribute differently to carcinogenesis. HTLV-1 is directly mutagenic, while HCV, as HBV, is thought to produce oxidative stress in infected cells and thus to act indirectly through chronic inflammation (De Maria et al., 1996; Koike et al., 2002).

However, whatever their direct or indirect mechanisms of action, most of these human DNA or RNA viruses are oncogenic, meaning that they can initiate carcinogenesis by inducing mutations. They must be therefore distinguished from other retroviruses such as the human immunodeficiency viruses (HIV) (Gallo and Montagnier, 2003), which

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<tr>
<th>Virus family</th>
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<th>Human tumors</th>
<th>Non-malignant disease</th>
<th>Experimental tumors in animals</th>
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<tr>
<td>Papovaviridae</td>
<td>Human papillomavirus</td>
<td>Cervical cancer, Anogenital cancer, Skin cancer</td>
<td>Warts</td>
<td>Lymphoma in primates</td>
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<td>Herpesviridae</td>
<td>Epstein-Barr virus</td>
<td>Nasopharyngeal carcinoma, Burkitt’s lymphoma, Hodgkin’s lymphoma,</td>
<td>Infectious mononucleosis</td>
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<td>Kaposi’s sarcoma, primary effusion lymphoma, Adult T-cell Leukaemia (ATL)</td>
<td>Multicentric, Castleman’s disease</td>
<td>Not known</td>
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<td>Retroviridae</td>
<td>Kaposi’s sarcoma-associated herpesvirus HTLV-1</td>
<td>B-cell lymphoma, Kaposi’s sarcoma</td>
<td>Tropical spastic paraparesis AIDS</td>
<td>ATL in rabbits</td>
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<td>HIV</td>
<td>Liver cancer</td>
<td>Hepatitis, Cirrhosis</td>
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<td>Hepatitis B virus</td>
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<td>Hepatitis C virus</td>
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Adapted from Talbot and Crawford (2004).
are not per se mutagenic, but which have been classified as carcinogenic by IARC. They have been shown in epidemiological studies to be strongly linked with the occurrence of cancer, because they can promote the initiating effect of oncogenic viruses through immunosuppression induction (IARC, 1996a). In addition to a possible effect favoring chemically induced carcinogenesis, HIV infection accounts for the occurrence of AIDS-associated viral neoplasia (Frisch et al., 2001). Indeed, a variety of cancers of viral or presumed viral origin, including leukemia, lymphoma, soft tissue sarcoma and other solid tumors have been reported in HIV-infected people. This is the case in HIV-infected adults and children, be they AIDS-bearing or not. So, estimates of cancer incidence in HIV-infected children range from 1 to 4 per 1000 children per year, representing a 10–40-fold increased risk (Pollock et al., 2003).

In fact, in addition to the abovementioned well-established human virus-associated cancers, there are strong biological and epidemiological arguments for an infectious viral etiology of other cancers. This is the case for childhood acute leukemia, particularly for the common acute lymphoblastic leukemia (ALL), for which the virus presumably involved has not yet been isolated although it is strongly suspected (Belpomme et al., 1969a, b; Guibout et al., 1977; Greaves, 2002). Indeed, several additional observations have contributed to the hypothesis that a virus is potentially involved in ALL. In fact, given the biological diversity of leukemia, it is unlikely that it is the single cause (see Belson et al., 2007 for review). In the population mixing theory, it has been postulated that an extremely infectious but not highly pathogenic virus introduced into a previously unexposed rural community, may trigger clusters of ALL cases, due to the existence of an associated immune deficiency (Kinlen 1988; Kinlen et al., 1991; Alexander et al., 1997; Boutou et al., 2002). However, an alternative explanation based on a “delayed infection” hypothesis leads to consider the possibility of a “two hit” mechanism, involving an abnormal response to an initial common infection followed by a critical second event, promoting the ALL development (Greaves and Alexander, 1993). A viral origin has also been suggested for some non-EBV-related lymphoma (McNally et al., 2002; Karimi and Yarmohammadi, 2003; Talbot and Crawford, 2004; Harris, 2004) and for some pediatric and adult brain tumors (McNally et al., 2002), for which a polyoma virus as it is the case in animals (Krynska et al., 1999) has been suspected in humans (Weggen et al., 2000). Moreover, there are experimental data suggesting that some human soft tissue sarcomas (Elber and Morton 1970) and some breast carcinomas could be caused by oncogenic retroviruses. For example it has been shown that human milk from women at high risk for breast cancer (Moore et al., 1971), cancer human breast tissues (Schlom et al., 1971; Vaidya et al., 1974) and cultures of normal (Furmanski et al., 1974) and cancer human breast cells (McGrath and Jones, 1978; Keydar et al., 1984) contain virus particles associated with reverse transcriptase activity that are morphologically similar to the mouse mammary tumor virus (MMTV). Consequently these particles have been designated as the human homologue of the MMTV (HHMMTV) (Callahan et al., 1982; Miyazaki et al., 1997; Wang et al., 1998; Soble et al., 1999). Alternatively, it has been shown that HPV type 16 (Hennig et al., 1999), HPV type 33 (Yu et al., 1999) and EBV (Bonnet et al., 1999) may also be involved in the genesis of some human breast cancers and may act as cofactors in association with diet, oestrogens and other hormones in genetically susceptible women (Lawson et al., 2001).

It can therefore be assumed that infection-related cancers are probably more frequent in high-income countries than it is generally recognized, all the more so that, in addition to viruses, some microflora bacteria of the gastrointestinal tract, including Helicobacter pylori for gastric neoplasia (IARC, 1994a; Ando et al., 2006), some parasites such as Opisthorchis viverrini for gallbladder cancers, Schistosoma haematobium for bladder cancer and some oncogenic toxins from mycosis-induced moulds inducing aflatoxins-related HCC (IARC, 1994b) and more generally, several types of inflammation (Jackson and Loeb, 2001) have been clearly recognized as risk factors of carcinogenesis.

2. Radiations

Overall, it may be speculated that radiation-induced cancers may represent up to 10% of total cases. In fact there is no clear assessment of this population attributable risk, meaning that this estimate needs to be refined. For ionizing radiation, estimates of the magnitude of the risk in relation to dose have long been based on studies of the incidence of cancers following medical irradiations or exposure to radiation from the atomic bombs at Hiroshima and Nagasaki (UNSCEAR, 2000). Radiation-induced cancers are a stochastic late effect of ionizing or non-ionizing radiation. They include some leukemia and lymphoma, thyroid cancers, skin cancers, some sarcomas and some lung and breast carcinomas (Wakeford, 2004). Studies of radiation-exposed populations were initially based on occupational exposures and included those concerning radiologists, underground miners and radium dial painters. This began to change with the study of the survivors of atomic bombs at Hiroshima and Nagasaki. In the latest follow-up of atomic bomb survivors total malignancies were increased (Preston et al., 2004). Moreover, studies of patients treated by radiotherapy (Belpomme et al., 1974) and of populations specifically exposed for occupational reasons were carried out in an attempt at defining a causal relationship. These studies presently focus on radiation technologists, uranium miners and nuclear industry workers (UNSCEAR, 2000).

Findings based on the study of lung cancer deaths associated with exposure to radon and improved understanding regarding
the molecular basis of radon-induced cancers have provided support for incriminating low radon levels in the home environment as a cause of approximately 10% of lung cancers (Lubin and Boice, 1997; Darby et al., 2005). Exposure to radon and radon decay products at home and/or at workplace are the most widely found sources of exposure to ionizing radiation (Akerblom, 1999). In contrast, contribution of human nuclear activities to radiation exposure of the general population, although generally estimated to be small and within the variations in background radioactivity are nevertheless of serious concern (UNSCEAR, 1988; Lubin et al., 1994). Recent scientific concern appeared due to the numerous atmospheric nuclear explosions and the incidental exposure following some nuclear accident at power plants that occurred since the last world war. Indeed, artificial radioactivity adds to natural radioactivity in proportions that depend on localization and type of emission, geographic distribution of radioactive substances and type of radionuclides. Moreover, dose-response curves for the incidence of cancer, plotting the incidence as a function of dose are extremely complex. Radiation-induced cancers in humans depend on several variables, most of which are not possible to correct for in epidemiologic studies and as for low dose chemicals low doses of ionizing radiation cannot be considered insignificant for risks of somatic and heritable mutations (Prasad et al., 2004). Among other parameters to be considered are the synergistic interactions of radiation with other physical, chemical or biological carcinogens. Studies of cancer risks from nuclear power plant accidents are thus a challenge. Nevertheless, an increased incidence of total malignancies after the Chernobyl radioactive fallout was reported in Sweden (Tondel et al., 2006).

Non-ionizing radiations comprise ultraviolet (UV) rays, which have been rated as carcinogenic to humans by IARC (1992). Exposure to UV is a dose-dependent risk factor (Kopf et al., 1984; Gallagher et al., 2005), which can cause skin cancers, mostly basal cell and squamous cell carcinoma (Henriksen et al., 1990; Urbach, 1991; Feychting et al., 1995; Foliart et al., 2006) and can be also involved in carcinogenesis of melanoma (IARC, 1992) and consequently, in its current growing incidence. Increase in lifestyle-related natural or artificial (sun beds) exposure to UV has been incriminated to account for the growing incidence of melanoma. However, depletion of the stratospheric ozone layer by augmenting the dose intensity of UV-B or C to the skin (Cutches, 1974) is another factor that could also contribute to the growing incidence of skin cancers (Kellkens et al., 1990; De Fabo, 2005).

Electromagnetic fields (EMF) of very low frequency (VLF) or extremely low frequency (ELF) have been the object of many scientific research efforts to answer the question whether they can induce cancers. For a long time, many scientists were doubtful about the role of EMF in inducing cancers. This was mainly due to the difficulty in assessing a causal link between long-term exposure to weak EMF and cancer occurrence and because although it has been observed that pulsed EMF can be clastogenic by breaking DNA (Haider et al., 1994), the mechanism whereby VLF or ELF could induce cancer is not clear. To date many studies correlating EMF to childhood acute leukemia have been reported (Ahlbom et al., 2001; IARC, 2002a). Despite differences in study design and setting, results are sufficiently consistent to believe that an increased risk of leukemia does exist in children with high exposure. Indeed, from a meta-analysis of nine studies, it has been estimated that there is a relative risk of acute leukemia of 2 for children living in area associated with an average EMF strength above 0.4 μT and that the EMF-related relative risk of childhood leukemia is 2 for about 1% of the overall children population (Ahlbom et al., 2000). These data have been confirmed by a more extensive meta-analysis (Greenland et al., 2000). Moreover, it has been recently confirmed that children living within a distance of 200 m from high voltage power lines have a relative risk increase of leukemia of 69%, while those born between 200 and 600 m have a relative increase risk of leukemia of 23%. In this study, there was a significant dose-effect dependency in relative risk in relation to the reciprocal of distance from the line (Draper et al., 2005).

Other epidemiological studies revealed that EMF and mostly ELF could be also associated with brain tumors (Mack et al., 1991; Beall et al., 1996; Guenel et al., 1996; Feychting et al., 1997), breast carcinoma (Guenel et al., 1996; Feychting et al., 1997; Wakeford 2004) and melanoma (Hallberg and Johansson, 2002; Levi et al., 2006). The most visible source of ELF–EMF is power lines, in particular high voltage transmission lines, but other sources include transformers, electric train engines and more generally all types of electrical equipment. In a series of recent epidemiological studies, one of us has shown that long-term cellular or cordless phone use is also a risk factor for brain tumors (Hardell and Hansson Mild, 2006; Hardell et al., 2006a), whereas several previous studies were negative. This positive result has been recently challenged by an updated Danish cohort analysis, showing no correlation between cellular phone use and cancer risk (Schuz et al., 2006). However, results from this study are presumably limited, because there was no consideration about dose effect, i.e. the search for a correlation between duration of exposure and cancer risk. Indeed, in a recent meta-analysis of all available epidemiologic data, one of us has shown that daily prolonged use of mobile phones associated with a long-term use of it for ≥10 years give a consistent pattern of an increase risk of brain tumors including neuroma and glioma and that the risk is highest for ipsilateral exposure (Hardell et al., 2007). Moreover, it is assumed that X-rays-related medical imaging and magnetic resonance imaging (MRI) can induce a low number of cancer cases in selected populations (IARC, 2000b; Nitta et al., 2002).

Finally, it is concluded that in addition to ionizing irradiation, non-ionizing irradiation including UV and
pulsed EMF can cause cancers, in particular, skin cancers (UV) some acute leukemia and brain tumors in children (EMF). An explanation could be that EMF may be mutagenic per se or induce cellular epigenetic changes and thus contribute to cancer induction. Such a mechanism could be in fact complex. For example, it has been recently shown that corona ions induced by powerlines and increased chemical exposure to pollutant aerosols may be involved in carcinogenesis (Fews et al., 1999a, b).

3. Xenochemicals

The industrial revolution over the second half of the last century and its consequences in domains such as energy, transport, agriculture, food and health led to synthesize, produce and introduce into the environment, millions of man-made chemicals or substances. As a result, according to the European commission, about 100,000 chemicals have been so far marketed, since the last world war, without sufficient toxicological control. Such products can act as persistent toxic pollutants and contaminate air, soil, water and food. Many of them are carcinogenic, mutagenic and/or reprotoxic (CMR) molecules (Clapp et al., 2005) and therefore can act as mutagens, promoters or both or be cocarcinogenic, meaning that they can contribute to the genesis of cancers and therefore account for their currently growing incidence (Epstein, 1994, 2004).

3.1. Occupational cancers

Since the seminal report of Percival Pott in 1775, cancers of the scrotum were the first recognized occupational chemically-induced cancers. Today, occupational cancers are reported to represent 2–10% of all cancers, but this percentage is probably underestimated and may be as high as 15–20% in men. In 1996, the Harvard Center for Cancer Prevention (HCCP) classified 32 substances or industries as carcinogenic in humans (HCCP, 1996). Recently, 28 agents have been considered as definite occupational carcinogens in human, 27 as probable occupational carcinogens and 113 as possible occupational carcinogens (Siemiatycki et al., 2004; Clapp et al., 2005). Doll and Peto (1981) had listed only 16 in 1981. In Europe, there could be 32 million people exposed to hazardous carcinogenic chemicals at work (Kauppinen et al., 2000). Among substances, asbestos is a classical example. It is a calcium and magnesium hydrate silicate that comes from the transformation of the mineral. It was widely used owing to its fireproofing and heat-retaining properties. There is no doubt that asbestosis is carcinogenic and induces occupational cancers, including mesothelioma and approximately 10% of lung cancers (IARC, 1977, 2002b). Although asbestosis was recognized as carcinogenic one century ago in the UK, its legal use was forbidden in Europe just about one or two decades ago. Likewise, wood-dust-related cancers, though their occurrence in joiners or cabinetmakers is limited, are also occupational cancers, insufficiently declared (ethmoid cancers) or even not yet declared (sinus cancers) (Hayes et al., 1986; Blot et al., 1997), although they are both acknowledged as occupational cancers by IARC (1995b). Solvents, paints, dyes, gasoline and other petroleum products can also cause occupational cancers. After the leukemogenic effect of benzene was first recognized (Goguel et al., 1967; Surralles et al., 1997), the mutagenic effect of other solvents was established. For example, trichloroethylene (TCE) has been reported to be strongly associated with kidney, liver, esophageal cancers and non-Hodgkin’s lymphoma (IARC, 1995c; ASTDR, 1997; Wartenberg et al., 2000; Hansen et al., 2001; Wartenberg and Siegel Scott, 2002; Raaschou-Nielsen et al., 2003) and perchloroethylene (PCE) with oesophageal cancers (Ruder et al., 1994; Weiss, 1995). Likewise, dye products or byproducts of aromatic amines and/or aminophenol groups are strongly associated with bladder cancer (Cantor et al., 2006). Moreover mineral oils and lubricants have been associated with some types of cancers, including larynx, skin and bladder cancers (Kane et al., 1984; IARC, 1984, 1989; Hewstone, 1994; Tolbert, 1997; Mackerer et al., 2003).

Phthalates are widely used since the last world war, due to their plasticizing and emulsifying properties. For this reason, they are added to polyvinyl chloride (PVC) in particular in common medical devices and cosmetics. Phthalates are the cause of repeated abortions in rats and mice (Saillenfait et al., 2003, 2006) and of sterility in man (Latini et al., 2006). In addition, di(2-ethylhexyl)phthalate (DEHP) and butyl-benzyl-phthalate have been suspected to be carcinogenic (Shea, 2003). Some phthalates may therefore be potential CMR substances due to reprotoxic and carcinogenic properties. Toxicological studies in rodents indicate that DEHP exposure can cause liver cancer (Rao et al., 1990) and pancreatic tumors (David et al., 1997). Three studies in humans revealed an elevated pancreatic cancer risk in workers in flexible PVC processing (Chiazze and Ference, 1981; Dell and Teta, 1995; Selenskas et al., 1995). IARC initially classified DEHP as a 2B possible carcinogen to humans, but subsequently downgraded it to a non-classifiable grade 3 molecule (IARC, 2000a). However, none of the studies indicating elevated risk of pancreatic cancers in humans exposed to DEHP were considered (Melnick et al., 2000). Thus the IARC evaluation on DEHP, because it omitted critical and available information from relevant animal and human studies, was criticized by many scientists to such an extent that they asked IARC to schedule a new thorough and unbiased DEHP evaluation. In addition, vinylchloride monomer, but not PVC is mutagenic and thus can cause liver angiosarcoma and hepato-cellulars-carcinoma (HCC) (Kielhorn et al., 2000). Other occupational risks are related to many industrial substances and particularly to agrochemicals, more precisely to the use of pesticides by selected population of workers in agriculture and agrochemical industry (see further).

A major concern is the risk of childhood cancers following either parental or child exposure to occupational pollutants. Several studies, evaluating the effect of parental
exposure to solvents, paints, gasoline, gasoline exhaust confirmed an increased risk of leukemia and brain tumors in children (Wilkins and Koutras, 1988; Savitz and Chen, 1990; Smulévich et al., 1999; O'Leary et al., 1991; Feingold et al., 1992) to such an extent that in 1998, Colt and Blair (1998) wrote that there is “sufficient evidence that certain parental exposures may be harmful for children”. However, how these different types of mutagenic chemicals or substances relate to the general population is still under investigation and needs further research efforts. Indeed, many mutagenic synthetic products, organochlorines or not, used to manufacture adhesives, resins, coatings, paints, dyes have been marketed over the post-war period without sufficient toxicological investigations and regulatory control.

3.2. Outdoor air pollution

Polycyclic Aromatic Hydrocarbons (PAH) resulting from the combustion of organic substances are mutagens (IARC, 1989). They are found in tobacco smoke as well as in factory smoke, waste incinerator emission and vehicle exhaust. They can adhere on fine carbon particles (PM 2.5) suspended in the air and thus penetrate the organism more extensively because particles accumulate near the ground at the level we breathe. In adults, long-term exposure to particles and so to PAH, i.e. in air of polluted cities increases the risk of death due to lung cancer by 8%, after controlling for tobacco smoking (Dockery et al., 1993; Pope et al., 2002; Cohen, 2003). In 2002, the American Cancer Society published the results of the widest survey carried out to date on 500,000 people residing in American cities: the higher the concentration of fine particles in the air, the higher the number of deaths due to lung cancer. This risk is significantly higher for the more polluted cities than for the less polluted ones, and smoking potentiates that effect (Pope et al., 2002). Moreover, in a recent European study, the proportion of lung cancers attributable to traffic-related air pollution and environmental tobacco smoke (ETS) in never- and ex-smokers was precisely estimated to be 5–7% and 16–24%, respectively (Vineis et al., 2007). In addition to PAH and fine and ultrafine carbon particles the air pollutant nitrogen dioxide (NO2) may also be involved. NO2 is the expression of an increased rate of respiration and so inhale more pollutants per kg of body weight than adults, children are more susceptible to air pollution. Traffic exhaust is a major cause of children’s exposure to air pollutants (IARC, 1989) and several authors in US as well as in Europe found a positive correlation between local traffic density at time of diagnosis and childhood leukemias with an estimated relative risk between 1.6 and 4.7 (Wertheimer and Leeper, 1979; Savitz and Feingold, 1989; Feychtling et al., 1998; Harrison et al., 1999).

3.3. Indoor air pollution

Indoor air pollution is a growing scientific concern because indoor air can accumulate many carcinogenic pollutants. In addition to carbon particles and PAH, indoor air can accumulate ETS as well as chemicals such as biocides and also formaldehyde in addition to volatile organic compounds (VOC) such as benzene and 1,3 butadiene, which have been rated as carcinogens by IARC (1995b). The risk of lung cancer due to ETS exposure is much higher at work than at home and higher for ex-smokers than for never smokers (Vineis et al., 2007). Since children are most affected by chronic household exposure, they may be at higher risk of cancer. Particularly of concern is the association between parental and/or childhood exposure and the risk of childhood cancers and cancers in adulthood. In addition to an increased risk of adulthood lung cancer in children exposed to ETS (Vineis et al., 2007), several epidemiological studies have shown that indoor air pollution can be an important contributing risk factor for childhood cancers (Zhang and Smith, 2003). There is an increased relative risk of leukemia and lymphoma caused by indoor VOC (Smith, 1987; Weaver et al., 1998; Viegi et al., 2004) as well as by the indoor use of insecticides (Infante-Rivard et al., 1999; Meinert et al., 2000; Menegaux et al., 2006).

3.4. Biocides and pesticides

Over the last decades, several hundreds of pesticides have been marketed for intensive farming or domestic use (biocides). Many of them especially those bearing to the organochlorines, carbamates and carbinols groups are rated as probable or possible carcinogens, according to the US EPA and the IARC classification (IARC, 1991) while several are recognized as carcinogens in humans. Most of them having a molecular structure close to estrogens are endocrine disruptors. They may thus act as promoters, while others can in addition be mutagenic. Moreover many of them are also strong immunosuppressors, meaning that they can act also as promoters through immunosuppression (Repetto and Baliga, 1997; Hayes et al., 2006). In children, several epidemiological studies revealed an increased relative risk of cancers associated with parental exposure to pesticides be it occupational or non-occupational (Daniels et al., 1997; Zahm and Ward, 1998). The exposure observed occurs prior to and during pregnancy as well as post-natally. Paternal exposure to
pesticides is associated with an excess relative risk of leukemia (Ma et al., 2002), and of central nervous system (CNS) tumors (Cordier et al., 2001; Feychting et al., 2001) as well as of Wilm's tumors (Fear et al., 1998). Moreover a positive association has been found in several studies testing the direct exposure of children to pesticides (Daniels et al., 1997; Zahm and Ward, 1998; US-EPA, 2003; Menegaux et al., 2006). Collectively, these studies revealed an overall increase in relative risk of leukemia, NHL, brain tumors, Wilm's tumors, Ewing's sarcoma and germ cell tumors associated with parental or child exposures to pesticides. By contrast, in adults, epidemiological studies have provided conflicting results. A positive link between pesticides and breast or prostate cancers has been put forward (Charlier et al., 2003; Muir et al., 2004; Ibarluzea et al., 2004; Mills and Yang, 2006), whereas in other studies it cannot be confirmed (Post et al., 1999; Stellman et al., 2000; Gammon et al., 2002; Van Maele-Fabry and Willems, 2003). However, a strong association between pesticides and the relative risk of sarcoma (Hardell et al., 1995; Dich et al., 1997) and of Hodgkin and NHL (Hardell and Eriksson, 1999; Zheng et al., 2001; McDuffie et al., 2001; Hardell et al., 2003) has been found for 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), chlorophenols and phenoxyherbicides. Likewise an increased risk of adult leukemia has been shown for carbon disulfide, phosphine (such as PH₃) and methylbromide (Dich et al., 1997). Indeed, due to their CMR effects, organochlorine pesticides are today almost universally banned in most industrialized countries. The danger of pesticides lies in the fact that as Persistent Organic Pollutants (POPs), they can persist over long periods in the environment and contaminate drinking water and food (Dougherty et al., 2000). Food component and ingredient analysis remains one of the most pertinent application of chemistry. However, policy is now insufficient to control pesticide use in many countries while the relevance of pesticides in carcinogenesis is steadily increasing. Indeed, pesticides can contaminate the body not only through ingestion, but also through air inhalation and skin contact, accumulate in adipose tissue (Lassiter and Hallam, 1990; Geyer et al., 1990, 1997), more specifically in fatty breast tissue (Muscat et al., 2003; Zou and Matsumura, 2003), pass through the placenta (Simonic and Hites, 1995) and accumulate in the milk of nursing mothers (Sharpe and Irvine, 2004). This led to the conclusion that children are at risk during three periods: in utero during pregnancy, during breast feeding and in the course of childhood, by inhaling biocides at home or by ingesting contaminated food (Guvenius et al., 2003; Menegaux et al., 2006). During recent years there has been an increasing incidence of male developmental reproductive disorders. These diseases have been grouped together in the testicular dysgenesis syndrome and include testicular cancer, cryptorchidism, hypospadias and low sperm count (Skakkebæk et al., 2001). Exposure to endocrine disrupting chemicals during foetal period has been postulated to be a risk factor. In a case-control study concentrations of certain persistent organic pollutants such as polychlorinated biphenyls were higher in mothers of young men with testicular cancer compared with mothers of controls (Hardell et al., 2006b).

3.5. Dioxins and other organochlorines

Organochlorines are CMR molecules, which result either from the combustion of organic substances in contact with chlorine or from industrial chemical synthesis. Examples are dioxins, which may be produced from the incineration of halogenated plastics (such as PVC), pesticides such as hexachlorobenzene (HCB) and Polychlorinated biphenyls (PCB). On the basis of a myriad of in vitro and animal studies, it has been clearly shown that these molecules are endocrine disruptors, may interfere with the developmental process in utero and can cause cancer through a promoting or cocarcinogenic effect (Stohs, 1990; Schiestl et al., 1997; Amaral-Mendes, 2002; Mandal, 2005). Moreover, some of them, such as PCB and dioxins have been shown in addition to be mutagenic (Giri, 1986; Schiestl et al., 1997). In 1979, following the Seveso accident, IARC rated 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a 2B possible human carcinogen (IARC, 1979), but this categorisation was upgraded to a recognized class 1 carcinogen in humans in 1997 (IARC, 1997b). Since then, some cluster studies have shown an increased relative risk of sarcoma and lymphoma in the vicinity of incinerators and related this increased risk to dioxin emission (Mukerjee, 1998; Viel et al., 2000; Floret et al., 2004). Although the carcinogenic mechanism of dioxins is not clear, a strong association between chronic exposure and an increased incidence of all cancer types has been put forward (IARC, 1997b) indicating the important and extensive spectrum of their carcinogenic effect. Other suspected carcinogenic organochlorines deal with the problem of long term exposure to chlorinated water which has been shown to be associated with an increased risk of cancer including bladder cancer (Cantor et al., 1987; Zierler et al., 1988; King and Marrett, 1996; Cantor et al., 1998; Villanueva et al., 2003, 2004), colorectal cancers (Hildesheim et al., 1998; King et al., 2000) and adult leukemia (Kasim et al., 2006). Chlorine is not itself carcinogenic but can combine with organic matter in drinking water and form chlorination disinfection by-products including trihalomethanes and haloacetic acids which have been demonstrated to be mutagenic in vitro and in vivo (Geter et al., 2004) and carcinogenic in animal models (Melnick et al., 2007). Finally, the danger of organochlorines lies in the fact that, as pesticides, they are POP and accumulate in the body’s adipose tissue from which they are permanently released.

3.6. Food contaminants and food additives

Nitrates, pesticides and dioxins can contaminate drinking water and food. As pesticides, nitrates are used in intensive farming. Nitrates are not intrinsically carcinogenic, but can
be endogenously transformed into nitrates by the digestive bacterial microflora, while nitrates can be further transformed into N-nitroso compounds (NOC), i.e. into alkyl-nitrosamines and nitrosamides through nitrosation (Tannenbaum et al., 1980; Ward et al., 2005). Nitrites, alkyl-nitrosamines and nitrosamides are highly mutagenic molecules. Secondary or tertiary amines and amides are found as common dietary contaminants (Ward et al., 2005). Long-term exposure to food additives, including nitrite preservatives and artificial azo-dyes may be also involved in chemically-induced carcinogenesis, due to their mutagenic properties (Palmer and Mathews, 1986; Weisburger, 1986; Sasaki et al., 2002). In addition, Bisphenol A, a xenoestrogen used in plastic food containers, because it can migrate in food and be repetitively ingested, has been recently suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing suspected to be carcinogenic in humans on the basis of gen used in plastic food containers, because it can migrate in food and be repetitively ingested, has been recently suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing.

3.7. Metals and metalloids

Several metals and metalloids have been rated as certain or probable carcinogens by the (IARC, 1980). Inhalation of arsenic oxides can cause lung cancer, but if they are swallowed, cancer can develop in bladder, kidney, liver and lung (Szymanska-Chabowska et al., 2002). Thus exposure to arsenic oxides has been reported to be associated with a very large spectrum of common cancer types. Aside from arsenic oxides exposure, lung cancer has also been reported to be associated with exposure to many metals, including lead, hexavalent chromium and nickel (IARC, 1990). Furthermore, exposure to hexavalent chromium or nickel has been found to be associated with nasopharyngeal carcinoma, exposure to lead or mercury to brain tumors, exposure to lead or cadmium to kidney cancer and exposure to cadmium to prostate cancer (Hayes, 1997; Cocco et al., 1999; Landrigan et al., 2000; Navas-Acien et al., 2002; Wesseling et al., 2002; Waalkes, 2003). The mechanisms of action of metals and metalloids are not clear yet. They could act as cocarcinogens by activating procarcinogens in the liver (Hayes, 1997; Cantor et al., 2006) or by increasing the promoting effect of estrogens (Gurpide et al., 1984). They could also act by replacing the natural enzyme-associated metal, thus inactivating the metabolic pathway of key enzymes. Carcinogenic metals and metalloids, such as arsenic, cadmium and nickel, and putative carcinogens including cobalt and lead can inhibit zinc finger containing DNA repair proteins. Damage of zinc finger in DNA repair proteins can therefore be regarded as a novel mechanism in carcinogenesis (Wiikiewicz-Kucharczyk and Bal, 2006). Moreover, some metals and metalloids may also be mutagenic through other mechanisms. Indeed many of them can interact with DNA. Metal compounds such as Chromium(VI) are taken up by cells as chromate anion and are reduced intracellularly via reactive intermediates to stable Cr(III), which can directly interact with DNA. These Cr(III) intermediates may affect DNA by terminating replication or reducing replication fidelity thus leading to mutations (Snow, 1991, 1994). Cr(III) can also form DNA-proteins and DNA-aminocids and glutathione crosslinks (Zhitkovich, et al., 1995, 1996). Platinum compounds (i.e. cis-diaminedichloroplatinum) are well-known strand breakers. They can form DNA crosslinks and DNA-protein crosslinks leading to mutations (Zwelling et al., 1979; Donahue et al., 1990). There is evidence that nickel may act via an epigenetic mechanism involving heterochromatic regions of the genome (Costa, 1991; Salnikow et al., 1994). However, how contamination of the environment by metals and metalloids may relate to the actual growing incidence of cancer is still under investigation.

3.8. Medicines and cosmetics

The best acknowledged class of pharmaceutical drugs classified as carcinogens corresponds to hormonal products, which include oral contraceptives and hormone replacement therapy (IARC, 1996b; Beral, 2003), as well as selected anti-estrogens such as tamoxifen (IARC, 1996b). Other carcinogenic medicines include many anticancer chemotherapeutic agents which can cause the late occurrence of secondary cancers in apparently cured cancer patients due to their mutagenic properties (Belpomme et al., 1974; Etiemble et al., 1979; Zahm and Devesa, 1995). However, the ratio between benefit and toxicity is so high that the use of chemotherapeutic agents in oncology is not questioned although efforts are made to adapt the dose or look for replacement products. By contrast the question is more difficult for drugs given to healthy persons. A serious
risk-benefit analysis has to be carried out for women, be-
they in search of contraception, management of menopau-
sal symptoms by using substitutive treatments or preven-
tion of breast cancer by tamoxifen. Several years ago, some
anticancer agents were found to contaminate industrial
workers involved in drug making and manufacturing, and
nurses working in oncology departments, so that legal
protection has followed, prohibiting their use by pregnant
women (Sorsa and Anderson, 1996; Sorsa et al., 1985). A
pending question remains, however, release of these
mutagenic drugs in the environment through urine.
Cosmetics which include some recognized carcinogenic
molecules such as formaldehyde or hormonal products or
some putative ones such as phthalates or parabens have
been presently the object of many concerns. Parabens in
underarm deodorants has been suspected to be an
The hypothesis was based on observations showing a
disproportionately high incidence of breast cancer in the
upper outer quadrant of the breast and that the left breast
is more prone to the development of cancer than the right
one in women as well as in men. However, this hypothesis
is not validated yet and to our knowledge, no formal study
has been designed and carried out to clarify the role of
parabens. By contrast, it has been found that permanent
hair-dyes, containing aromatic amines may increase the
relative risk of bladder cancer by 3.3-fold among regular
users relative to non-users (Gago-Dominguez et al., 2001),
but by 1.22–1.50 in a more recent meta-analysis, indicating
that personal use of hair-dyes increases bladder cancer risk
only by 22–50% (Huncharek and Kupelnick, 2005). In
addition, it has been shown that permanent hair-dyes
increase the relative risk of adult acute leukemia by 2.4
in women for a use of up to six times per year for more
than 15 years (Rauscher et al., 2004). Although these
data have been recently challenged (Takkouche et al.,
2007), they have been confirmed in a systematic review of
the scientific literature published since 1992: positive
associations between personal hair-dye use and bladder
cancer, acute leukemia, lymphoma and myeloma have
been clearly observed in well-designed studies which have
suggested that negative results may in fact be explained
by differences in susceptibility to exposures (Rollison et al.,
2006).

4. Conclusion

Finally, from this overview, although there are still some
persisting areas of uncertainty, it clearly appears that due
to their mutagenic and/or promoting properties or to their
cocarcinogenic effects, many exogenous environmental
factors, including viruses, radiations and xenocarcinogens
can contribute to cause a variety of cancers. In Table 2,
we summed up most of the recognized environmental
factors that are considered to be involved in carcinogenesis and
tried to establish the weight of evidence according to which
they can express their carcinogenic (i.e. mutagenic and/or
promoting) or cocarcinogenic effects. This analysis could
open a new way in considering the actual causes of cancers:
it remains indeed to estimate the overall risk fraction for
cancer attributable to these environmental factors.

| Table 2 |
| Classification of some exogenous environmental factors according to their carcinogenic and cocarcinogenic properties |
| Mutagen | Promoter | Cocarcinogen |
| Microorganisms |
| EBV | M | P |
| HBV/HCV | M | P |
| HMMTV | M | C (?) |
| HHV-8 | P |
| HIV | P |
| HTLV-1 | M |
| HPV | M |
| Helicobacter Pylori | C |
| Radiations |
| Radioactivity | M | P |
| UV | M | P |
| EMF | M | P (?) | C |
| Particles and Xenochemicals |
| Air fine particles | M | C |
| Asbestos | M | C |
| Azotic dyes | M | C |
| Biphenol A | M (?) | P |
| β Naphthylamine | M | C |
| Benzene and derived molecules | M | C |
| DEHP, BBP | M | P |
| Dioxins | P |
| Formaldehyde and derived | M | P |
| Hormonal residues | M | C |
| Metals, metalloids | M | C |
| N-nitroso compounds | M | C |
| NO2 | M | P |
| Organochlorines | M (some ?) | P |
| PAH | M (≥ 5 rings) | P (< 5 rings) | C |
| PCB | M (some) | P |
| Pesticides | M (some) | P |
| Vinyl chlorides (monomers) | M |

5. References

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