Chapter 1 : Protein Adduct Forming Chemicals for Exposure Monitoring: Chemicals Selected for Further St

The IARC Scientific Publications aim to disseminate the results of IARC-coordinated scientific research. Topics span the range of IARC's research scope, and the series includes the Cancer Incidence in Five Continents volumes.

Structural and molecular formulae and relative molecular mass 1. Colourless gas with a characteristic pungent odour; colourless liquid under pressure Boiling-point: Insoluble in water; soluble in ethanol, ether, acetone, benzene and chloroform Vapour pressure: Production and use 1. One plant in China reported a production capacity of million tonnes per year in Loyal Gain, Use According to a notice in the Federal Register Anon. Current applications of vinyl bromide include its use as an intermediate in the synthesis of pharmaceutical products, as a component of fire extinguishers in blends with compounds that contain fluorine, as a monomer in the formation of copolymers that possess flame-retardant properties and as a starting material for the preparation of vinylmagnesium bromide, which is a component of variety of other polymers Far Research, According to the Chinese manufacturer Loyal Gain , vinyl bromide is also used in the pharmaceutical industry in the production of the coenzyme Q10 and in the synthesis of organic bromo compounds. Occurrence Vinyl bromide is not known to occur naturally in the environment. Occupational exposure Vinyl bromide has been available commercially since Occupational exposure may occur during the production of vinyl bromide and its polymers. Other estimates of the number of workers exposed to vinyl bromide in Europe are available only from the Finnish Register of Occupational Exposure to Carcinogens which reported one individual who was notified as having been exposed to vinyl bromide in Saalo et al. Median 8-h time-weighted average exposures at a vinyl bromide manufacturing plant ranged from 0. Personal air samples showed that a plant operator was exposed to 0. Environmental occurrence Vinyl bromide may form in the air as a degradation product of 1,2-dibromoethane IARC, It may also be released into the environment from facilities that manufacture or use vinyl bromide as a flame retardant for acrylic fibres. Vinyl bromide has been qualitatively identified in ambient air samples National Library of Medicine, Regulations and guidelines No international guidelines for vinyl bromide in drinking-water have been established WHO, Many countries, regions or organizations have established guideline values for vinyl bromide in the workplace Table 1. Table 1 Guidelines for levels of vinyl bromide in the workplace. Studies of Cancer in Experimental Animals 3. A group of males and females served as untreated controls. Tumour incidences in rats exposed to vinyl bromide are summarized in Table 2. Treatment-related increases in the incidence of liver angiosarcomas were observed in all exposed groups: An increased incidence of Zymbal gland squamous-cell carcinomas also occurred in both sexes of exposed rats: Hepatic neoplastic nodules [hepatocellular adenomas] and hepatocellular carcinomas were also observed, the incidence of which was significantly increased in some but not all treatment groups. Failure of the highest dose to increase the incidence of hepatocellular tumours was most probably a consequence of the reduced survival and early termination of these animals. No exposure-related increased incidence of brain tumours was observed Benya et al. Tumour incidence in rats exposed to vinyl bromide by inhalation for up to weeks. No skin tumours were observed. Additional groups of mice received TPA alone or no treatment. One of 30 mice treated with vinyl bromide followed by TPA had a skin papilloma at days, and one of 30 mice treated with TPA alone had a skin carcinoma at 44 days. No tumours were found in untreated mice. Systemic carcinogenesis was not assessed Van Duuren, No tumours were reported in vinyl bromide-treated mice or in vehicle or in 60 untreated controls. Mechanistic and Other Relevant Data 4. Absorption, distribution, metabolism and excretion 4. Humans No data were available to the Working Group. Experimental systems The limited available data on absorption, distribution, metabolism and excretion of vinyl bromide in experimental systems have been reviewed previously IARC, , The following section summarizes the salient features of the studies that were reviewed at that time, as well as significant new information on the metabolism and pharmacokinetics of vinyl bromide in experimental animals. Vinyl bromide is readily absorbed upon inhalation by rats IARC, Vinyl bromide is metabolized in a similar manner to vinyl chloride

and vinyl fluoride, and it is a substrate for human cytochrome P CYP 2E1. In this study, the in-vitro formation of 1,N6-ethenoadenosine that resulted from bromoethylene oxide was also demonstrated Guengerich et al. Bromoethylene oxide can be deactivated by epoxide hydrolase and glutathione-S-transferases, or can re-arrange to bromoacetaldehyde National Toxicology Program, Following inhalation of vinyl bromide by rats, rabbits and monkeys, plasma levels of non-volatile bromide increased with duration of exposure, and were formed more rapidly in hepatic CYP-induced rats IARC, In rats, the conversion of vinyl bromide to reactive metabolites occurs primarily in hepatocytes. Irreversible binding of such metabolites to proteins and RNA has been established with rat liver microsomes in vitro as well as in rats in vivo Bolt et al. These metabolites can also alkylate the CYP prosthetic group of phenobarbital-treated rat liver microsomes. Genetic and related effects 4. Experimental systems a DNA adducts Vinyl bromide metabolites bind covalently to DNA and proteins; 2-bromoethylene oxide is the major DNA-binding moiety and 2-bromoacetaldehyde is the major protein-binding metabolite Guengerich et al. The major adduct that results from exposure to vinyl bromide is N 2-oxoethyl guanosine Bolt et al. Bromoacetaldehyde and bromoethylene oxide can react with adenine or cytosine bases to produce the cyclic etheno adducts 1,N6-ethenoadenosine and 3,N4-ethenocytosine, which can cause miscoding by modifying base-pairing sites Bolt, Cyclic etheno adducts have a longer half-life than N 2-oxoethyl guanine and, therefore, may have a greater potential to accumulate with long-term exposure Swenberg et al. The comet assay was used to assess the genotoxicity of vinyl bromide in the stomach, liver, kidney, bladder, lung, brain and bone marrow of male CD-1 mice. Mechanisms of carcinogenesis The metabolism of vinyl bromide is similar to that of vinyl chloride and vinyl fluoride. Vinyl bromide is metabolized to bromoethylene oxide and bromoacetaldehyde by human CYP2E1. In-vitro studies have shown that these intermediates, in the presence of adenosine, form 1,N6-ethenoadenosine. The same promutagenic adduct is formed with chloroethylene oxide, the primary intermediate of vinyl chloride metabolism. It is one of the adducts that are implicated in the mutagenicity and carcinogenicity of vinyl chloride. Summary of Data Reported 5. Exposure data Vinyl bromide is a flammable gas that is produced in a limited number of countries. It is used predominantly for the manufacture of polyvinyl bromide and to a smaller extent as a flame retardant in a large variety of industrial and consumer products. Workers may be exposed during the manufacture of vinyl bromide monomer and during production of the polymer. Cancer in humans No data were available to the Working Group. Cancer in experimental animals In a study of inhalation exposure in both sexes of rats, vinyl bromide caused a significant increase in the incidence of angiosarcomas of the liver, hepatocellular adenomas and carcinomas, and squamous-cell carcinomas of the Zymbal gland. In limited studies in female mice, vinyl bromide neither induced nor initiated skin tumours after dermal application and did not cause injection-site tumours after repeated subcutaneous injection. Mechanistic and other relevant data Vinyl bromide is readily absorbed upon inhalation. It is a substrate for human cytochrome P 2E1 and is metabolized by this enzyme in a manner similar to that of vinyl chloride and vinyl fluoride. Bromoethylene oxide and bromoacetaldehyde are known metabolites of vinyl bromide that can form DNA adducts that are similar to those formed by metabolites of vinyl chloride. These include N7- 2-oxoethyl guanosine the major adduct and the cyclic adducts, ethenodeoxyadenosine and ethenodeoxycytidine, which can cause miscoding by modifying base-pairing sites. Vinyl bromide caused DNA damage in mice treated in vivo, and has been shown to be mutagenic in bacteria and in Drosophila. Evaluation and Rationale There is inadequate evidence in humans for the carcinogenicity of vinyl bromide. Carcinogenicity in experimental animals There is sufficient evidence in experimental animals for the carcinogenicity of vinyl bromide. Overall evaluation Vinyl bromide is probably carcinogenic to humans Group 2A. Rationale In making the overall evaluation, the Working Group took into consideration the fact that all available studies showed a consistently parallel response between vinyl bromide and vinyl chloride. In addition, both vinyl chloride and vinyl bromide are activated via a human cytochrome P 2E1-dependent pathway to their corresponding epoxides. The weight of positive evidence for both compounds was also noted among the studies for genotoxicity, although the number and variety of tests for vinyl bromide were fewer. For practical purposes, vinyl bromide should be

considered to act similarly to the human carcinogen, vinyl chloride. Characterization by two-endpoint comparisons of the genetic toxicity profiles of vinyl chloride and related etheno-adduct forming carcinogens in Drosophila. Preferential formation of deletions following in vivo exposure of postmeiotic Drosophila germ cells to the DNA etheno-adduct-forming carcinogen vinyl carbamate. Inhalation carcinogenicity bioassay of vinyl bromide in rats. Roles of etheno-DNA adducts in tumorigenicity of olefins. Binding kinetics of vinyl chloride and vinyl bromide at very low doses. Covalent binding of haloethylenes. Pharmacokinetics and metabolism of vinyl fluoride in vivo and in vitro. Pharmacokinetics of halogenated ethylenes in rats. Roles of 2-haloethylene oxides and 2-haloacetaldehydes derived from vinyl bromide and vinyl chloride in irreversible binding to protein and DNA. Role of human cytochrome P IIE1 in the oxidation of many low molecular weight cancer suspects. Occupational exposure to carcinogens in the European Union. PMC] [PubMed: Mutagenicity of vinyl compounds in Salmonella typhi-murium.

DOWNLOAD PDF EXOCYCLIC DNA ADDUCTS IN MUTAGENESIS AND CARCINOGENESIS (DISCONTINUED (IARC SCIENT PUB))

Chapter 2 : IARC Publications Website - IARC Scientific Publications

Abstract. DNA-bound carcinogen adducts reflect the amount of an exogenous chemical or its metabolite that covalently interacted with nucleic acid bases at the target site (biologically effective dose) or in surrogate tissues.

Mention of trade names or commercial products does not constitute endorsement or recommendation for use. Accurate dose measurements are critical in the evaluation of health risks and in the development of regulations that may be needed for protection from chemicals released into the environment. The EPA has developed an initiative designed to develop, refine and apply appropriate biomarkers that can be used in conjunction with environmental monitoring data to provide a better estimate of risk to individuals and populations. Only by relating biological measurements to environmental monitoring measurements may the relationships between total exposure, effective dose and disease be determined. Introduction, Literature Summary and Recommendations", it was recognized that hemoglobin and serum albumin adducts may be more advantageous than DNA adducts as biological markers of exposure, because the protein adducts are more stable and are accessible from humans in much larger quantities. Subsequently, a U. Literature Summary and Recommendations" summarized the literature regarding adducts formed by xenobiotics with proteins, particularly hemoglobin and serum albumin, and examined the feasibility of their use as dosimeters of exposure. Conclusions were drawn and proposals made with respect to those compounds, protein adducts and detection methods best suited to monitoring human exposure to toxic chemicals, particularly those occurring at Superfund sites and others of interest to the EPA. The recommended chemicals were ranked by their potential for exposure monitoring by protein adduct-based methods. The prioritized list of selected chemicals is here reproduced in the introduction, where the ranking scheme is also explained. The individual chemicals are discussed in subsequent sections in the same order in which they appear on the prioritized list. The topics covered for each individual chemical are as follows: Relationship between environmental exposure, biologically effective dose, and chemical carcinogenesis Procedure for analysis of total protein i. Edman degradation procedure applied to A unmodified and B alkylated N-terminal valine in Hb Proposed scheme for formation in vivo and hydrolysis in vitro of acid-sensitive hemoglobinABP adducts Hemoglobin adduct formation as a linear function of single intraperitoneal doses of 4-aminobiphenyl Accumulation and elimination of hemoglobin adducts with chronic administration of 4-aminobiphenyl Procedure for analyzing arylamine-hemoglobin adducts by GC-MS Prioritized list of protein adduct-forming compounds of interest to the EPA 10 2. Manufacturers of Ethylene Oxide 26 3. Production of Propylene Oxide 42 5. Production of Styrene 48 6. Production of 0-Toluidine 78 8. Production of Vinyl Chloride 97 9. Production of Ethylene Dichloride Production of Acrylonitrile Production of Chloroform Production of Benzene Production of Formaldehyde Production of Epichlorohydrin The emphasis is on monitoring human exposure to genotoxic chemicals in the environment. Traditionally, human exposure to an environmental pollutant has been estimated from direct measurements of its concentration in one or more environmental compartments, i. Exposure assessments based on ambient monitoring cannot, however, take into account the effects of: Consequently, ambient monitoring can provide only crude estimates of the potential exposure of populations; for a given individual, the data cannot accurately reflect either actual exposure or degree of risk. Only that portion of the total exposure dose actually absorbed by the organism is relevant to the exposure-related health risk incurred by the organism. Biomarkers of exposure reflect actual absorption via all routes of entry from single and multiple sources, integrate the consequences of intermittent as well as continuous exposure, and take into account subsequent metabolism and distribution in the body Figure 1. Not only can biomarkers of exposure serve as dosimeters of exposure for a single individual, but, collectively, their measurement could provide a more accurate and detailed picture of exposure and risk at the population level. Biological monitoring in humans should also help bridge the gap between animal experimentation and human epidemiology, provide an improved basis for species extrapolation, and define the nature and scope of

interindividual variation Vahakangas, ; Calabrese, Relationship between environmental exposure, biologically effective dose, and chemical carcinogenesis. While these endpoints are not themselves considered to be adverse health effects, they may indicate the presence of either the chemical or adverse health effects resulting from exposure to the chemical. With some chemicals, levels of urinary metabolites correlate reasonably well with exposure dose. However, measurements of urinary metabolites ignore that proportion of the dose that evades detoxification and exerts its effect at the site of action, and they generally can only reflect exposures that have occurred during the previous hours. Similar disadvantages apply to measurements made in other body fluids. However, the biological significance of these endpoints remains unclear, and the methods are generally non-specific and subject to methodological problems related to sampling time. By contrast, macromolecular adducts tend to be more specific for the responsible exposure, and their biological significance is less obscure. The same topics are addressed in a text by Hodgson and Guthrie Jeffrey has reviewed DNA adduct formation by chemical carcinogens. The majority of xenobiotics that enter the body are lipophilic, hence their ability to penetrate cell membranes and be transported by lipoproteins in the body fluids. In various tissues of the animal body, but especially in the liver, several enzyme systems exist that render lipophilic xenobiotics more water soluble and, thus, more readily excreted. This biotransformation is generally accomplished in two phases. In Phase II, reaction between the modified xenobiotic and an endogenous substrate produces a more water-soluble conjugate which may then be readily excreted. The most important Phase I reactions are catalyzed by the microsomal mixed-function monooxygenases, a non-specific, multienzyme system having cytochrome P as the terminal oxidase. As the term "microsomal" indicates, this enzyme system is located in the endoplasmic reticulum of the cell; it is most abundant in hepatocytes, i. Among the reactions catalyzed by the cytochrome Pcontaining monooxygenases, the most important ones for protein-adduct formation are epoxidation and hydroxylation. Epoxidation is the primary activation pathway for many unsaturated compounds, especially polynuclear aromatic hydrocarbons. Examples include ethylene, propylene, styrene, vinyl chloride, acrylonitrile, acrylamide, benzo a pyrene E a P and 1,2-dimethylbenzanthracene DMBA. N-hydroxylation is the primary activation pathway for aromatic amines such as 4- aminobiphenyl 4-ABP , benzidine, and methylenebis- 2-chloroaniline MBOCA. Reactive metabolites generated by phase I reactions in the liver can react directly with macromolecules of the liver and the blood that perfuses that organ. If the biological half-life of the ultimate electrophile is long enough, the latter may migrate to and covalently bind at distant sites of action. Short-lived reactive intermediates may undergo phase II reactions to form more stable conjugated species. These can be transported to extrahepatic target tissues where they may be enzymatically deconjugated. The "re-activated" ions or radicals thus created may then bind to DNA and proteins at the remote site of action. Adverse health effects such as cancer and isocyanate lung disease can be caused by specific adducts of DNA and protein, respectively. By monitoring the formation of other, relatively innocuous macromolecular adducts, potentially hazardous exposures may be terminated at a pre-symptomatic stage. In addition, protein adducts, unlike most other biomarkers, can quantitatively reflect exposure that has occurred during the previous weeks or months, depending on the lifespan of the protein Ehrenberg, ; Poirier et al. As the target molecules of genotoxic xenobiotics or their electrophilic metabolites, DNA would be the preferred macromolecule in which to measure the formation of carcinogen- protein adducts as a biomarker of both exposure and effect. However, DNA adducts occur at very low levels in vivo, and the rates of repair and excretion usually limit their usefulness as biomonitors to hours after exposure. Proteins, on the other hand, tend to form relatively high levels of adducts with electrophilic compounds in general, including virtually all those known to bind to DNA. Perhaps more important, protein adducts are generally not repaired. Also, blood sampling is more convenient and less invasive than sampling of other tissues such as fat. Of course, protein adducts generally cannot be used as biomarkers of genotoxic risk as certain DNA adducts can, because the adducts formed between carcinogens and blood proteins are not directly relevant to carcinogenesis. However, in those special cases where the two share a common ultimate electrophile, a protein adduct may serve as a surrogate dosimeter for the corresponding DNA adduct.

Theoretically, any protein will form adducts at nucleophilic centers with electrophilic chemicals or metabolites, and, thus, could serve as a biomonitor of exposure to such agents. However, hemoglobin Hb and serum albumin SA are particularly suitable because large quantities are readily available for analysis in a ml sample of human blood. Hemoglobin adducts in particular show great potential as biomarkers of exposure to genotoxic compounds. It is synthesized in the immature red cell as the latter develops in the bone marrow, and shares with the erythrocyte a lifespan of approximately days in man. The number of fully characterized adducts, while very much smaller, is, and will most probably remain, greater for Hb than for any other protein. This is important, since only fully characterized adducts are of any real use as biomarkers of specific exposures. The main nucleophilic centers in proteins are 1 the sulfur atoms of cysteine and methionine; 2 the nitrogen atoms of amine groups, ring systems, and guanido groups; and 3 the oxygen atoms of hydroxyl and carboxyl groups. The most intensively studied protein adducts have been selected alkyl histidines, N- terminal valines, and cysteine sulfinyl aromatic amines. Interest in the alkyl histidines has declined in recent years as improved methodologies have made it possible to study the same alkyl moieties at alternate sites without the necessity of analyzing total protein hydrolysates. These two methods are described here in the sections on ethylene oxide and 4-aminobiphenyl, respectively. In addition, intact adducts or their cleavage products that are strongly fluorescent may be measured using fluorescence spectrophotometry Jankowiak et al. Immunoassays are currently under development and show great promise for application to both environmental and biological monitoring Vanderlaan et al. In general, the protein adducts studied by these methods have exhibited a linear dose-response curve over some specified dose range. Sometimes, as in the case of 4-aminobiphenyl, that dose range may be quite large. Stable protein adducts also tend to be accumulated in a dose-related manner and, upon cessation of the exposure, eliminated at a rate that reflects the turnover of the adducted protein. Along with the ready availability in blood of large quantities for analysis, it is the predictable pharmaco- kinetics of Hb adducts that makes them useful as biomarkers of exposure to environmental contaminants. The ability to monitor chemical exposures via Hb adducts is limited not so much by the sensitivity of available analytical techniques as it is by the presence in some cases of background levels that tend to mask the effects of low level exposures. Such chemicals may be metabolized in the liver to reactive species with half-lives too short to allow significant migration to and reaction with extrahepatic targets. In such cases, protein adducts may, nevertheless, be measurable in another blood protein, serum albumin Sabbioni et al. Newly synthesized albumin is secreted by the hepatocytes directly into the systemic circulation, from which compartment it later equilibrates with lymph and interstitial fluid. These facts would have to be taken into account in any calculation of tissue dose from levels of serum albumin adducts. Because it is not protected by a cell membrane as hemoglobin is, serum albumin becomes modified with age e. The mean half-life of human serum albumin HSA and, hence, HSA adducts is days, which results in a normal daily turnover of 8. Serum albumin may be lost at a much faster rate in response to gastrointestinal disease, nephrosis, or severe burns, and in the rare disorder analbuminemia, serum albumin is lacking altogether. Brown and Shockley, Serum albumin functions primarily as a transport protein and possesses a profusion of binding sites for fatty acids, steroids, etc.

Chapter 3 : Aflatoxin B1 | C17H12O6 - PubChem

The observed QSAR between the initial level of miscoding O-alkyl-DNA adducts and carcinogenic potency of a chemical provides strong support for a crucial role of DNA adducts in the carcinogenesis process.

Carcinogen Save A carcinogen is any substance, radionuclide , or radiation that promotes carcinogenesis , the formation of cancer. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes. Several radioactive substances are considered carcinogens, but their carcinogenic activity is attributed to the radiation, for example gamma rays and alpha particles , which they emit. Common examples of non-radioactive carcinogens are inhaled asbestos , certain dioxins , and tobacco smoke. Although the public generally associates carcinogenicity with synthetic chemicals, it is equally likely to arise in both natural and synthetic substances. Cancer is any disease in which normal cells are damaged and do not undergo programmed cell death as fast as they divide via mitosis. 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. Usually, severe DNA damage leads to programmed cell death, but if the programmed cell death pathway is damaged, then the cell cannot prevent itself from becoming a cancer cell. There are many natural carcinogens. Aflatoxin B, which is produced by the fungus Aspergillus flavus growing on stored grains , nuts and peanut butter , is an example of a potent, naturally occurring microbial carcinogen. Certain viruses such as hepatitis B and human papilloma virus have been found to cause cancer in humans. The first one shown to cause cancer in animals is Rous sarcoma virus , discovered in by Peyton Rous. Other infectious organisms which cause cancer in humans include some bacteria e. Helicobacter pylori [2][3] and helminths e. Opisthorchis viverrini [4] and Clonorchis sinensis [5]. Dioxins and dioxin-like compounds , benzene , kepone , EDB , and asbestos have all been classified as carcinogenic. Co-carcinogens are chemicals that do not necessarily cause cancer on their own, but promote the activity of other carcinogens in causing cancer. After the carcinogen enters the body, the body makes an attempt to eliminate it through a process called biotransformation. The purpose of these reactions is to make the carcinogen more water-soluble so that it can be removed from the body. However, in some cases, these reactions can also convert a less toxic carcinogen into a more toxic carcinogen. DNA is nucleophilic ; therefore, soluble carbon electrophiles are carcinogenic, because DNA attacks them. For example, some alkenes are toxicated by human enzymes to produce an electrophilic epoxide. DNA attacks the epoxide, and is bound permanently to it. This is the mechanism behind the carcinogenicity of benzo[a]pyrene in tobacco smoke, other aromatics, aflatoxin and mustard gas. Ability or tendency to produce cancer. In general, polymers are not known as carcinogens or mutagens,however, residual monomers or additives can cause genetic mutations. Carcinogenicity of radiation depends on the type of radiation, type of exposure, and penetration. For example, alpha radiation has low penetration and is not a hazard outside the body, but emitters are carcinogenic when inhaled or ingested. For example, Thorotrast , a incidentally radioactive suspension previously used as a contrast medium in x-ray diagnostics, is a potent human carcinogen known because of its retention within various organs and persistent emission of alpha particles. Low-level ionizing radiation may induce irreparable DNA damage leading to replicational and transcriptional errors needed for neoplasia or may trigger viral interactions leading to pre-mature aging and cancer. Low-energy waves on the electromagnetic spectrum including radio waves , microwaves , infrared radiation and visible light are thought not to be, because they have insufficient energy to break chemical bonds. Evidence for carcinogenic effects of non-ionizing radiation is generally inconclusive , though there are some documented cases of radar technicians with prolonged high exposure experiencing significantly higher cancer incidence. For most people, ultraviolet radiations from sunlight is the most common cause of skin cancer. In Australia, where people with pale skin are often exposed to strong sunlight, melanoma is the most common cancer diagnosed in people aged 15â€”44 years. In contrast, non-electromagnetic neutron radiation produced inside nuclear reactors can produce

secondary radiation through nuclear transmutation. In prepared food Chemicals used in processed and cured meat such as some brands of bacon, sausages and ham may or may not produce 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 2â€”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. In cigarettes There is a strong association of smoking with lung cancer; the lifetime risk of developing lung cancer increases significantly in smokers. Potent carcinogens found in cigarette smoke include polycyclic aromatic hydrocarbons PAH, such as benzo[a]pyrene , Benzene , and Nitrosamine. Genotoxins cause irreversible genetic damage or mutations by binding to DNA. Genotoxins include chemical agents like N-nitroso-N-methylurea NMU or non-chemical agents such as ultraviolet light and ionizing radiation. Certain viruses can also act as carcinogens by interacting with DNA. Nongenotoxins do not directly affect DNA but act in other ways to promote growth. These include hormones and some organic compounds.

Chapter 4 : Hisar PAH paper | Anil Haritash - calendrierdelascience.com

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide).

Abstract Tobacco carcinogen and toxicant biomarkers are metabolites or protein or DNA adducts of specific compounds in tobacco products. Highly reliable analytical methods, based mainly on mass spectrometry, have been developed and applied in large studies of many of these biomarkers. A panel of tobacco carcinogen and toxicant biomarkers is suggested here, and typical values for smokers and non-smokers are summarized. This panel of biomarkers has potential applications in the new and challenging area of tobacco product regulation and in development of rational approaches to cancer prevention by establishing carcinogen and toxicant uptake and excretion in people exposed to tobacco products. Attesting to their addictive power is the fact that more than one billion people in the world smoke cigarettes and other tobacco products while hundreds of millions use smokeless tobacco 1. The consequences are enormous: The latest evaluation by the International Agency for Research on Cancer lists 19 cancers for which there is sufficient evidence that tobacco smoking is a cause, and 3 caused by smokeless tobacco use 3. Tobacco control efforts in the U. Worldwide, the results are varied, and there are still major areas of high tobacco use such as China which has more male smokers than there are people in the U. There is a great deal of work left to do in tobacco control. This perspective will discuss the potential use of tobacco carcinogen and toxicant biomarkers in tobacco product regulation with respect to cancer. Tobacco products are also a cause of cardiovascular and pulmonary disease, but those effects and their biomarkers are not considered here 7 , 8. Major recent regulatory legislative actions have changed the landscape with respect to tobacco. In , the U. This perspective will also discuss the application of tobacco carcinogen and toxicant biomarkers in cancer prevention. Biomarkers also promise to increase our understanding of the mechanisms by which tobacco products cause cancer. This can lead to innovative approaches to cancer prevention by identifying and targeting those individuals who are particularly susceptible to the cancer causing effects of tobacco products. In the cancer research field in particular, this term is often associated with early detection of cancer. That is not the context here. A Panel of Biomarkers A panel of tobacco toxicant and carcinogen biomarkers that could be used in product regulation and studies on prevention of tobacco-induced cancer is presented in Table 1 and their structures are illustrated in Figure 1. All biomarkers have been validated analytically. Most have been used in multiple studies on hundreds or even thousands of smokers and non-smokers. Some typical recent data are summarized in Table 1. Although some of the ranges of values overlap between smokers and non-smokers for certain biomarkers, biomarker levels are consistently higher in smokers compared to non-smokers in individual studies. Biomarkers of the tobacco-specific compounds are similar in smokers and smokeless tobacco users, while those of the volatile organic compounds are considerably lower in smokeless tobacco users, based on our unpublished data.

Chapter 5 : Meiqx | C11H11N5 - PubChem

Bulky DNA adducts, 4-aminobiphenyl-haemoglobin adducts and diet in the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study. Authors.

Anil Haritash This article was downloaded by: To cite this article: Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material. Polycyclic Aromatic Compounds, Kaushik,1 Parmila Sangwan,1 and A. Vehicular emission was the chief source and diesel-vehicle dominated areas represented higher concentration of PAHs associated with coarse fraction. An in- crease in PAH associated with fine fraction was observed with an increase in vehicular density. Maximum average concentration Among the PAHs studied, maximum levels were observed for pyrene, followed by Benzo b fluoranthene, Benzo e pyrene, benzo k fluoranthene, fluoranthene, phenanthrene, benzo ghi perylene, anthracene, and naphthalene. The isomeric ratios revealed that most of the PAHs originate from combustion of diesel, gasoline, Received 9 February ; accepted 16 May Address correspondence to A. The association of PAHs with fine fraction of health concern since it can penetrate and get accumulated in deep respiratory regions. They occur as colorless, white or pale yellow solids with low solubility in water, high melting and boiling points, and low vapor pressure 1, 2. With an increase in Downloaded by [Anil Haritash] at They are formed during the thermal decomposition of organic molecules and their subsequent recombina- tion. The common sources of PAHs in the environment include natural as well as anthropogenic sources. Natural sources include forest fires and volcanic eruptions, and anthropogenic sources include vehicles and in- dustries. PAHs are widely distributed environmental contaminants that have detrimental biological effects, including acute and chronic toxicity, mutagenic- ity, and carcinogenicity 5. Many individual PAHs are carcinogenic to animals and may be carcinogenic to humans, and exposure to several PAH-containing mixtures has been shown to increase the incidence of cancer in human popula- tion. There is concern that those PAHs found to be carcinogenic in experimen- tal animals are likely to be carcinogenic in humans 6. The particulate matter, especially the respirable suspended particulate matter RSPM , is of major concern as most of the pollu- tants of air are associated with it and they have a high probability of depositing on the respiratory tract 8. Although there are studies regarding the estima- tion of commonly occurring pollutants of air, such as oxides of sulphur and nitrogen 9 and heavy metals 10 , estimation of PAHs with particle size char- acterization has become imperative for studying associated health aspects. The fate of PAHs in the environment includes volatilization, photo- oxidation, chemical oxidation, bio-accumulation, adsorption on soil particles, leaching, and microbial degradation 11, PAHs are present in every com- ponent of environment and are chief pollutants of air. Atmospheric PAHs have a strong affinity for particles since they have lower vapor pressure and there- fore readily can condense onto particulate matter in air and move to distant places with the wind currents. These PAHs occur in two phases in air. They partition between the particulate phase and vapor phase depending upon the prevailing atmo- spheric conditions and the particular physical characteristics of the compounds C. The particulate-bound PAHs are further associated with different particle sizes. It is observed that vehicles are major sources of PAHs and a majority of the volatile PAHs is observed in the gas phase whereas the less volatile and carcinogenic PAHs are especially adsorbed on particles Keeping in view the toxicity associated with PAHs, the site-specific activ- ities and sources, association with different particle sizes, and contribution of diesel and gasoline vehicles, the present study was undertaken to assess the levels of different PAHs in atmospheric suspended dust in Hisar city of Downloaded by [Anil Haritash] at Hisar has

moderate to high industrial activity with a steel plant, dis- tillery, number of small- and medium-scale industries, and a fair number of registered vehicles. Most of the industries are located in an industrial estate situated in its northeast outskirts. The climate is characterized by its dryness and extremes of temperature: On average, there are 24 rainy days in the year with an average annual rainfall of mm. Generally, light winds blow but dust storms occur in summer and thunderstorms in monsoon season. Weak inversions are commonly observed in winter. The samples were collected Octoberâ€"December , once in every month from each loca- tion on the same day. A total of 15 samplings were done during the study. At each stage, jets of particle-laden air impinge upon an impaction plate. Location of sampling sites in Hisar City, Haryana color figure available online. The smaller particle with less inertia do not cross the stream- line and proceed to the next stage until the smallest particles are collected at the last stage. An aluminium foil was used as substrate for the collection of particles. The substrates of impaction plates were treated with silicon spray C. Sample Extraction and Analysis The substrates were weighed to determine the amount of particles col- lected. The PAHs from the substrates were extracted in Toluene using ultra- sonic extraction for 30 min. The extracts were eluted through silica-sodium sulphate column and reduced to 5 ml volume using a rotary vacuum evapora- tor. The conditions for chromatographic analysis were injection volume: UV at a wavelength of excitation nm. Site-specific Variations Considerable concentration of PAHs was observed at all the sites Tables 1 and 2 , but sites with vehicular activity represented higher levels. Mean concentration at Nagori Gate was maximum in October It was followed by the average concentration at National Highway, The high concentration in fine fraction 0. Although the number of vehicles com- pared to Nagori Gate is more, the movement is smooth and fast. More- over, NH passes through an open area which results in early disper- sion and it minimizes building up of concentration. The mean concentra- tion varied from 9. Bus Terminus of Hisar city, representing vehicular activity only buses running on diesel , reported an average con- centration of The mean concentration var- ied from 9. The majority of PAHs were associated with the intermediate range 0. Similar findings have been reported in another study on characterization of particle-bound PAHs at bus terminus Although the PAHs produced by diesel-run vehicles were associated with coarse fraction, the proximity to the major road bisecting Hisar city could be reason for the PAHs associated with smaller fraction. NH is the reason for addition of PAHs. Padaw Chowk representing com- mercial area had minimum average concentration of 8. Major association with fine fraction was con- tributed to a high number of petrol-driven two-wheelers and its proximity to Auto Market of Hisar city. Similar results have been reported by Handa et al. Burning of garbage, refuse, used lubricating oil, and oil filters in the auto market could also be a source Classifying the sites with respect to the percent fraction of Downloaded by [Anil Haritash] at The total PAH concentration associated with different particles is presented in Table 1 and Figure 3. Maximum average concentra- tion Among the PAHs analyzed, maximum levels were observed for Figure 2: Percent fraction of total PAHs at different locations in Hisar city during October-December color figure available online. Pyrene 4-ring PAH at all the sites. It was followed by Benzo e acephenanthrylene 4-ring derivative which varied from The association of high molecular weight PAHs with coarser particles could be rea- son for a high concentration of these PAHs and higher levels are cause for concern since the PAHs with more than 4 benzene rings have greater carcino- genic potential. Minimum levels were observed for naphthalene 2-ring with an average of 3. Downloaded by [Anil Haritash] at At the same time small PAHs 2â€"3 rings present in vapor phase are susceptible to photo-degradation. On the other hand, the thermal non photolytic reaction with oxides of nitro- gen can significantly enhance half-life of particle-bound as well as vapor-phase PAHs 20 and the atmospheric chemical lifetimes of particle-bound PAH with respect to thermal reactions tend to be longer than those of gas-phase PAH Source Identification In order to identify the probable sources of emission at each location, the isomeric ratios of PAHs were calculated. Generally, the stability of lighter PAH isomers is calculated to support such interpretations. The so calculated isomeric ratios are given in Table 5. Based on the ob- served isomeric ratios, PAHs in Hisar city were found to be pyrolytic combus- tion based in origin. The source may also be correlated on the basis of traffic census done at different locations during the study. Health

DOWNLOAD PDF EXOCYCLIC DNA ADDUCTS IN MUTAGENESIS AND CARCINOGENESIS (DISCONTINUED (IARC SCIENT PUB))

Aspects of PAHs The effects of inhaling particulate matter have been established in hu- mans and animals and include asthma, lung cancer, cardiovascular issues, and Downloaded by [Anil Haritash] at Yang, premature death. The size of the particle determines its penetration into the Downloaded by [Anil Haritash] at Similarly, particles smaller than 2. Particles emitted from modern diesel engines are typically in coarser range and carry carcinogenic PAHs adsorbed on their surface PAHs bind with the cellular proteins and DNA leading to biochemical disruptions, cell damage, mutations, developmental malformations, tumors, and cancer Coke oven workers exposed to a high concentration of soot and PAHs have been found to have reduced level of serum immunoglobulins. High lung cancer rate has also been associated with smoky coal used A positive correlation has also been established for PAH-DNA adducts in placentas from women burning coal with- out a chimney. However, when PAHs enter living beings, they are oxidized by P cytochrome oxidases to a variety of metabolites. One of the major pathways is the epoxidation leading to the formation of the optically active epoxides. Subsequently, the epoxide is hydrolyzed by microsomal epox- ide hydrolase to initiate the enzymatic attack at the allylic position to form dihydrodiol. Further oxidation of the dihydrodiol by CYP generates diol- epoxide isomers. These diastereomeric diol-epoxides covalently bind to DNA, forming adducts that can lead to mutagenesis and carcinogenesis Figure 5.

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of carcinogen exposure [3], especially those arising from endogenous sources [4, 5], (ii) to quantify carcinogen DNA-damage in populations and measure the effect of ge-.

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The promutagenic and genotoxic exocyclic DNA adduct 1,N(2)-ethenoguanine (1,N(2)-epsilonG) is a major product formed in DNA exposed to lipid peroxidation-derived aldehydes in vitro.

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In addition, bulkier b[a]a 2 G or b[a]a 6 A exhibit significantly greater mutagenicity in human cells than in E. coli, which further emphasize the importance of studying the site-specific mutagenesis by carcinogen-modified DNA bases in human cells.

Chapter 9 : Is tamoxifen a genotoxic carcinogen in women? | Mutagenesis | Oxford Academic

DNA adducts represent a major primary damage that can lead to the induction of gene mutations. Usually, DNA adducts are detected using radiolabeled test compounds, postlabeling of adducts (e.g., with 32 P), immunochemistry, and capillary electrophoretic or chromatographic techniques coupled with fluorescence or mass spectrometric detection.