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Chemical Carcinogen and Cancer Risk: An overview

Ashwani Arya*[1], Sandeep Arya[2] and Minakshi Arya[3]

[1] School of Pharmaceutical Education and Research, South Campus, Bhainswal Kalan, Bhagat Phool Singh Women University, Khanpur Kalan, Sonepat (Haryana), India.
*[*2]Institute of Environment & Developmental Studies, Bundelkhand University, Jhans, (UP), India*
[3]Dept. of Environmental Science and Engg. Guru Jambheshwar University of Science and Technology, Hisar (Haryana), India

ABSTRACT

Human risk estimates and cancer etiology attributed to the consumption of mutagens and carcinogens are difficult to evaluate, as these toxicants come from numerous sources. People are continuously exposed exogenously to varying amounts of chemicals that have been shown to have carcinogenic or mutagenic properties in experimental systems. The word carcinogenic was defined as the capacity of a compound to unchain the process of cancer development in man and animals under the appropriate conditions, by acting on one of several organs or tissues. Epidemiological studies of cancer incidence demonstrated that the risk of developing cancer varies between population groups. Unhealthy lifestyle habits such as: inhalation of tobacco and related products; the ingestion of certain foods are responsible for higher incidences of certain types of neoplasias in a number of population groups. Exposure can occur exogenously when, these agents are present in food, air or water, and also endogenously when they are products of metabolism or pathophysiologic states. It has been estimated that exposure to environmental chemical carcinogens such as polycyclic aromatic hydrocarbon, aromatic amines, amino azo dyes, N- Nitro compounds, natural carcinogens (aflatoxin βI and asbestos) may contribute significantly to the causation of a sizable fraction, perhaps a majority, of human cancers.

Key words: Chemical Carcinogen, Asbestos, Aflatoxin, Cancer, Aflatoxin, Aromatic Amines.

INTRODUCTION

Human risk estimates and cancer etiology attributed to the consumption of mutagens and carcinogens are difficult to evaluate, as these toxicants come from numerous sources [1]. Public opinion considers cancer to be an increasingly threatening disease, affecting people of all ages. After cardiovascular diseases, it is the second cause of death amongst the global population [1,

2]. People tend to accept cancer with stoicism and submit themselves to prolonged periods of treatments, which are not always effective [2]. The word carcinogenic was defined as the capacity of a compound to unchain the process of cancer development in man and animals under the appropriate conditions, by acting on one of several organs or tissues [3]. From an experimental point of view, a compound is considered carcinogenic, when its administration to laboratory animals induces a statistically significant rise in the incidence of one or more histological types of neoplasia, compared with the animals in the control group which, are not exposed to the substance [4].

The factors responsible for cancer development are classified as exogenous and endogenous [5] . Unhealthy lifestyle habits such as: inhalation of tobacco and related products; the ingestion of certain foods and their contamination by mycotoxins; are responsible for higher incidences of certain types of neoplasias in a number of population groups [5]. Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes, and induces the uncontrolled, malignant division, ultimately leading to the formation of tumors [6]. Cancer is a leading cause of death worldwide. The disease accounted for 7.4 million deaths (around 13% of all deaths) in 2004 [1] . The transformation from a normal cell into a tumour cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumours [6]. Epidemiological studies of cancer incidence demonstrated that the risk of developing cancer varies between population groups and these differences are associated with lifestyle factors and habits. It has been estimated that exposure to environmental chemical carcinogens such as polycyclic aromatic hydrocarbon, aromatic amines, amino azo dyes, N- Nitro compounds, natural carcinogens (aflatoxin βI and asbestos) may contribute significantly to the causation of a sizable fraction, perhaps a majority, of human cancers [7, 8, 9, 10,11] .

Carcinogenic Mechanisms

Despite the proof that most chemical carcinogens undergo metabolic conversion into DNA-reactive intermediates, some compounds do not bind to DNA and are not mutagenic, yet they are carcinogenic in animal models and possibly also in humans [7]. When chemical carcinogens are internalized by cells, they are often metabolized, and the resulting metabolic products are either excreted or retained by the cell. Inside the cell, carcinogens or their metabolic products can either directly or indirectly affect the regulation and expression of genes involved in cell-cycle control, DNA repair, cell differentiation or apoptosis. Some carcinogens act by genotoxic mechanisms, such as forming DNA adducts or inducing chromosome breakage, fusion, deletion, mis-segregation and non-disjunction. For example, carcinogenic ions or compounds of nickel, arsenic and cadmium can induce structural and numerical chromosome aberrations. Others act by non-genotoxic mechanisms such as induction of inflammation, immunosuppression, formation of reactive oxygen species, activation of receptors such as arylhydrocarbon receptor (AhR) or oestrogen receptor (ER), and epigenetic silencing. Together, these genotoxic and non-genotoxic mechanisms can alter signal-transduction pathways that finally result in hypermutability, genomic instability, loss of proliferation control, and resistance to apoptosis — some of the characteristic features of cancer cells [7, 12] .

Carcinogens exposure and cancer risk

Epidemiological studies of cancer incidence demonstrated that the risk of developing cancer varies between population groups and these differences are associated with lifestyle factors and habits. It has been estimated that exposure to environmental chemical carcinogens such as polycyclic aromatic hydrocarbon, aromatic amines, amino azo dyes, N- Nitro compounds,

natural carcinogens (aflatoxin βI and asbestos) may contribute significantly to the causation of a sizable fraction, perhaps a majority, of human cancers [7, 8, 9, 10,11] (See the Table -1).

Table:1 Carcinogens exposure and cancer risk

Group	Compound	Afected organs/ Cancer type	References
Polycylic aromatic hydrocarbon	Benzo(a)pyrene Polychlorinated biphenyls	Skin, lungs, stomach Liver skin	[7, 8]
Aromatic amines/ amides	2-acetylaminofluroene 4-Aminobiphenyl 2-naphthylamine	Liver, Bladder Bladder Bladder	[7, 13, 14]
Aminoazo dyes	o-Aminoazotoluene N, N –dimethyl-4-aminoazobenzene	Liver, lungs, bladder Lungs , liver	[9]
N-nitroso compounds	N-Nitrosodimethylamine	Liver, lungs, kidneys	[15, 16]
Halogenated compound	Trichloroethylene	Experimental results showed liver, kidneys and lung cancer.	[17]
Natural Carcinogen	Aflatoxin b1 Asbestos	Liver Lung, Mesothelioma	[7, 18, 19, 20]
Metals	Aresenic Cadmium Nickel	Skin, lungs, liver Lungs, prostate, kidney Lungs, nasal cavity	[21, 22]

Aflatoxin Exposure and Hepatocellular Carcinoma Risk

There are many natural carcinogens. Aflatoxin B_1, which is produced by the fungus *Aspergillus flavus* growing on stored grains, nuts and peanut butter. As far back as the 1930s, industrial smoke and tobacco smoke were identified as sources of dozens of carcinogens, including benzo[*a*]pyrene, tobacco-specific nitrosamines such as nitrosonornicotine, and reactive aldehydes such as formaldehyde [23] . A causative relationship between exposure to aflatoxin, a strongly carcinogenic mold-produced contaminant of dietary staples in Asia and Africa, and elevated risk for primary liver cancer has been demonstrated through the application of well-validated biomarkers in molecular epidemiology [20,24]. The aflatoxins are ubiquitous contaminates of the human food supply throughout the economically developing world. The adverse toxicological consequences of these compounds in populations are quite varied owing to a wide range of exposures that lead to acute effects, including rapid death, and chronic outcomes, such as hepatocellular carcinoma (HCC) [10]. Aflatoxin exposures multiplicatively increase the risk of liver cancer [7]. The public health impact of aflatoxin exposure is pervasive in economically developing countries. The adverse health consequences of aflatoxins in populations are quite varied, eliciting acute effects, such as rapid death, and chronic outcomes, such as hepatocellular carcinoma [7, 20] .

The Monographs Program on the Evaluation of Carcinogenic Risks to Humans of the International Agency for Research on Cancer (IARC) publishes authoritative carcinogenic risk assessments based on examination by experts of all relevant information to assess the strength of available evidence that exposures to the chemicals could alter the incidence of cancer in humans [7]. The mold-produced aflatoxins are among the few environmental chemicals in this list that were first identified as carcinogens in animals, and subsequently shown to pose carcinogenic risks to humans through epidemiologic studies. Extensive research has produced a comprehensive database addressing risks resulting from the high prevalence of their contamination of major food staples in many parts of the world, together with their carcinogenic potency in animals. Indeed, the aflatoxin-liver cancer risk relationship is among the most extensively documented examples demonstrating the significance of a widely disseminated environmental chemical carcinogen as a determinant of increased risk for a major form of cancer

[20,7]. Aflatoxins belong to a large group of mycotoxins, toxic metabolites that contaminate food and feed commodities during growth of certain spoilage molds. In addition to causing acute toxicity, aflatoxins are also liver carcinogens in experimental animals. These data implicate aflatoxin as a potential liver carcinogen in humans [20].

Health Hazards of Exposure to Asbestos?

Asbestos (in Greek meaning "unquenchable") is a set of six naturally occurring silicate minerals exploited commercially for their desirable physical properties. The inhalation of asbestos fibres can cause serious illnesses, including malignant lung cancer, mesothelioma (a formerly rare cancer strongly associated with exposure to asbestos), and asbestosis (a type of pneumoconiosis) [10]. Although asbestos is a hazardous material it can only pose a risk to health if the asbestos fibres become airborne and are then inhaled. Therefore, most asbestos materials pose little risk unless they are disturbed in some way that allows the fibres to be released into the air. Inhalation of asbestos fibres can lead to serious diseases such as lung cancer, mesothelioma (a cancer of the linings of the lungs - the pleura, or lower digestive tract - the peritoneum) and asbestosis (a chronic fibrosis of the lungs) [10] .

Asbestos is the generic name for a group of six naturally occurring fibrous silicate minerals, including the fibrous serpentine mineral chrysotile and the five fibrous amphibole minerals actinolite, amosite, anthophyllite, crocidolite, and tremolite. Asbestos minerals possess a number of properties useful in commercial applications, including heat stability, thermal and electrical insulation, wear and friction characteristics, tensile strength, the ability to be woven, and resistance to chemical and biological degradation. The forms are ranked from greatest to least tensile strength as follows: crocidolite, chrysotile, amosite, anthophyllite, tremolite, and actinolite. Their ranking from greatest to least acid resistance is tremolite, anthophyllite, crocidolite, actinolite, amosite, and chrysotile. The forms that have been used commercially are chrysotile, anthophyllite, amosite, and crocidolite. Asbestos has been used in roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials, coatings, plastics, textiles, paper, and other products [25, 26]. Asbestos and all commercial forms of asbestos are known to be human carcinogens based on sufficient evidence of carcinogenicity in humans. Studies in humans have demonstrated that exposure to asbestos causes respiratory-tract cancer, pleural and peritoneal mesothelioma (tumors of the membranes lining the chest and abdominal cavities and surrounding internal organs), and other cancers [26].

Asbestos has been classified as a known human carcinogen (a substance that causes cancer) by the U.S. Department of Health and Human Services, the EPA, and the International Agency for Research on Cancer [18]. Asbestos exposure and smoking increased the risk of lung cancer in a synergistic manner (i.e., the effects of co-exposure on risk were multiplicative, rather than additive). The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the carcinogenicity of asbestos in humans [27]. Since asbestos was reviewed for listing in the First Annual Report on Carcinogens and by IARC, additional information has been published regarding asbestos exposure and cancer other than mesothelioma and lung cancer (mainly lymphoma and cancer of the larynx, digestive tract, and kidney); however, the evidence that asbestos causes cancer at these other tissue sites remains inconclusive [18, 27] . Studies have shown that exposure to asbestos may increase the risk of lung cancer and mesothelioma (a relatively rare cancer of the thin membranes that line the chest and abdomen). Although rare, mesothelioma is the most common form of cancer associated with asbestos exposure [10]. In addition to lung cancer and mesothelioma, some studies have suggested an association between asbestos exposure and gastrointestinal and colorectal cancers, as well as an elevated risk for cancers of the throat, kidney, esophagus, and gallbladder [10, 28]. However,

the evidence is inconclusive. Asbestos exposure may also increase the risk of asbestosis (an inflammatory condition affecting the lungs that can cause shortness of breath, coughing, and permanent lung damage) and other nonmalignant lung and pleural disorders, including pleural plaques (changes in the membranes surrounding the lung), pleural thickening, and benign pleural effusions (abnormal collections of fluid between the thin layers of tissue lining the lungs and the wall of the chest cavity). Although pleural plaques are not precursors to lung cancer, evidence suggests that people with pleural disease caused by exposure to asbestos may be at increased risk for lung cancer [19].

Heterocyclic Amine and Human Cancer

Human risk estimates and cancer etiology attributed to the consumption of mutagens and carcinogens in our food are difficult to evaluate, as these toxicants come from numerous sources in our diet [7]. Mycotoxins, such as aflatoxin B*l* are formed by fungi growing on poorly stored grain products and can be strong liver carcinogens. PAH (Poly Aromatic Hydrocarbon such as benzo[a]pyrene, as combustion products, are present in wood fires or flame grilling and can be deposited on food from fat dripping onto the coals during this type of cooking [29, 30]. Another important class of carcinogens in food is the heterocyclic amines [30] . These compounds are potent mutagens and moderately potent carcinogens at numerous organ sites in rodents and in the liver of non-human primates. They are produced when muscle foods are heated above 180 ◦C for long periods of time. At least sixteen, and possibly more, different heterocyclic amines have been isolated from cooked foods. However, a causal linkage has not been firmly established, since some welldesigned studies found no statistically significant positive correlation between consumption of diets containing heterocyclic amines and incidence of colon or other cancers. A related chemical, acrylamide, has recently been identified in starch-based foods such as potato chips and French fries cooked using high temperature deep-frying and baking methods. This compound is weakly- or non-mutagenic in in vitro tests and weakly carcinogenic to experimental animals, but in comparison to the heterocyclic amines are present in large (part-per million) quantities in these starch-derived products [7, 31, 14]. Heterocyclic amines produced from overcooked foods are extremely mutagenic in numerous in vitro and in vivo test systems. One of these mutagens, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), induces breast tumors in rats and has been implicated in dietary epidemiology studies as raising the risk of breast cancer in humans [30]. Cooking food at high temperatures, for example grilling or barbecuing meats, can lead to the formation of minute quantities of many potent carcinogens. Charring of food resembles coking and tobacco pyrolysis, and produces similar carcinogens. There are several carcinogenic pyrolysis products, such as polynuclear aromatic hydrocarbons, which are converted by human enzymes into epoxides, which attach permanently to DNA. Pre-cooking meats in a microwave oven for 2–3 minutes before grilling shortens the time on the hot pan, and removes heterocyclic amine (HCA) precursors, which can help minimize the formation of these carcinogens.. Reports from the Food Standards Agency have found that the known animal carcinogen acrylamide is generated in fried or overheated carbohydrate foods (such as french fries and potato chips) [32, 33] .

Heterocyclic amines (HCAs) such as 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx,), and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) are found in meats cooked at high temperatures. In rodents, MeIQx induces lung tumors. In conclusion, MeIQx may be associated with lung cancer risk, but DiMeIQx and PhIP are probably not associated with lung cancer risk [30, 34] . One of these mutagens, 2-amino-1-methyl-6- phenylimidazo[4,5-b]pyridine (PhIP), induces breast tumors in rats and has been implicated in dietary epidemiology studies as raising the risk of breast cancer in humans. This work is suited to investigate individual exposure and risk, especially for breast

cancer, from these potent dietary mutagens [30]. Heterocyclic amines represent an important class of carcinogens in foods. They are mutagens and carcinogens at numerous organ sites in experimental animals, are produced when meats are heated above 180 degrees ^{0}C for long periods. Heterocyclic amines (HCAs) are the carcinogenic chemicals formed from the cooking of muscle meats such as beef, pork, fowl, and fish. HCAs form when amino acids (the building blocks of proteins) and creatine (a chemical found in muscles) react at high cooking temperatures [30, 35] . Researchers have identified 17 different HCAs resulting from the cooking of muscle meats that may pose human cancer risk. Studies have shown that an increased risk of developing colorectal, pancreatic, and breast cancer is associated with high intakes of well-done, fried, or barbequed meats. Four factors influence HCA formation: type of food, cooking method, temperature, and time. HCAs are found in cooked muscle meats; other sources of protein (milk, eggs, tofu, and organ meats such as liver) have very little or no HCA content naturally or when cooked. Temperature is the most important factor in the formation of HCAs. Frying, broiling, and barbecuing produce the largest amounts of HCAs because the meats are cooked at very high temperatures [36, 37].

2-Acetylaminofluorene is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. When incorporated in the diet, 2-acetylaminofluorene induced increased incidences of carcinomas of the urinary bladder and subcutaneous carcinomas on the face (possibly arising from the auditory canal) in rats of both sexes. The same route of administration of 2-acetylaminofluorene in another study induced increased incidences of carcinomas of the liver and urinary bladder in mice of both sexes. In a separate study, incorporation in the diet induced a high incidence of hepatocellular carcinomas, testicular mesotheliomas, and Zymbal gland tumors in rats [7] . Because of the potency of this compound and its known carcinogenic action, it is used extensively as a positive control for assaying other compounds for carcinogenicity. No data were available to evaluate the carcinogenicity of 2- acetylaminofluorene in humans. Despite this complexity, carcinogenicity in mice and rats often predicts carcinogenicity in humans [7] .

Carcinogens In Cigarettes

Cigarette smoking increases the risk of all histological types of lung cancer. It causes cancer of the oral cavity, and this risk is greatly increased by the use of smokeless tobacco or by alcohol consumption in combination with smoking [38]. Cigarette smoking is also causally associated with laryngeal, oropharyngeal and hypopharyngeal cancer, and increases the risks for sinonasal and nasopharyngeal cancer. Cigarette smoking is causally associated with cancer of the esophagus, both squamous cell carcinoma and adenocarcinoma. Furthermore, cigarette smoking causes cancer of the stomach, liver, and pancreas, as well as transitional cell carcinomas of the bladder, ureter and renal pelvis, and renal cell carcinoma. Finally, cigarette smoking is also a cause of squamous cell cervical carcinoma and myeloid leukaemia, and the risk of colorectal cancer can also be increased by smoking. Environmental tobacco smoke (ETS) causes lung cancer. Smokeless tobacco products are established causes of oral cavity cancer. Most tobacco carcinogens require metabolic activation to exert their carcinogenic effects; there are competing detoxification pathways and the balance between metabolic activation and detoxification differs among individuals and affects cancer risk. In general, the stronger carcinogens such as polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and aromatic amines occur in lower amounts in cigarette smoke (1–200 ng per cigarette) than the weaker carcinogens such as acetaldehyde (nearly 1mg per cigarette). The total amount of carcinogens in cigarette smoke add up to 1–3 mg per cigarette (similar to the amount of nicotine, 0.5–1.5 mg per cigarette), although most of this total is comprised of weaker carcinogens such as acetaldehyde, catechol, and isoprene. Levels of PAH in unburned tobacco are typically low. Nitrosamines, particularly the

tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N_-nitrosonornicotine (NNN), are by far the most prevalent strong carcinogens in unburned tobacco [39] . The levels of NNK and NNN in smokeless tobacco products are hundreds to thousands of times higher than those of carcinogenic nitrosamines in any other consumer product designed for ingestion. NNK, several other cigarette smoke nitrosamines, and furan are effective hepatocarcinogens in rats. NNK and its major metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are the only known pancreatic carcinogens to which people who use tobacco products are exposed, and biochemical data from studies with human tissues support their role in smoking related pancreatic cancer. The aromatic amine, 4-aminobiphenyl (4-ABP), is an environmental and occupational contaminant generated mainly from cigarette smoking, the combustion of fossil fuels and also from rubber, coal, textile and printing processing industries. 4-ABP has been shown to be a major etiological agent of human bladder cancer, and also a potent urinary bladder carcinogen in experimental animals. Cigarette smokers have a 2–10-fold increased incidence of bladder cancer and individuals occupationally exposed to 4-ABP have a high incidence of bladder cancer [40] .

Tobacco smoke contains over 4000 chemical compounds, many of which are carcinogenic or otherwise toxic. Use of tobacco products provides a clear example of cancer causation by a life-style factor involving carcinogen exposure. Tobacco carcinogens and their DNA adducts are central to cancer induction by tobacco products, and the contribution of specific tobacco carcinogens (e.g. PAH and NNK) to tobacco-induced lung cancer, can be evaluated by a weight of evidence approach [23]. Cigarette smoking increases the risk of all histological types of lung cancer. It causes cancer of the oral cavity, laryngeal, oropharyngeal and hypopharyngeal cancer, and increases the risks for sinonasal and nasopharyngeal cancer. Cigarette smoking is causally associated with cancer of the esophagus, both squamous cell carcinoma and adenocarcinoma. Furthermore, cigarette smoking causes cancer of the stomach, liver, and pancreas, as well as transitional cell carcinomas of the bladder, ureter and renal pelvis, and renal cell carcinoma. Finally, cigarette smoking is also a cause of squamous cell cervical carcinoma and myeloid leukaemia, and the risk of colorectal cancer can also be increased by smoking. Environmental tobacco smoke (ETS) causes lung cancer. Smokeless tobacco products are established causes of oral cavity cancer [23]. Carcinogens are the key connection between nicotine addiction and cancer. Nicotine addiction is the major reason why people continue to use tobacco products. While nicotine itself is not carcinogenic, each cigarette or dip of smokeless tobacco contains a mixture of carcinogens, tumor promoters, and co-carcinogens. Most tobacco carcinogens require metabolic activation to exert their carcinogenic effects; there are competing detoxification pathways and the balance between metabolic activation and detoxification differs among individuals and affects cancer risk [23]. NNK and its major metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are the only known pancreatic carcinogens to which people who use tobacco products are exposed, and biochemical data from studies with human tissues support their role in smoking related pancreatic cancer. The most probable cause of leukemia in smokers is benzene, which occurs in large quantities in cigarette smoke, and is a known cause of acute myelogenous leukemia in humans.. Polycyclic aromatic hydrocarbons are ubiquitous environmental chemical carcinogens existing in cigarette smoke, charred foods, and exhaust gas from incomplete combustion of fossil fuels. Benzo[a]pyrene (B[a]P), as the first identified carcinogenic component of polycyclic aromatic hydrocarbons, is the most extensively studied carcinogen in cigarette smoke and has been regarded as a critical mediator of lung cancer for a long time [29].

Absorption and Metabolism of Chemical Carcinogens

Chemical carcinogens may be absorbed in a number of ways (oral, inhalator, cutaneous, and injection) and distributed across several tissues. Absorption depends on the physicochemical properties of the substance and can take place via passive or active transport. The substances absorbed orally pass through the liver and only then are they distributed in the body; those absorbed in the lung are distributed by the blood before reaching the liver at a later stage [41]. Those carcinogenic compounds classified as direct act directly on DNA, butmost require enzymatic conversion and are thus labelled as indirect or procarcinogens [7] .Metabolic activation is controlled by phase I reactions, while phase II reactions protect the body through the transformation of activated compounds into inert products which are easily eliminated from the body [42] . The performance of metabolic enzymes is essential for understanding chemical carcinogenesis and learning the differences between species as far as their susceptibility to neoplasic development is concened [43] . The enzymes in phase I participate in the reactions of oxidation, reduction and hydrolysis, and are classified as oxidoreductases (cytochrome P450 dependent monooxygenases, flavine monooxygenases, cyclooxygenases and alcohol dehydrogenase) and hydrolases (epoxide hydrolases). Phase II enzymes participate in the conjugation and inactivation of chemical carcinogens and include transferases (glutathione S-transferases, Nacetyltransferases, UDP-glucuronosyltransferases, sulphotransferases) [43] . Although these enzymes were originally only thought to be involved in the detoxification stages of biotransformation, they can also contribute to the activation of certain procarcinogens *in vivo [7* .

Metabolic activation occurs predominantly in the liver at the plain endoplasmic reticulum where the cytochrome P450 is more abundant, and to a lesser degree in the bladder, skin, gastrointestinal system, oesophagus, kidneys, and lungs [41] . During this phase the cytochrome P450 mono-oxygenases introduces a reactive polar group into the carcinogenic, making it lipophylic. It then converts it into a powerful electrophilic product capable of establishing adducts with DNA [42] . Phase II reactions are catalysed by hepatic and extra hepatic, cytoplasmic and cytochromic enzymes, acting separately or joined together [43] . Conjugation reactions enable these enzymes to decompose the polar group in glucose, amino acids, glutathione and sulphate, which are less toxic metabolites that are more soluble in water and more easily expelled by the urine and bile [41] . Peroxidations also occur parallel to metabolic reactions with the continuous production of reactive oxygen species (ROS) [44, 12] . These radicals are associated with several chronic diseases including chemical carcinogenesis [12]. TheROS damage DNA, RNA, and proteins by chemical reactions such as oxidation, nitration/ nitrosation and halogenation. This leads to an increase in mutations and alterations in the functions of important enzymes and proteins [42] . Several experiments have proved that chemical compounds, which create ROS in excess, encourage initiation, promotion and neoplasic progression through genotoxicity [12, 44]. The impact of the ROS controlled by a cellular mechanism that operates at different levels: metabolism; reactions that maintain the redox balance in cells; transduction of the signal regulator of oxidation and DNA reparation. Park et al [42] says that the same enzyme may have the capacity to activate one chemical and deactivate another, all depending on its chemical structure. The specificity of the activation systems of different tissues regulate neoplasic development and is dependent on genetic polymorphism, which requires the expression and distribution of the enzymes involved in phase I and II reactions, and the resulting susceptibility to cancer development [7] . People with a high quantity of phase I and a low quantity of phase II enzymes have a higher probability of synthesizing intermediate compounds and exhibiting more DNA damage [46] . The previously described metabolic methods are equally important for both humans and animals, although there exist qualitative and quantitative differences between them [43] . Several studies have been developed

in order to evaluate the differences between several exogenous and endogenous factors on individual susceptibility to carcinogenesis [43].

Carcinogenic Classification

Carcinogenic classification is by no means consensual. It is not easy to incorporate a carcinogenic compound into a certain group because the information obtained from different studies is increasingly complex. Some authors classify them in function of their participation in each of the stages of carcinogenesis. In this way, incomplete carcinogens are mutagenic chemicals that instigate irreversible DNA damage. A complete carcinogen displays properties of both initiators and promoters simultaneously depending on the dosage and exposure time. Other authors classify chemical carcinogens in function of their mechanisms of action as being genotoxic and non-genotoxic (mitogenic and cytogenic) [47] . The knowledge about the mechanism of action of non-genotoxic carcinogens is known to be inferior to that of genotoxic carcinogens. Genotoxic carcinogens are complete carcinogens and qualitatively and quantitatively change a cell's genetic information. They exhibit a direct analogy between their structure and activity, are mutagenic on in vitro assays, are active in high doses, and may affect several animal species, and damage different organs [47, 7]. In high doses, they cause toxicity and cell proliferation, increasing DNA replication and influencing its carcinogenic activity. Following transmembranar diffusion they are metabolized in electrophilic compounds that enter the nucleus and interact with nucleophilic sites (DNA, RNA and proteins) changing their structural integrity and establishing covalent bonds known as adducts. The formation of adducts constitutes the first critical step of carcinogenesis and if these are not repaired before DNA replication then mutations may occur in the proto-oncogenes and tumour suppressor genes, which are essential for the initiation stage [5] . The number of adducts formed by carcinogens is changeable and each of them may cause a specific damage to DNA. Mutations linked to adducts can appear through deletion, frameshift, or by nucleotide substitution [48] . Mutations cause an undefined number of cell changes, translated into aberrant protein expression and in changes in cell cycle control. Adducts assume importance in chemical carcinogenesis because of the way they change DNA, possibly inducing an incorrect transcription and causing mutations of the new DNA chain. The existence of many adducts can break the DNA chain, causing mutation or loss of genetic material. Adduct repair is coordinated by several enzymes and controlled by different genes. It can be done via the excision of bases, or nucleotides, recombined repair or mismatch repair [49]. The identification of adducts suggests that chemical carcinogens are absorbed, metabolized and distributed by tissues, thus fleeing from the body's detoxification and repair mechanisms. There are also monoclonal and polyclonal antibodies available on the market which are used to identify adducts by immunohistochemistry. There is a positive correlation between the quantity of adducts detected in animal models and the number of neoplasias developed [40]. Non-genotoxic carcinogens act as promoters and do not need metabolical activation. They do not react directly with DNA, do not raise adducts and show negative on mutagenicity tests carried out in vivo and in vitro [47] . These compounds modulate growth and cell death, potentate the effects of genotoxic compounds, do not show a direct correlation between structure and activity, and their action is limited by their concentration. They are tissue- and species-specific [47]. Non-genotoxic carcinogens are classified as cytotoxic and mitogenic in function of whether their activity is mediated by a receptor or not. Mitogenic compounds such as phorbol esters, dioxins, and phenobarbital induce cell proliferation in target tissue through interaction with a specific cellular receptor. Cytotoxic carcinogens cause cell death in susceptible tissues followed by compensatory hyperplasia, taking chloroform as an example [47]. If the carcinogen dose is high, some cells cannot survive. The more that nearby cells increase the number of cell divisions through regenerative procedures, the more likely it is that they will end up being prematurely recruited for the cell cycle and that the time available for reparation DNA will be inferior – this

increases the probability of mutations occurring. On the other hand, necrosed cells are destroyed by the immune system and ROS, reactive nitrogen species (RNS), and proteolytic enzymes are produced [44]. When production of these ROS and RNS exceeds the cellular anti-oxidant capacity, it may cause oxidative damages to lipids, proteins, carbohydrates, and nucleic acids, leading to carcinogenesis and cell death [44].

CONCLUSION

A carcinogen is any substance, radionuclide or radiation that is an agent directly involved in the exacerbation of cancer or in the increase of its propagation. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes. Carcinogens can be classified as genotoxic or nongenotoxic. Exogenous exposure to carcinogens can occur through food consumption, air, occupational exposure. It has been estimated that exposure to extrinsic or environmental carcinogens may contribute significantly to the causation of a sizable fraction of human cancers. The prediction of chemical carcinogenicity is of great importance to human risk assessment.

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