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Carcinogenicity, allergenicity, and lupus-inducibility of arylamines

King-Thom Chung[1]

[1]*Department of Biological Sciences, University of Memphis, Memphis, Tennessee 38152*

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1. ABSTRACT

Arylamines are widely used in food, drugs, and cosmetics as well as other industries. These chemicals are present ubiquitously in cigarette smoke, smoke emitted from cooking fume hoods as well as are generated by diverse industries. Arylamines can be generated by cleavage of azo dyes by intestinal and skin microbiota. Some arylamines are used as drugs while others are constituents of human metabolism. Many of the arylamines are mutagenic and carcinogenic. They are generally recognized as the major cause of human bladder cancer, but arylamines can induce cancers of other organs in humans and animals. Some arylamines are allergenic, causing lupus like syndrome, or other maladies. In view of their unbiquitious nature and the diseases they cause, arylamines are probably the most important chemicals causing health problems.

2. INTRODUCTION

Arylamines, including aromatic amines, are one of the major chemical industrial compounds. They are also significant environmental pollutants, which cause many maladies including cancer, allergenicity, and other diseases. Commonly used examples of arylamines are benzidine, *3, 3'*-dimethyl-benzidine (*o*-tolidine), *3, 3'*-dichlorobenzidine, *3, 3'*-dimethoxybenzidine (*o*-diansidine), magenta, *4, 4'*-methylene(*2*-chloroaniline) (MOCA), *4*-aminobiphenyl, β-naphthylamine, *o*-toluidine and *4*-chloro-*o*-toluidine. The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) classified the above mentioned chemicals as carcinogens. Arylamines contain at least one amino group, which is an important functional group responsible for most of the key biochemical reactions.

3. APPLICATION AND SOURCES OF ARYLAMINES

Arylamines are primarily used in the dye industries. Arylamines are also used in antioxidants, epoxy, explosives, fungicides, pesticides, rubber, polyurethane, pharmaceuticals, food, cosmetics, colorants, and pigments (1). Arylamines are derived from various sources, primarily from azo dyes, which are widely used in food, as well as paper and textile industries. Over 3,000 tons of azo dyes were certified by the U. S. Food and Drug Administration (FDA) in 1991 for use in food, drugs, and cosmetics (2). Scientists discovered that intestinal microbiota, skin bacteria, and environmental microorganisms including bacteria, fungi, and helminths produced aromatic amines by cleavaging azo dyes ingested from food or contaminated water (3-8). Another source of arylamines is the combustion of nitrogen-containing organic materials including cigarettes smoke and smoke from cooking meat (9,10). Arylamines can also be generated from the reduction of nitrated polycyclic aromatic hydrocarbons (nitro-PAHs), including munitions by human intestinal microbiota or environmental microorganisms (11-14). Nitrated PAH and munitions are ubiquitous environmental contaminants that are formed from various combustion sources (15-18). In addition arylamines are also present in many drugs (19-20). Chemical reducing agents such as sodium hydrosulfite, sodium dithionite, zero-valent iron (Fe^{o}), and reduced flavin adenine nucleotides (FADH), reduced nicotinamide adenine dinucleotide (NADH), reduced nicotinamide adenine dinucleotide phosphate (NADPH) are reported to reduce azo dyes in order to produce aromatic amines (21-26).

Some arylamines are formed endogenously as metabolic end products or intermediates. Under certain

conditions, they can be produced in high concentrations. Chung and Godupudu (27) pointed out that excess intake of tryptophan, deficiency of vitamin B_6, or the induced activity of tryptophan dioxygenase (TDO) or indoleamine-2, 3-dioxygenase (IDO), various tryptophan metabolites, such as kynurenine, *3*-hydroxykynureine, anthranilic acid, *3*-hydroxyanthranilic acid and *3*-methoxykynurenine may accumulate (27-31). Higher concentrations of some tryptophan metabolites have been reported to be involved in bladder cancer (27,28). Other endogenous arylamines include *5*-hydroxytrytamine (serotonin), melatonin, putrecine, ornithine, citruline, dopamine, histamine, argenine, glutamine, tryptamine, tyramine, spermine, spermidine, cadaverine, norepinephrine, epinephrine, thyroxine, sphingosine, etc. These arylamines can certainly affect human health.

Therefore, we are unavoidably exposed to arylamines, which are profusely present in the modern industrial world and cause damage to our health and environment.

4. ARYLAMINES AND HUMAN HEALTH

4.1. Carcinogenicity

Rehn (1895) reported that arylamines cause bladder cancer in workers employed in a plant manufacturing magenta (fuchsine) (32). Also, Hueper (1942) suggested that aromatic amines were responsible for bladder cancer in humans (33). Dyestuff workers, chemical industrial workers, and handlers of certain rodenticides as well as pigment, printing, textile, rubber, cable, gas, tar, pitch and laboratory workers were reported to have a high incidence of bladder cancer because they were frequently exposed to arylamines (34,35). Other professions such as bus drivers, leather (including shoe) workers, blacksmiths, machine setters, mechanics, and hairdressers are also high risk groups of bladder cancer. Smokers also have a triple risk of bladder cancer relative to those who have never smoked (36). Cigarette smoking is also linked with an increased risk of cancers of lung, larynx, oral cavity, nose and sinuses, pharynx, esophagus, stomach, pancreas, cervix, kidney, ovary, colorectum, and acute myeloid leukemia. Cigarette smoking accounts for at least 30% of all cancer deaths including lung cancer, which is the leading cause of cancer deaths in both men and women.

Bladder cancer is ranked ninth in worldwide cancer incidences and is the seventh most common malignancy in men and seventeenth in women (37). Jemal (38) estimated that 386,300 new bladder cancer cases and 150,200 deaths from bladder cancer were diagnosed worldwide in 2008. In the United States, bladder cancer is ranked the fifth most common type of cancer with an estimated 68,000 newly diagnosed cases and 14,000 deaths in 2008 (39).

The most common type of bladder cancer is transitional cell carcinoma (urothelial carcinoma), which is reported to be caused primarily by carcinogenic chemicals (i.e. arylamines). The second predominant type of bladder cancer is squamous cell carcinoma, which is reported to be caused by infections (schizosomiasis). The third type is adenocarcinoma that occurs in glands, specialized structures that produce and release fluids such as mucus. The specific cause of the third type has not been reported.

Bladder cancer was probably one of the first documented occupational cancers reported and is often used as the paradigm for the study of arylamine-induced carcinogenesis. Arylamines can also induce cancer of other organs or tissues of humans. For example, benzidine has been reported to be the cause of genitourinary, pancreatic, liver, gall-bladder, bile duct, lung, intestinal, stomach, lymphopoietic and renal cancers as well as non-Hodgkin's lymphoma (40). Benzidine also induces various types of cancers in different animals including mouse, rat, hamster, rabbit, dog, and frog (40,41).

Benzidine and *p*-phenylenediamine are revealed to be mutagenic moieties of azo dyes (6). Since benzidine is a proven human carcinogen, the IARC of the WHO classified benzidine and azo dyes metabolized to benzidine as category 1 carcinogen (42). Many benzidine-congeners such as *3, 3'*-dimethylbenzidine (*o*-tolidine) and *3, 3'*-dimeththoxylbenzidine (*o*-dianisidine), etc. are also carcinogenic. Although more than 300 benzidine-based azo dyes are listed in the Color Index of the U. S. A., access to these dyes for home use is prohibited. By the end of 1979, most manufacturers started phasing out the use of benzidine-based dyes and replaced them with other dyes (43,44). Industrial use of benzidine has been drastically reduced. In 1994, the German Consumer Goods Ordinance restricted the use of certain azo dyes in consumer goods. The European Union banned certain azo dyes, which can be broken down under reductive conditions including human intestinal or liver enzymes. According to the European Parliament Directive 2002/61/EC of July 2002, the European Union (EU) decided that by September 11, 2003, harmonized legislation regarding some azo dyes in consumer goods had to be enacted. In order to protect human health, azo dyes that can be broken down under reductive conditions to release any of a group of defined aromatic amines are prohibited from being used in consumer goods considered to have regular skin contact (45). The list has been updated since 1994 and now includes 22 aromatic amines, which include *4*-aminobiphenyl (case no. 92-67-1), *4*-aminoazobenzene (case no. 60-09-3), benzidine (case no. 92-87-5), *4*-chloro-o-toluidine (case no. 95-69-2), *2*-naphthylamine (case no. 91-59-8), *4*-amino-*2',3*-dimethylazobenzene (case no. 97-56-3), *2*-amino-*4*-nitrotoluene (case no. 99-55-8), *4*-chloroaniline (case no. 106-47-8*), 2, 4*-diaminoanisole (case no. 615-05-4), *4,4'*-diaminodiphenylmethane (case

no. 101-77-9), *3,3'*-dichlorobenzidine (case no. 91-94-1), *3,3'*-dimethoxybenzidine (case no. 119-90-4*), 3,3'*-dimethybenzidine (case no. 119-93-7), *3,3'*-dimethyl-*4,4'*-diaminodiphenylmethane (case no. 838-88-0), *4*-cresidine (case no. 120-71-8), *4,4'*-methylene-bis(*2*-chloroaniline) (case no. 101-14-4), *4,4'*-oxydianiline (case no. 101-80-4), *4,4'*-thiodianiline (case no.139-65-1), *2*-aminotoluene (case no. 95-53-4), *2,4*-diaminotoluene (case no. 95-80-7), *2, 4, 5*-trimethylaniline (case no. 137-17-7), and *2*-methoxyaniline (45).

Many other industrial arylamines such as auramine, *4, 4'-methylene* (2-chloroaniline) (MOCA), etc. are also known to cause bladder cancer (40). Some of the endogenous arylamines such as tryptophan metabolites may also be implicated as etiological agents of bladder cancer formation (27,28).

The incidence of bladder cancer in the developed world has been reported to be slowly decreasing (37). Such trend of decreasing is probably due to the ban of using the above mentioned aromatic amines. Public awareness of the danger of using arylamines and their regulation may also contribute to the decreasing trend of bladder cancer incidences. However, the incidence of bladder cancer is predicted to be still increasing in less developed areas of the world because of smoking prevalence that goes along with economic development, which is also accompanied with the increased use of azo dyes in various textile industries (37,46).

4.2. Allergenicity

Arylamines such as benzidine and its congeners are not only important carcinogens but also important chemicals that have been reported to cause a variety of maladies such as headaches, lethargy, urinary burning, hematuria, etc. Many arylamines are allergens or sensitizers to skin. For example, the Food and Drug Administration (FDA) of the United States lists *p*-phenyenediamine (PPD) as being a contact allergen. Exposure routes of PPD are through inhalation, skin absorption, ingestion, and skin or eye contact. *p*-Phenylenediamine can cause throat irritation, bronchial asthma, and dermatitis {Registry of Toxic Effects of Chemical Substances (RTECS) entry PPD}. Likewise, *o*-phenylenediamine causes eye irritation, skin irritation, and allergic reaction. Other maladies include methemoglobinemia, which is characterized by dizziness, drowsiness, headache, shortness of breath, and rapid heart rates.

4-Aminobiphenyl has been reported to cause cyanosis, headache, lethargy, urinary burning, and hematuria in humans (47). *2*-Naphthythylamine (*2*-NA) can interfere with the ability of blood to carry oxygen causing headache, fatigue, dizziness, and a blue color to skin and lips (methemoglobinemia). *4*-Chlor-*o*-toluidine was reported to cause acute hemorrhagic cystitis with hematuria (48). Also, *4*-chloro-*o*-toluidine has been reported to cause human dysuria, reduced bladder capacity, and pain in the lower abdomen.

4.3. Lupus-inducibility

Some arylamines are reported to cause autoimmune diseases such as drug-induced lupus (DIL) (19,49). It has been estimated that 15,000-30,000 cases of DIL occur in the United States every year. DIL generally affects more older patients than idiopathic systemic lupus erythematosus (SLE) patients (50,51). Rubin and Kretz-Rommel (1999) indicated that there is no feature of chemical, pharmacological, or therapeutic properties that makes drugs likely to induce DIL, except that "some of these drugs are aromatic amines" (52). The most notable DIL causing drugs are isoniazid for treating tuberculosis; hydralazine for treating high blood pressure, heart failure, pulmonary hypertension, and pre-eclampsia; and procainamide for treating cardiac arrhythmia. Borcher *et al.* (53) reported that over 80 drugs were implicated in DIL, and the number is still increasing. These drugs differ widely in their pharmacological, chemical, and therapeutic characteristics, as indicated by their belonging to at least 10 major categories of drugs: antiarrhythmics, antihypertensives, antipsychotics, antibiotics, anticonvulsants, antithyroidals, anti-inflammatories, diuretics, cholesterol-lowering (statins), biologicals, and miscellaneous (53). Drugs with convincing evidence for a causal association with DIL are hydralazine, procainamide, isoniazid, methyldopa, quinidine, minocycline and chlorpromazine (Figure 1). The remainder of the drugs implicated in DIL is less compelling (53). Some examples of DIL drugs, which are catalyzed as aromatic amines, are shown in Table 1. General symptoms of DIL include loss of appetite, blurred vision, fever, weight loss, and malaise (Medline). Specific symptoms are joint pain and swelling, pleuritic chest pain, and skin rashes that get worse with exposure to sunlight and promote the development of a butterfly rash on the bridge of the nose and cheeks (Medline). Possible complications include infection, hemolytic anemia, nephritis, myocarditis, pericarditis, and low platelet levels in the blood can cause thrombocytopenia purpura (Medline). Usually, symptoms resolve within a period of a few days or weeks after stopping the offending drugs. The marked symptom is that the patients will produce anti-DNA antibodies usually only after months, and quite commonly, years of treatment with the DIL drugs although latencies of days or weeks have been described in some instances. There are indications that the risk of DIL can increase with higher daily and cumulative doses and with longer duration of therapy. This delay of formation of autoantibodies is different from the regular SLE (52).

Susceptible hair dye users have been reported to have a higher risk of SLE (54). Hair dye contains aromatic amine *p*-phenylenediamine, which was discussed in the earlier section. Lipstick has been shown to induce flares and photosensitivity as well as production

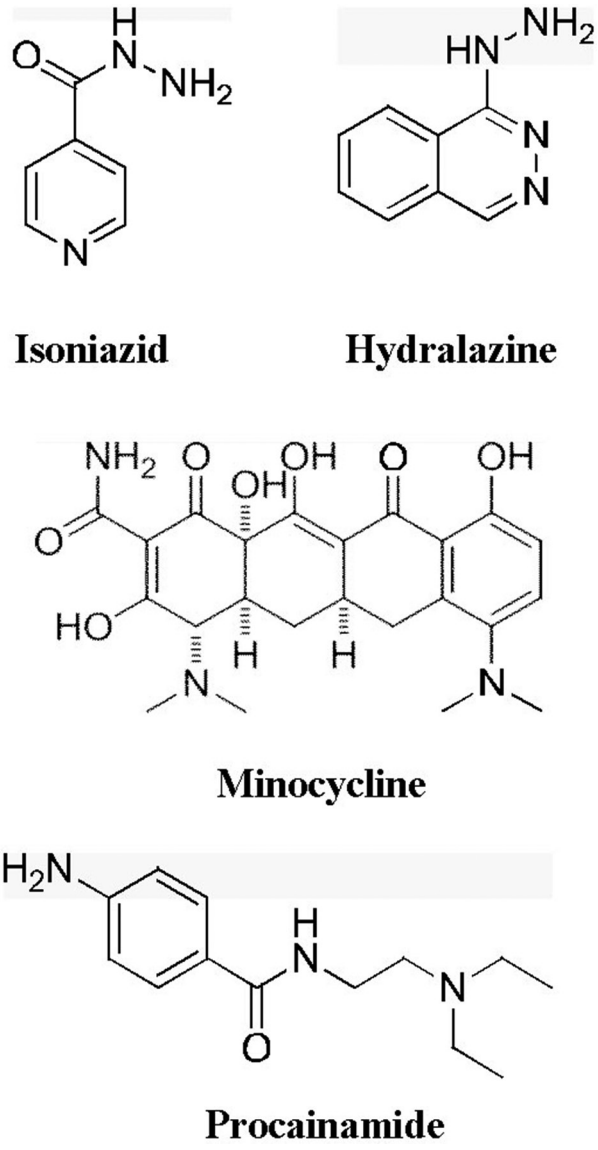

Figure 1. Chemical structures of some examples of lupus inducing drugs.

of anti-dsDNA antibodies (54). Lipstick contains eosin B. Eosin B is a nitrated-aromatic compound, which can be easily converted into aromatic amines by oral and/or intestinal microflora. So both hair dye and lipstick users are a high risk group for this allergenic disorder.

5. DISCUSSION

Many enzymes are involved in the metabolic activation/detoxification of xenobiotics including arylamines, such as cytochrome-P450, prostglandin H synthase, *N*-acetyltransferase, glutathione transferase, glucouronyl transferase, sulfotransferase, and *o*-acetylase. The expression and balance of these enzymes and their interplay are important factors for the onset of carcinogenesis and may help to partially interpret organ, tissue, and species specificity of the arylamines-inducing diseases.

The molecular mechanism of arylamine induced carcinogenesis needs to be addressed. Arylamines are reported to be oxidized to their hydroxy derivatives in the liver by the cytochrome P-450 IA2 isozyme (55). The *N*-hydroxy derivatives are esterified by acetyltransferase to acetoxy derivatives or by UDP-glucuronidase to form *N*-glucuronides. Both acetoxy derivatives and *N*-glucuronides are transported by the blood to the urine (56,57). The acetoxy derivatives and *N*-glucuronides are eventually converted to highly active arylnitrenium ions, which can react with DNA to form DNA adducts (58). Using *4*-aminobiphenyl (*4*-ABP) as an example, the DNA adducts have been identified in bladder tumors (59), bladder epithelial healthy cells (60), in exfoliated bladder cells, and in many other human tissues such as mammary glands (61). The formation of electrophilic metabolites of aromatic amine and amide carcinogens was also reviewed by Josephy and Novak (62). The metabolic activation of arylamine leads to the formation of reactive esters such as *N*-acetoxyarylamines, which are believed to be precursors of short lived nitrenium ions. Nitrenium ions chemistry has been well demonstrated through advanced techniques such as trapping with azide ion and laser flash photolysis. Nitrenium ions were involed as an intermediate in the formation of arylamine-derived DNA adducts (62).

Murata and Kawanish (55) also demonstrated that the *N*-hydroxyl and nitroso forms of arylamine can induce DNA damage such as DNA adduct *7*, *8*-dihydro-*8*-oxo-2'-deoxyguanosine (*8*-oxo-dG) lesions via reactive oxygen species (ROS) formation. Metal-mediated oxidative DNA damage by arylamines can occur via NADH-dependent, NADH-enhanced, or superoxide dismutase (SOD)/manganese-enhanced redox reactions. The *N*-hydroxyl and nitroso derivatives of carcinogenic arylamines such as *4*-aminobiphenyl and *2*-naphthylamine may contribute to the carcinogenic process through H_2O_2 formation. *N*-Hydroxy derivatives induce metal-mediated DNA damage with remarkable enhancement by NADH. Nitroso derivatives induce NADH-dependent DNA damage in the presence of metal ions.

Martelli and Brambilla (20) also reported that 105/109 (96.3%) arylamine drugs tested, were able to react with nitrite to form *N*-nitroso derivatives, which have genotoxic and carcinogenic effects; hydroxy derivatives of arylamines formed by enzymatic hydroxylation of *o*- or *p*-aminophenols can also induce DNA damage in the presence of metal ions. The auto-oxidation of *o*-phenylenediamine and several arylamine metabolites is accelerated in the presence of SOD or manganese, resulting in the enhancement of metal-mediated DNA damage. The formation of reactive oxygen species (ROS), which may contribute to oxidative DNA-damages, and mutations induced by *2*-naphthylamine

Table 1.

Amine groups	Reference
A. Drugs with primary amine group	
• Aminoglutethimide (125-8408), p-Aminosalicyclate (65-49-6), Atenolol (29122-68-7), Canavanine (L-) (543-38-4), Hydralazine (86-54-4), Cabamazepine (298-46-4), Chlorthalidone (77-36-1), COL-3 (15866-90-7), Dapsone (80-08-0), Debrisoquine (1131-64-2), Disopyramide (3737-09-5), Guanoxan (2165-19-7), Hydralazine (86-54-4), Hydrazine (302-01-2), Interferon(α, y), Isoniazid (54-85-3), Labetalol (36894-69-6) • Leuprolide acetate (74381-56), Levodopa (59-92-7), Lisinopril (76547-98-3), • Methyldopa (555-30-6), Minocycline (10118-90-8), Minoxidil (38304-91-5), • Nitrofurantoin (67-20-9), Nomifensine (24526-64-5), Penicillamine (52-67-5), • Phenelzine (51-71-8), Prazosin (19216-56-9), Procainamide (51-06-9), • Streptomycin (57-92-1), Sulfathiazole (72-14-0), Sulphamethoxypyridazine (80-35-3), • Sulphasalazine (599-79-1), Sulphonamides (63-74-1), Tetracyclines (60-54-8), Thionamide (62178-61-4)	19,53,83,84
B. Drugs with secondary amine group	
• Acebutolol (37517-30-9), Allopurinol (315-30-0), Cimetidine (51481-61-9), Clonidine (4205-90-7), Diclofenac (15307-86-5), Ethosuximide (77-67-8), Mephenytoin (50-12-4), Methimazole (60-56-0), Methimazole (60-56-0), Methysergide (361-37-5) • Oxprenolol (6452-71-7), Oxyphenisatin (125-13-3), Penicillin (1406-05-9), Phenopyrazone ((3426-01-5), Pindolol (6673-35-4), Practolol (6673-35-4), Primidone (l25-33-7), Propranolol (525-66-6), Propylthiourtacil (51-52-5), Timolol (26839-75-8), Tolazamide (1156-19-0)	19.53,83,84
C. Drugs with tertiary amine group	
• Benoxaprofen (51234-28-7), Captopril (62571-86-2), Chlorpromazine (50-53-3) • Chlorprothixene (413-59-7), Cinnarizine (298-57-7), Danazol (17230-88-5), • Nalidixic acid (389-08-2), Perazine (84-97-9), Perphenazine (58-39-9), • Phenylbutazone (50-33-9), Phenylethylacetyl-urea (90-49-39), Promethanzine (60-87-7), • Pyrathiazine (84-08-2), Tetrazine (70816-59-0), Thioridazine (50-52-2), • Tolmetin (26171-23-3)	19,53,83,84

(*2*-NA), *4*-aminobiphenyl (*4*-ABP), and benzidine have been reported (63,64). The oxidative DNA damage induced by arylamine compounds may participate in chemical carcinogenesis in addition to the DNA adduct formation (55).

Correlation between DNA adduct formation and mutation was clearly supported by the finding that DNA adducts were pro-mutagenic lesions. Mutation can cause the activation of oncogenes. For example, c-*H-ras*, the oncogene that has been found in normal mouse liver as well as in mouse liver tumors, could be activated by a point mutation caused by the adduct that is formed by the reaction of the reactive *2*-aminofluorine (AF) metabolite with the C-8-position of guanine (guanine-C-*8*-AF) (65).

A large-scale pathway-based analysis of bladder cancer genome-wide association data from five studies (3,532 cases and 5,120 controls) of European background (n = 5 studies) was performed by Menashe, *et al*. (66). Many pathways and genes were included in their investigations. They revealed that seven pathways (aromatic amine metabolism, NAD biosynthesis, NAD salvage, clathrin derived vesicle budding, lysosome vesicle biogenesis, retrograde neurotrophin signaling, and mitotic metaphase/anaphase transition pathways) are involved with the development of bladder cancer. These pathways belong to three fundamental cellular processes, i.e. metabolic detoxification, mitosis, and clathrin-mediated vesicles. Identification of the aromatic amine metabolism and NAD biosynthesis (which are also related to aromatic amines) pathways involved in the development of bladder cancer, indicated that aromatic amines are important factors in the induction of bladder carcinogenesis. In a brief summary, arylamine-DNA adduct formation, reactive oxygen species (ROS), oxidative DNA damages and other factors such as promotion, tissue growth, differentiation, genetic susceptibility, metabolic pathways, expression/suppression of oncogenes and suppressor genes, etc. are all important determinants of arylamine-induced carcinogenesis. How arylamine is involved in detail in all these processes needs to be further illustrated.

To assess the mode of action and the carcinogenic potential, it is also necessary to analyze both the genotoxic and epigenotoxic effects of these carcinogens. It is possible that both genotoxic and epigenotoxic effects are necessary for tumor development (67,68). How these epigenetic effects enhance the genotoxic effects or vice versa needs to be investigated.

It is of interest to note that aromatic amines are also required to be metabolically activated in

order to induce lupus. Hofstra *et al.* (69) indicated that isoniazid is oxidized by activated leukocytes (white blood cells), possibly to a reactive intermediate, which may have implications for isoniazid-induced lupus. Myeloperoxidase is likely the enzyme in the leukocyte involved. Rubin and Cumutte (70) demonstrated the capacity of neutrophil (a kind of white blood cell) to mediate metabolism of procainamide and established the role of myeloperoxidase released during degranulation and H_2O_2 derived from the respiratory burst in the direct cooxidation of procainamide to procainamide-hydroxylamine (PAHA). Experiments with procainamide and rat or human liver microsomes cause the production of the unstable PAHA, which is taken up by erythrocytes and oxyhemoglobin to enhance the biological activity of PAHA (52). Jiang, *et al*. (71) also indicated that the neutrophil-dependent cytoxicity of lupus-inducing drugs required the enzymatic action of myeloperoxidase, resulting in the chemical transformation of the drug to a reactive intermediate. Hepatic oxidative metabolism also occurs with isoniazid and hydralazine (52). The capacity of lupus-inducing drugs to serve as myeloperoxidase substrates *in vitro* was associated with the ability to induce lupus (52).

Stites *et al*. (72) studied the hydralazine induced lupus and reported that the respiratory burst in leukocytes induce an increased production of free radicals and oxidants such as hydrogen peroxide. These oxidants have also been found to react with hydralazine to produce reactive species that are able to bind with protein (73). Monocytes, one type of leukocyte, detect the antigen and relay the recognition of T (helper cells), creating antinuclear antibodies leading to an immune response (74).

In 1986, Thomas and Messner studied the lupus inducing drugs on the B-DNA to Z-DNA transition of synthetic DNA{(polydG-me^{5}dC), poly(dG-me^{5}dC)} using circular dichroism spectroscopy. Procainamide and hydralazine were found to reduce the midpoint of B-DNA to Z-DNA transition from 0.8 M NaCL to 0.5 M NaCL, and to increase the rate of this transition at 1 M NaCL. Procainamide caused a slight reduction in the helix-coil transition (melting) temperature of calf thymus DNA. At the concentration of 1:1 (DNA phosphate: drug ratio), procainamide and hydralazine also caused the aggregation of calf thymus DNA. Since altered DNA conformations, such as Z-DNA, are more immunogenic, these results suggest that the induction or stabilization of Z-DNA by these drugs might be important in the pathogenesis of at least some cases of lupus (75).

Zacharias and Koopman (76) investigated how procainamide and hydralazine altered the structure of superscoiled circular DNA domains. They demonstrated, indeed, the different potentials to interact with DNA and altered the tertiary topology of DNA domains. They concluded that the *in vivo* capacity of procainamide and hydralazine to induce antinuclear antibodies may be related to their ability to influence structural features in chromosomal DNA domains or nucleosomes, thus liberating antigenic structural epitopes in DNA and/or DNA-associated proteins (76).

Although many studies have been conducted on DIL, there is no common thread; however, at least one theory that explains all of DIL has been identified thus far. Nevertheless, DIL affords an opportunity to understand the pathophysiology of lupus in general (53). Lupus genesis is a complicated process.

Therefore, both lupus inducing drugs and carcinogens require metabolically activation into reactive intermediates, which interact with DNA. The metabolic activation is reported mainly by cytochrome P450 IA2 in the liver for carcinogens, but the activation of lupus inducing drugs is by myeloperoxidase in the liver or blood. There seems to be a common metabolic pathway for both carcinogenesis and lupus genesis. This pathway leads to the interaction of the unstable reactive intermediates with DNA to form DNA adducts, which lead to mutations with the end result of cancer or induces biotransformation of DNA from normal B-DNA into Z-DNA, which is immunogenic (75,76) and results with the formation of lupus. This is certainly an interesting hypothesis and deserves further investigation.

Most studies report an association of the slow *N*-acetylator status with elevated bladder cancer risk (77). Lathita (78) also showed that 29 out of 30 patients with DIL were slow acetylators. Fink *et al*. (79) reported that patients with the genetically determined fast acetylator status have a much lower risk of developing DIL in response to a variety of drugs. Both arylamines induced cancer patients and patients with DIL are slow acetylators. It seems that aromatic amine carcinogenesis and lupus genesis are sharing some similar molecular pathways. Would the lupus patients eventually develop cancer?

Further, Usha (80) reported that eczema, contact dermatitis, asthma, chronic bronchitis, tuberculosis, hematoma, irritation of eyes, and bladder cancer were common among the workers of textile industries in Sanganer, India. The major cause of these diseases may be partially due to the aromatic amine released from azo dyes, which are the major dyes used in the textile industry. In view of the many diseases due to arylamines, the impact of arylamines on human health is much more serious than we can imagine.

Exogenous arylamines or an endogenous arylamines at the xenobiotic concentrations would no doubt interfere with the balance of various normal biochemical and physiological functions. How

malfunction of the normal metabolism in the presence of a carcinogenic (or allergenic) arylamine could facilitate the development of carcinogenesis (or lupus genesis) is a critical question. It is vital to have a better understanding of the detailed mechanisms. Indepth understanding of molecular mechanisms would certainly be beneficial to the development of a strategy of design of chemotherapy of arylamine-induced cancer or other maladies.

The structure-activity relationship of carcinogenic compounds is an important subject. Benigni and Passerini (82) illustrated that the gradation of potency of aromatic amines and arylamines depends on their hydrophobicity and on electronic (reactivity and the propensity to be metabolically transformed) and steric properties. Chung and Cerniglia (6) also found that some functional groups within the molecule of these amines affect their genotoxicities. The SO_3 group will increase the solubility and decrease genotoxicity of the compounds, but halogen or NO_2 group will increase their genotoxicities. Such a study will help develop safer and more environmentally friendly industrial chemicals. In addition, one approach is to look for chemical substituents that will decrease the genotoxicities of arylamines. Another approach is to look for antimutgenic, antigenotoxic, and antilupusgenic chemicals. As an example, Makena and Chung (83) found that various plant polyphenols can decrease the benzidine-induced genotoxicity. Would these plant polyphenols prevent the formation of lupus or other immunologic disorders?

6. CONCLUSION

Arylamines are human carcinogens and environmental pollutants; they can be generated by many ways and enter the human body through various routes. Arylamines can also cause various human maladies including cancer, lupus, and/or other allergenic/immunological diseases. Regulation, minimization, or elimination of arylamines from exposure to the environment will certainly benefit public health. A strong investment in arylamine-related studies would be worthwhile for human welfare.

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Send correspondence to: King-Thom Chung, Department of Biological Sciences, University of Memphis, Memphis, Tennessee 38152, Tel: 901-6784458, Fax: 901-678-4457 E-mail: kchung@memphis.edu