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Occurrence, uses, and carcinogenicity of arylamines

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1. ABSTRACT

Arylamines are chemically synthesized and contained in oxidants, epoxy polymers, explosives, fungicides, pesticides, colorants, polyurethanes, and are used in various chemical industries. Many arylamines are present in cigarette smoke, cooking fume hoods, foods, automobile exhaust, industrial sites, *etc.* Arylamines can be generated through azo reduction by intestinal, skin, and environmental microbes from widely used azo dyes; by reduction of the nitro-group containing polyhydrated hydrocarbons; or by release of burning nitrogen containing organic materials. Some medicines are arylamines. Some arylamines are essential constituents, or the result of abnormal metabolism of foods. Some arylamines are mutagenic or carcinogenic. Arylamines can also cause various diseases. Some arylamine are the major etiological agents of bladder tumors but may induce other types of cancers. The organ, tissue, and species specificity of the arylamine-inducing carcinogenesis may be determined by their availability, distribution, and the presence of metabolic activation/detoxicification enzymes of each organ or tissue of different species. The ubiquitous arylamines, therefore, pose serious hazards to human health and environment. This article will address the occurrence, uses, carcinogenicity, and other arylamines-induced diseases.

2. INTRODUCTION

Arylamine is a chemical group with at least one amino group bound to an alkyl hydrocarbon or an aromatic system. The term is called aromatic amine if the arylamine component is an aromatic hydrocarbon. Heterocyclic aromatic amine contains a heterocyclic ring structure. For example, *2*-amino-*1*-methyl-imidazole(*4,5-f*) (IQ), *2*-amino-*3-8*-dimethyl-imidazole (*4,5-f*) quinolone (MeIQx), *2*-amino-*1*-methylphenylimidazo(*4,5-b*)pyridine (PhIP), etc. are known food-derived mutagens and carcinogens and are not included in this definition. Information about the mutagenicity and carcinogenicity of heterocyclic aromatic amines is available elsewhere and therefore will not be included in this article. For aromatic amines, the chemical reactivity of this amino group is dependent on the mesomeric interaction with the aromatic system, which is determined by further substitutes and steric factors (1, 2). Based on the substitution, these arylamines may form primary, secondary, or tertiary amines. Common examples

of arylamines are *4*-aminobiphenyl, auramine, benzidine, *3, 3'*-dimethyl-benzidine (*o*-tolidine), *3, 3'*-dichloro-benzidine, *3, 3'*-dimethyoxybenzidine, magenta, *4, 4'*-methylene-*(2*-chloroaniline) (MOCA), *2*-naphthylamine, *o*-toluidine, and *4*-chloro-*o*-toluidine. The amino group is an important functional group responsible for most of the key biochemical interactions.

This article addresses the occurrence, use/application, the various types of cancer, and other maladies in humans and animals caused by some commonly used arylamines. Research perspectives concerning arylamine inducing diseases are also discussed.

3. OCCURRENCE AND USES

Many arylamines are chemically synthesized and used in industry. A few examples are mentioned below.

3.1. Auramine

Auramine (Case No. 2465-27-2) {*4, 4'*-carbonimidoyl-bis-(*N, N'*-dimethyl)-hydrochloride (1:1) also called C.I. Basic Yellow 2, is a benzenamine. Currently, auramine manufacturing is mainly located in India and China. It is available from various suppliers in many countries. Of the suppliers, Amesco offers this dye in bulk form and Wako Chemical USA in pure form.

Auramine is used extensively as a yellow dye for paper, textiles, and leather (3). Historically, it was used in brilliantine (4). Particularly in the 1930s, it was used to prepare Solvent Yellow 34, which is used as a solvent dye in inks in typewriter ribbons, ballpoint inks, printing inks, and stamp inks. The presence of auramine in ballpoint ink has been used for forensic research (5, 6). It has also been used as a solvent dye in oils and waxes in Brazil (7). Auramine is also widely used as a florescent staining agent to stain acid-fast bacteria in septa or infected tissues, in combination with the dye rhodamine in the truant auramine-rhodamine stain for Mycobacterium tuberculosis (8). Auramine has also been reported to be used as a food colorant in some countries of Latin America (9). Some fishermen used it to dye maggots through internal dyeing involving feeding the larvae meat treated with auramine or other dyes such as rhodamine or chrosoidine (10, 11). Auramine has also been reported to color the smoke in military applications (12) and firework displays (13). Auramine is present in fresh peas in India (14, 15) and bean products in China (16). The major source of auramine pollution in the environment is possibly released from Solvent Yellow 34.

The U.S. National Occupational Exposure Survey (1981-1983) estimated that 19,092 workers were exposed to auramine. The workers included the paper and health products and the health services industries (17). Case and Pearson (18) described groups of workers in Britain who used auramine.

3.2. Benzidine

Benzidine (Case No. 92-87-5) (*1, 1'*-biphenyl)-*4, 4'*-diamine) is used mainly as an intermediate in the production of azo dyes, sulphur dyes, fast color salts, naphthols, and other dyeing compounds (19). Benzidine based-dyes were primarily used to color textiles, leather, and paper products, and were also used in the petroleum, rubber, plastics, woods, soap, fur, and hair dyes industries.

Total U.S. production of benzidine reached 14 million kilograms (31 million lbs.) in 1948 (19). In 1974, nine U. S. manufacturers produced benzidine-based dyes. By 1979, only one manufacturer remained, producing 17 benzidine-based dyes. Domestic production was about 2.9. million kilograms in 1976 and dropped to about 780 kg in 1978. By the end of 1979, most manufacturers started phasing out the use of benzidine-based dyes and replacing them with other types of dyes. More than 300 benzidine based dyes are listed in the Colour Index, including 18 commericially available in the United States. Access to these dyes for home use is no longer permitted (20).

Benzidine is released by the reduction of benzidine-based azo dyes such as Acid Black 29, Acid Black 232, Acid Black 94, Acid Orange 45, Acid Red 85, Azoic Diazo Component 112, Direct Black 4, etc. (Table 1). Occupational exposure to benzidine and benzidine congeners and their related dyes can occur during the production and use of these substances. Benzidine-based dyes and benzidine congeners-based dyes can be metabolized to benzidine and the respective congeners, which may result in aromatic amine exposure (21, 22, 23, 24, 25).

3.3. Benzidine congeners

3, 3'-Dimethylbenzidine (also called *o*-tolidine) (Case No. 119-93-7) (*4, 4'*-diamino-*3, 3'*-dimethylbiphenyl) is used as a dye or an intermediate for producing dyestuffs and

Table 1. Examples of arylamine and their sources or references

Names of Arylamines	Sources or references
Auramine	Released from paper and allied industry, and the health service industry, auramine-production, and other process chemicals (e.g. dimethylaniline, formaldeyde sufur, ammonium chloride, ammonia , etc., (3, 4, 8, 9, 10, 14, 15, 16, 209.)
Benzidine*	Released from Acid Black 29; Acid Black 232; Acid Black 94; Acid Orange 45; Acid Red 85; Azoic Diazo Component 112; Direct Black 4; Direct Black 29; Direct Black 38; Direct Blue 2; Direct Blue 6; Direct Brown 1; Direct Brown 1:2; Direct Brown 2; Direct Brown 6; Direct Brown 25; Direct Brown 27; Direct Brown 31; Direct Brown 33; Direct Brown 51; Direct Brown 59; Direct Brown 74; Direct Brown 79; Direct Brown 95; Direct Brown 101; Direct Brown 154; Direct Dye (C.I. No. 21060); Direct Green 1; Direct Green 6; Direct Green 8; Direct Green 8:1; Direct Orange 1; Direct Orange 8; Direct Red 1; Direct Red 10; Direct Red 13; Direct Red 17; Direct Red 28; Direct Red 37; Direct 44; Direct Violet 1; Direct Violet 4; Direct Violet 12; Direct Violet 22; Direct Yellow 1; Direct Yellow 24; Mordant Red 57; Direct Black 100; Direct Black 126; Direct Black 131;Direct Blue 11, Direct Blue 16: Direct Blue 19, Direct Blue 26, Direct Blue 38;Birect Blue 42 Direct Blue 43: Direct Blue 47; Direct Blue 49; Direct Blue 51; Direct Blue 58; Direct Blue 63; Direct Blue 64; Direct Blue 131;Direct 177; Direct Blue 230; Direct Brown; Direct Brown 5; Direct Brown 7, etc.
3, 3'-Dichlorobenzidine*	Released from Direct Red 46; Direct Orange 60: Acid Dye (C. I. No. 23070), Direct Red 61, etc.,
3, 3'-Dimethylbenzidine (*o*-tolidine)*	Released from Acid Black 209; Acid Red 114; Acid Red 24; Azoic Diazo Component 113; Direct Black 154; Direct Blue 3;Direct Blue 14; Direct Blue 21; Direct Blue 25; Direct Blue 295; Direct Brown 222; Direct Brown 223; Direct Green 85; Direct Orange 6;Direct Orange 7; Direct Orange 10; Direct Red 2; Direct Red 21; Direct Red 22; Direct Red 39; Direct Blue27; Direct Blue 31; Direct Blue 39; Direct Blue 53; Direct Blue 60 Direct Blue 231; Direct Red 67; Acid Red 167; Direct Violet 21' Direct Yellow 48.etc.
Magenta {Magenta 0, Magenta 1, Magenta II, Magenta II I (New fuchin)}	Released from dyestuffs manufacturing plant, commercially produced by various countries. (17, 18, 41, 43, 234)
4, 4'-Methylene-bis-(2-chloroaniline) (MOCA)	Released from coating and casting polyurethane plants, commercially produced by various countries.(43, 47, 48)
p-Phenylenediamine	Released from hair dyes, commercially available from various countries (85, 86, 87)
4-Aminobiphenyl	Released from drugs, D & C Yellow 1, tobacco smoke, cooking oil, etc., (50, 56, 57, 58, 64, 65, 159)
2-Naphthylamine*	Released from Acid Red 16, Azoic Diazo Component (C.I. No. 37270), Direct Dye (C. I. 29260); Solvent Orange 8, hair dyes. etc.
o-Toluidine*	Released from Acid Red 114, Acid Red 115, Acid Red 148, Acid Red 158, Acid Red 24, Acid Red 265, Acid Red 35, Acid Dye (C. I. No. 19610), Direct Red Dye (C.I. No. 19565), prilocaine and lidocaine administration, hair dyes, rubber industry, etc., (59, 64, 65, 69; 72)
4-Chloro-*o*-toluidine*	Released from Azoic Diazo Component 11, Disperse Red 220, Direct Brown 147 (C. I. No. 23360), chlordimeform, etc.(15, 161)
*Source: Opinion of the Scientific Committee on Cosmetic Products and Non-Food Product Intended for Consumers (SCCNFP) Concerning the Safety Review of the use of certain Azo-Dyes in Cosmetic Products, adopted by the SCCNFP during the19th plenary meeting of 27 February 2002, SCCNFP/0495/01, final	

pigments, or to produce polyurethane-based high strength elastomers, coatings, and rigid plastics. *3, 3'*-Dimethylbenzidine is used in small quantities by clinical laboratories in test tapes for the detection of blood, and is used by water companies, swimming pool owners, and others to test for chlorine in water or air (26). It is also used in chemical tests for the detection of gold.

In 1978, the major company producing *3, 3'*-dimethylbenzidine in the United States stopped producing this compound; its annual production had averaged approximately 200,000 lb from report of National Toxicological Program (2005). Imports appeared to be the major source of *3, 3'*-dimethylbenzidine in the United States. The major sources of *the 3, 3'*-dimethylbenzidine released to the environment are the reduction of *3, 3'*-dimethylbendine-based azo dyes including Acid Black 209, Acid Red 114, Direct Black 154, Direct Blue 45, etc. (Table 1).

3, 3'-Dichlorobenzidine (Case No. 1331-47-1) (dichloro(*1,1'*-biphenyl)-*4, 4'*-diamino) is used for the production of dichlorobenzidine-based dyes. The United State International Trade Commission (USITC) reported that the 1983 production volume of *3, 3'*-diclorobenzidine-based dyes was over 18 million lbs. However, *3, 3'*-dichlorobenzidine is no longer used to manufacture dyes in the United States (27). Available information indicates that *3, 3'*-dichlorobenzidine was produced and/or supplied in Hong Kong Special Administrative Region, India, China, the United Kingdom, and the USA (28).

The *3, 3'*-dichlorobenzidine released into the environment is probably not from reduction of the *3, 3'*-dichlorobenzidine-based azo dyes. Studies in which azo compound based on *3, 3'*-dichlorobenzidine such Pigment Yellow 13 orally administered to rats, hamsters, rabbits, and monkeys were generally not detected in significantly amount of *3, 3'*-dichlorobenzidine in the urine (29). The potential exposure to *3,3'*-dichlorbenzidine is probably during the production of dichlorobenzidine-based dyes.

3, 3'-Dimethoxylbenzidine (also called *o*-Danisidine) (Case No. 119-90-4) (*1, 1'*-biphenyl)-*4, 4'*-diamine) is used almost exclusively as a chemical intermediate for production of dyes and pigments. *3, 3'*-Dimethoxy-benzidine is also used as a dye for paper, plastics, rubber, and textiles, and a test substance to detect metals, thiocyanates, and nitrite (30, 31). The Society of Dyers and Colourists reported its use in the production of 89 dyes in 1971, including Direct Blue 218, Pigment Orange 16, Direct Blue 1, Direct Blue 15, Direct Blue 8, and Direct 76, and Direct Blue 98. Some of *3, 3'*-dimethoxylbenzidine are used as a chemical intermediate to produce *o*-dianisidine diisocyanate for use in adhesives and a component of polyurethane.

Data on production of *3, 3'*-dimethoxybenzidine in the USA were last reported in 1967 when five companies produced approximately 368,000 lbs. (30). The aggregate production volume of *3, 3'*-dimethoxybenzidine dihydrochloride was less than 500,000 lbs. (31). Available information indicates that *3, 3'*-dimethoxybenzidine was produced and/or supplied in Germany, Hong Kong Special Administrative Region, India, Japan, Switzerland, the United Kingdom, and the USA (28), whereas *3, 3'*-dimethoxybenzidine dihydrochloride was produced and/or supplied in the following Countries: Germany, Hong Kong Special Administrative Region, India, Japan, China, and USA (28).

3.4. Magenta

Magenta is another common arylamine. Historically, the dye Magenta has been referred to the mixture of major constituents comprising Basic Fuchsin, Basic Red 9 (Magenta O) (Case No. 569-61-9) (*4, 4'*-((*4*-imino-*2, 5*-cyclohexandien-*1*-ylidene)methylene)bis(benzenamine), (Magenta 1) (Rosaniline) (Case No. 632-99-5){(*4*- aminophenyl)-*4*-(*4*-imino-*2, 5*-cyclohexadien-1-ylidene)methyl)-*2*-methylbenzenamine monohydrochloride}, Magenta II (Case No. 26261-57-4) {*4*-(*4*-aminophenyl(*4*-imino-*3*-methyl-*2, 5*-cyclohexadien-1-ylidene)methyl)-*2*-methylbenzenamine monohydrochloride}(1:1), and Magenta III (New Fuchsin) (Case No. 3248-91-7) {*4*-(*4*-amino-*3*-methyl)(*4*-imino-*3*-methyl-*2, 5*-cyclohexadien-ylidenemethyl)-*2*-methyzenamine monohydrochloride (1:1).

Magenta III is used as thin-layer chromatography (TLC) developing for perfluorinated organics. Under the name of Basic Violet 14, Magenta is used in hair dyes and also in cosmetic products not intended to come in contact with mucous membranes (EU Directive 76/768/EEC). Magenta stains animal fibers directly and vegetable fibers after mordanting. Under the name of Basic Red 9, magenta is also used as a colorant in artists' paints (32). Magenta is antiseptic against gram positive bacteria and can be used in dermatology for the treatment of pyoderma, dermatitis, intertrigo, eczema, and burns in solution of 2-5 % (33). Known as Castellani's paint or Magenta paint, Magenta has been used topically since it was introduced in the 1920s (34) to treat skin conditions such as fungal skin lesions (35) or infective dermatitis (36). Carbol-Fuchsin solution, containing less than 1% of Basic Red 9, is used to treat postoperative phenol nail procedure and also as a dermal first aid antiseptic drying agent (37). Magenta is reported to be used as food irradiation dosimeter in an aqueous solution of

3.1.3 x 10^{-5} mol/L (38) and as a meat-marking color in New Zealand (39).

The group of workers exposed to Magenta includes those who worked in the dyestuffs manufacturing plant in Germany (40), the manufacture of Magenta in the British chemical industry (1910-1952) (18), and the manufacture of New Fuchsin in an Italian dyestuffs factory (41, 42). Occupational exposure can occur during its use as a dye intermediate and when dyeing textiles (cotton and wool), fabrics, and paper products (43).

3.5. *4, 4'*-Methylene (*2*-chloroaniline) (MOCA)

4, 4'-Methylene (*2*-chloroaniline) (MOCA) (Case No. 101-14-4) (bis-*4*-amino-chlorophenyl)-methane is a synthetic chemical used in industry for coating and casting polyurethanes. There is no commercial use for MOCA other than laboratory work (44).

US manufacturers stopped producing MOCA in 1983, and MOCA in the US is imported (45). The amount of import was 5 million lbs. in 1983 and 2.0. million lbs. in 1991 (45). Most of MOCA used in the US is manufactured in Taiwan and China where the annual production is about 5,000 to10, 000 tons (46).

Occupational exposure to MOCA occurs during its production. MOCA is present in various form of liquid emulsion, solid pellets with dust, or solid pellet without dust. Workers can be exposed through contact by inhalation, ingestion, or dermal absorption. It was estimated that the number of workers potentially exposed in the U. S. in 1977 ranged from 2,100 to 30,000; in 1979, 1,400 workers were directly exposed and 7,400 indirectly exposed while working in polyurethane manufacturing processes involving MOCA (47). In 1982, the EPA estimated that 1,400-2,700 workers were directly exposed, and 7,600-15,200 were indirectly exposed. Rappaport and Morales (48) estimated in 1972, that 10,000 people in industrialized countries worldwide were exposed occupationally.

3.6. *4*-Aminobiphenyl

4-Aminobiphenyl (*1, 1'*-biphenyl)-*4*-amine (Case No. 92-67-1) has been used formerly as rubber antioxidant. It is still used in the detection of sulfates and as a model carcinogen in mutagenicity studies and cancer research (Merck on-line).

4-Aminobiphenyl has not been produced commercially in the U. S. since the mid-1950s (49). It was present in the drugs and cosmetic color additive D & C Yellow No 1; however, use of this color additive was discontinued in the late 1970 (50). *4*-Aminobiphenyl also has been reported as a contaminant in diphenylamine (50) and in food dyes (51). It can also occur in workers exposed to benzidine and benzidine-based dyes, from which *4*-aminobiphenyl can be metabolically released by deamination of benzidine (52, 53). It is also present in tobacco smoke (54, 55) and fumes from cooking oils (56).

Living near benzidine-contaminated sites could entail *4*-aminobiphenyl exposure, as benzidine in the environment can be degraded into *4*-aminobiphenyl by bacterial culture (57). Historically, occupational exposure to *4*-aminobiphenyl mainly occurred during its production and its use as a rubber antioxidant and dye intermediate.

P-Phenylenediamine, the key constituent of color development for many permanent hair dyes, can be contaminated with *4*-aminobiphenyl up to 500 ppb (58). *4*-Aminobiphenyl was detected in 8 out of 11 different oxidative and direct hair dyes tested (58, 59). In other words, not only smokers and occupational workers, but also the general population is likely to have chances to be exposed to this carcinogen.

3.7. *2*-Naphthylamine (*2*-NA)

2-Naphthylamine (*2*-NA) or *β*-naphthylamine (Case No. 91-59-8) (*β*-naphthaleneamine), is now used only in laboratory research. It was formerly used commercially as an intermediate in the manufacturing of dyes, as an antioxidant in the rubber industry, and to produce *2*-chloronaphthylamine (30, 50). According to the European Union (EU) legislation, the manufacture of *2*-NA has been banned since 1998.

2-NA is formed in the pyrolysis of nitrogen-containing organic matter and can occur in nature (60, 61). It may occur in the waste streams from plants where it is produced and used; it has been reported to be present in the effluent from certain dyestuff factories in Japan (62). Occupational exposure of the *2*-NA mainly occurs in its production and in the manufacture of azo dyes. It can occur in the laboratory when *2*-NA is used for cancer research and in workers exposed to pyrolysis fumes containing *2*-NA

such as foundry fumes, environmental tobacco smoke, heated cooking oils or workers exposed to *2*-nitronaphthalene (e. g. foundry workers), a nitro-PAH that can be metabolized to *2*-NA. Exposure can also occur in workers exposed to products containing *2*-NA as a contaminant such as certain rubber chemicals. Several dye intermediates have been shown to contain a small amount of *2*-NA in *1*-naphylamine, *6*-amino-*2*-naphthalene sulfonic acid, auramine (63), hair dyes (59, 64) and rubber antioxidants such as Nonox S and Agerite Resin. The general population can be exposed to *2*-NA environmentally via tobacco smoke, via fumes containing *2*-NA, or hair dyes contaminated with *2*-NA. Exposure to the nitro-PAH *2*-nitronaphthalene can also form an indirect source of exposure to *2*-NA. The nitro-PAH *2*-nitronaphthalene is formed by the incomplete combustion of organic material and generally occurs in the environment as a mixture of other nitro-PAH and non-nitro-PAH compounds.

3.8. *o*-Toluidine

o-Toluidine (Case No. 95-53-4) is also called *2*-methylaniline or *2*-aminotoluene, *2*-methylbenzanamine or *1*-amino-*2*-methylbenzene. *o*-Toluidine and *o*-toluidine hydrochloride are used primarily as intermediates in the manufacture of more than 90 dyes and pigments. They are used in acid-fast dyestuffs, azo pigment, triarylmethane dyes, sulfur dyes, and indigo compounds. *o*-Toluidine is also used as an intermediate for synthetic rubber and rubber vulcanizing chemicals, pharmaceuticals, and pesticides (31,65). Other minor uses of *o*-toluidine and its hydrochloride salt are as an intermediate in organic synthesis and as an ingredient in a clinical laboratory reagent for glucose analysis (31).

o-Toluidine is not known to be present as a natural substance; however, the general population is known to be exposed to *o*-toluidine though the origin is not known. Occupational exposure to *o*-toluidine can occur during its production or the production of dyes, pigments, and rubber chemicals manufactured from *o*-toluidine. Laboratory and medical personnel may be exposed when using *o*-toluidine for staining tissues.

Unspecified isomers of *o*-toluidine were found in commercially available samples of kale, celery (1.1. mg/kg), and carrots (7.2. mg/kg) (66), and also has been identified in the volatile aroma components of black tea (67). *o*-Toluidine has been detected in part per billion levels in human breast milk samples (68) from both smokers and nonsmokers (<0.0.1 to 0.2.6 ppb). *o*-Toluidine occurs in the constituents of tobacco smoke (54). Eight U.S. commercial cigarette brands have been found to contain 8.6.-144.3.ng of *o*-toluidine per cigarette (60). In a study from Turkey (59, 64), *o*-toluidine was found in 34 of the 54 hair dyes tested, at quantities up to 1,547 (µg/g). Excretion of *o*-toluidine was detected in the urine of the smokers as well as nonsmokers (70). Riffelmann *et al*. (71) reported that there are significant differences between smokers and nonsmokers. *o*-Toluidine is a major metabolite of prilocaine (RS)-*N*-(*2*-methylphenyl)-N^2-propylalaninamide), which is a widely used for local anesthetic. Prilocaine can interact with hemoglobin to form hemoglobin (Hb) adducts. It was found that *o*-toluidine-Hb adducts were significantly increased 24 hr after prilocaine treatment from *o*-toluidine was assessed (72). Prilocaine, as a component of EMLA (eutectic mixture of local anesthetics), is also used as a pain reliever in neonates during circumcision (73) and during venipuncture in children (74).

3.9. *4*-Chloro-*o*-toluidine

4-Chloro-*o*-toluidine (Case No. 95-69-2) (*2*-amino-*5*-chlorotoluene) and its hydrochloride salt have been used commercially to produce azo dyes for cotton, silk, acetate, and nylon and as an intermediate in the production of Pigment Red 7 and Pigment Yellow 49. As an azoic diazo component, *p*-chloro-*o*-toluidine is used in the synthesis of some azoic dyes (65, 75, 76).

p-Chloro-*o*-toluidine has also been used in the manufacture of the pesticide chlordimeform (75). It has been used in the production of chlordimeform since the 1960s (65, 75, 77). *p*-Chloro-*o*-toluidine is also an impurity (as the hydrochloride salt) and a metabolite of chlordimeform, which is an insecticide and acaricide.

Occupations with the greatest potential for exposure to *4*-coloro-*o*-toluidine include those involved in the production and use of *4*-chloro-*o*-toluidine as an intermediate for the manufacture of dyestuffs, pigments, and chlordimeform. Exposure *to 4*-chloro-o-toluidine can also occur in workers applying chlordimeform. Chlordimeform has not been used in the USA since Nov. 30,1989 (31). Workers could be exposed to *4*-chloro-*o*-toluidine during its laboratory use as an immunochemical stain. Under the name Fast Red TR, *4*-chloro-*o*-toluidine is also reportedly used in colorimetric method to assess the authenticity of drugs.

4-Chloro-*o*-toluidine occurred in water as a result of the hydrolysis of chordimeform via hydrolysis of the intermediate *N*-formyl-*4*-chloro-*o*-toluidine (78). The microbial degradation of chlordimeform to *4*-chloro-*o*-toluidine in soils by a number of bacterial species has been reported (79). *4*-Chloro-*o*-toluidine has been identified in field samples of plant materials treated with chlordimeform, e.g. young bean leaves at concentrations of less than 0.1.- 0.2. ppm; in grape stems and berries at 0.0.2- 0.5. ppm; and in prunes and apples at less than 0.0.4 ppm (80)). *4*-Chloro-*o*-toluidine was found in rice grains at 3-61 ppb in straw parts 42 days after the last of three treatments with chlordimeform (81). *4*-Chloro-*o*-toluidine was also detected as a metabolic product of cotton plants, cargo rice and husks, cucumbers, and apples after treatment with chlordimeform (82, 83, 84).

3.10. Others

There are other arylamines used in various industries. For examples, *p*-phenylenediamine, *p*-aminophenol, *4, 5*-diaminopyrazol, pyrimidine, *m*-aminophenol, *m*-phenylenediamine, *2, 5*-diaminotoluene, *N*-phenyl-*p*-phenylenediamine, *o*-aminophenol, *2*-amino-*4*-chlorophenol, *2*-nitro-*p*-phenylenediamine, *4*-amino-*2*-nitrophenol are used as hair dye components (85, 86, 87). In medicine, there are many arylamines used to treat various diseases. For examples, procainamide is used to treat heart rhythms;isoniazid is known to treat tuberculosis; sulfonamides are well known sulfur drugs. Martelli and Bramibilla (88) reported that there were more than 109 arylamine drugs, representing a wide variety of therapeutic families. Many of the new drugs including arylamine entering the drug marketplace can cause an increasing number of disorders including lupus. Arylamines are a group of chemicals that are profusely exposed to the modern industrial world.

Arylamines can be produced by combustion of nitrogen-containing organic materials at high temperatures, and are present in cigarette smoke and cooking fume hood smoke (54 -56). A large amount of arylamine is released by degradation of azo compounds, which are widely used in a variety of industries including food, paper, textiles, and other industries. Chung *et al.* (21, 22, 23, 24, 25, 89) reported that intestinal microbiota and environmental microorganisms including bacteria, fungi, and helminths could produce aromatic amines by cleavage azo dyes ingested from food or contaminated water. Plazek *et al*. (90) reported that human skin bacteria can break down azo dyes to aromatic amines. Keck *et al*. (91) demonstrated that reduction of azo dyes to release aromatic amines could be accomplished by redox mediators free of living microorganisms. The azo dye degrading enzymes have been reviewed (92). The typical examples of aromatic amines produced by industrial and cosmetic dyes (mainly azo dyes) are listed in Table 1.

Arylamines can also be produced by reduction of nitrated polycyclic aromatic hydrocarbons (nitro-PAHs) by anaerobic bacteria of human intestine (93, 94, 95). Nitro-PAHs have been detected in carbon toners, urban air particulates, diesel fuel emissions, used motor oils, barbecued food, and tea leaves (96-99). Nitrated-PAHs are ubiquitous environmental contaminants that are formed from various combustion sources (98). They are potent mutagens in the *Salmonella typhimurium* test system and in mammalian cells and have carcinogenic activity in laboratory animals (98-101). Another source of arylamines is from munitions such as dinitrotoluene (DNT). DNT can be reduced by environmental microoraganisms to aromatic amines, which contaminate the groundwater. Stayner *et al.* (102) reported that there was excess hepatobiliary cancer mortality among munition workers exposed to DNT.

Furthermore, there are numerous arylamines generated endogenously. Endogenous arylamines are either the end products or intermediates of normal metabolism. However, under certain conditions, endogenous arylamines could accumulate in high concentrations through abnormal metabolism. For example, excess intake of a tryptophan-containing diet or deficiency of vitamin B6, or during the induced activity of tryptophan dioxygenase (TDO) or indoleamine-*2, 3*-dioxygenase (IDO), various tryptohan metabolites, such as anthranilic acid, *3*-hydroxyanthranilic acid, kynurenine, *3*-hydroxykynrenine, and *3*-methoxykynurenine may accumulate (103-107). Some of the tryptophan metabolites have been reported to be involved in cancer (103). Other metabolites such as tryptamine and serotonin are also produced from tryptophan and are involved in many physiological functions. Other arylamines such as cadaverine, glutamine, putrecine, spermidine, spermine, arginine, ornithine, citrulline, histamine, dopamine, norepinephrine, epinephrine, thyroxine, triiodothyronine, sphingosine (sphingenine) are also produced endogenously. These arylamines could

Table 2. Human cancers caused by benzidine

Names of cancer	References
Bladder cancer	(162, 163, 164, 65, 166, 167, 168, 169, 170, 171, 172)
Genitourinary cancer	(173, 174)
Pancreatic cancer	(173)
Liver cancer	(174)
Gallbladder	(174)
Bile Duct cancer	(174)
Lung cancer	(174, 175)
Large Intestine cancer	(174)
Stomach cancer	(175)
Lymphopoietic cancer	(176)
Non-Hodgkin' lymphomas	(177)
Renal Cell cancer	(178)

certainly affect the normal physiological functions and health. Whether or not these endogenously arylamines are involved in cancer has not been reported.

4. CANCERS INDUCED BY ARYLAMINE

In 1895 in Germany, Rhen first reported that three out of four women employed in a single plant manufacturing magenta (fuchsin), appeared at their clinic with bladder cancer. Hueper in 1942 (108) suggested that a limited number of aromatic amines are responsible for bladder cancer in humans. Many epidemiological studies indicate that arylamines are the primary cause of bladder cancer since the reports of Rhen (40) and Hueper (108). Bladder cancer ranks ninth in worldwide cancer incidence. It is the seventh most common malignancy in men and seventeenth in women (109). An estimated 386,300 new bladder cancer cases and 150,200 deaths from bladder cancer were diagnosed worldwide in 2008 (110). The incidence of bladder cancer in the developed world is slowly decreasing (109). Such a trend of decreasing is probably due to the restricted use of the arylamines or the ban of some of the arylamines or azo dyes used. It is predicted that the burden of bladder cancer will increase in less developed areas of the world because of smoking prevalence that goes along with economic development (109). In the United States, bladder cancer is the fifth most common type of cancer with an estimated 68,000 newly diagnosed cases and 14,000 deaths in 2008 (111).

Bladder cancer is often used as the paradigm for the study of arylamine-induced carcinogenesis. Arylamines are generally recognized as the primary chemical that induced the formation of bladder cancers in humans, primarily the transitional cell carcinoma. Although bladder cancer was one of the first documented occupational cancers reported, arylamines can also induce cancers of other organs or tissues of humans and animals. For example, auramine, beside bladder carcinomas and papilloma, was also suspected to induce prostate and stomach cancers in humans (112, 113), and fibrosarcoma and hepatoma in Wistar rats (32). Benzidine has been reported to be the cause of many human cancers (Table 2). Benzidine also induces various cancers in different animals (Table 3). Some other arylamines caused both human and animal cancers are also tabulated in Table 4.

The International Agency in Cancer Research (IACR) of the World Health Organization (WHO) classified chemicals as carcinogens to humans as IARC category 1 or chemicals that are probably carcinogenic to humans as IARC category 2A and chemicals that are possible carcinogenic to humans are IARC category 2B (114). The agent is not classifiable as to its carcinogenicity to humans is IARC category 3. The agent probably not carcinogenic to humans is IARC category 4. According to the IACR's classification, benzidine, dyes metabolized to benzidine, MOCA, *4*-aminobiphenyl, *2*-naphthylamine, *o*-toluidine were classified as IARC category 1 carcinogens. *4*-Chloro-*o*-toluidine and occupational exposure to a hairdresser were classified as IARC category 2A carcinogens; auramine is classified as IARC category 2B carcinogen because auramine could cause animal tumors, and many mechanistic data indicated that auramine is genotoxic, but there is insufficient data to support that auramine caused cancers in humans.

However, Neumann (115) pointed out that the chemical and biochemical properties of aromatic amines, as well as the primary lesions, are very similar. Their acute and chronic effects can be explained by a common mode of action. Therefore, it is implied that all aromatic amines have a carcinogenic potential.

Since some arylamines are proven to be human carcinogens, the European Union banned certain azo dyes, which can be broken down under reductive conditions including human intestinal

Table 3. Animal tumors caused by benzidine or benzidine congeners

Chemical/animal	Cancer or Disease	References
Benzidine/mouse	Liver cancer	(179, 180, 181, 182, 183, 184, 185, 186)
	Breast tumors	(187)
	Zambal gland tumors	(184, 185, 187, 188)
	Mammary tumors	(185, 187, 189)
	Intestinal tumor	(185)
	Sarcomas	(184, 185)
	Fibrosarcoma	(188)
	Rhabdomyosarcoma	(188)
	Myeloid Leukaemia	(184, 187)
	Harderian gland tumor	(171)
	Lung cancer	(179, 183)
	Lymphoreticular tumours	(179)
	Angioma of the uterus	(181, 190)
Rat	Mammary carcinoma	(191)
Hamster	Liver tumor	(192)
	Cholangima	(192)
Rabbit	Bladder tumor	(193)
Dog	Bladder tumor	(194)
Frog	Liver tumor	(195)
	Haematopoietic tumor	(195)
Fish	Hepatotoxicity	(196)
3, 3'-Dichlorobenzidine/	Liver tumor	(196, 197)
Mouse	Carcinoma of the sebaceous gland	(198)
	Lung tumor	(198)
	Haematopoietic system tumor	(198)
	Sarcomas	(198)
	Tumors of lower jaw	(198, 199)
Rat	Zambal gland tumors	(198, 199, 200)
	Skin tumors	(198)
	Mammary Gland tumors	(199, 200, 201, 202)
	Intestinal tumors	(199, 201)
	Bladder tumors	(199, 201)
	Tumours of haematopoietic system	(198, 199)
	Salivary Gland tumors	(198)
	Liver tumors	(198, 199)
	Thyroid tumors	(198, 199)

Contd...

Table 3. Contd...

Chemical/animal	Cancer or Disease	References
	Leukemias	(200, 202)
	Sarcomas	(199)
	Sebaceous tumors	(201)
	Bone tumors	(201)
	Lung tumors	(202)
Dog	Bladder tumors	(203)
	Lung tumors	(203)
3, 3'-Dimethoxybenzidine/Rat (*o*-Danisidine)	Zymbal Gland tumors	(201, 204, 205)
	Mammary gland tumors	(201, 205)
	Ovarian tumors	(201)
	Bladder tumors	(204)
	Skin tumors	(204, 205)
	Preputial tumors	(205)
	Clitoral Gland tumors	(205)
	Uterus tumors	(205)
	Oral Cavity tumors	(205)
	Intestine tumors	(205)
	Liver tumors	(205)
	Mesothelium tumors	(205)
3, 3'-Dimethylbenzidine (*o*-Tolidine)/Mouse	Lung tumors	(206)
Rat	Mammary tumors	(191, 207, 208)
	Liver tumors	(208)
	Lung tumors	(208)
	Skin tumors	(207, 208)
	Preputial Gland tumors	(207, 208)
	Forestomach tumors	(207)
	Oral Cavity tumors	(208)
	Intestine tumors	(208)
	Clitoral Gland tumors	(208)
	Zymbal Gland tumors	(207, 208)

or liver enzymes. According to the European Parliament Directive 2002/61/EC of July 2002, the European Union 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. The list of banned aromatic amines and azo dyes was followed in 1994 by the German Consumer Goods Ordinance that restricted the use of certain azo dyes in consumer goods. The list has been up-dated since 1994 and now includes 21 aromatic amines and two azo dyes, which are shown in Table 5 (116)).

Table 4. Cancers caused by some arylamines

Name of Arylamine	Name of human cancer (reference)	Name of animal cancer (reference)
Auramine (technical grade)	Bladder cancer (18, 63, 209)	Liver neoplasm and sarcoma in rats, liver neoplasm in dogs (114)
Magenta	Bladder cancer (40, 41, 43, 209)	
Para-Magenta (C.I. Basic Red 9)		Hepatocellular carcinoma and adenoma in mice; skin, subcutis, Zymbal gland, thyroid gland, and liver tumors in rats; adrenal cortex adenoma, papillary, intestinal adenocarcinoma, adenocarcinoma & subcutaneous fibrosarcoma in hamster (210, 210)
MOCA (*4,4'*-Methylene-bis-(2-chloroaniline)	Bladder cancer (46, 212)	Haemangioma, hepatoma in mice, lung tumors in rats, pleural mesotheliomas, hepatocellular adenomas, and mammary gland adenocarcinomas in rats; bladder tumors in dogs (210, 203, 213, 214, 215.)
4-Aminobiphenyl	Bladder cancer (49, 216, 217, 218, 219)	Bladder carcinomas in rats, angiosarcoma, hepatocellular tumors and bladder carcinoma in mice; intestinal tumors, liver sarcoma, mammary tumors, uterus in rats; bronchioalveolar adenoma in mice; uterus carcinomas in rat; bladder carcinomas in rabbits bladder papilloma and bladder carcinoma in dogs (193, 220, 222, 223, 224, 225, 226, 227)
2-Naphthylamine	Bladder cancer (41, 63, 156, 162, 165, 169, 174, 209, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237)	Liver cholangioma, hepatomas in mice, bladder papilloma in rats, bladder carcinoma and hepatoma in hamster, papilloma and carcinoma of bladder in dog (108, 192, 236. 237, 238, 239, 240, 241,242, 243, 244, 245, 246, 247, 248)
o-Toluidine	Bladder cancer (160, 239, 240, 249, 20, 251)	Hepatocellular adenoma, carcinomas in mice, fibromas of the skin, spleen mammary fibroadenoma, and sarcoma of rat, fibrosarcoma or osteosarcoma of multiple organs of rat (76, 252, 253)
4-Chloro-o-Toluidine	Bladder cancer (254)	Haemangiosma and haemangiosarcoma of mice (255, 76)

5. DISCUSSION AND PERSPECTIVES

To assess the mode of action and the carcinogenic potential, it is also necessary to analyze both the genotoxic and epigenotoxic effects of these compounds. It is possible that both genotoxic and epigenotoxic effects are necessary for tumor development (117, 118). However, there are limited reports available on the epigenotoxic data. How these epigenetic effects interact with the genotoxic effects needs to be investigated.

Exogenous arylamines or an endogenous arylamine at the abnormal concentration would no doubt interfere with the balance of various normal biochemical and physiological function. Whether malfunction of the normal metabolism in the presence of the non-carcinogenic arylamine could facilitate the development of carcinogenesis is a critical question. Indepth understanding of molecular mechanisms would certainly be beneficial to the development of strategy of design of chemotherapy.

Chung and Cerniglia (119) found that the mutagenic moieties of mutagenic azo dyes are benzidine and *p*-phenylenediamine. Benzidine has been identified as a carcinogen for the urinary bladder cancer (120, 121). Benzidine and its congeners such as *3, 3',*-dimethylbenzidine (*o*-tolidine) *3, 3'*- dimethooxybenzidine (*o*-dianisidine) and *3, 3'*- dichlorobenzidine are the starting materials for the synthesis of azo dyes referred to as benzidine-based or benzidine congener-based dyes. Examples of benzidine-based dyes are Direct Blue 6, Direct Brown 9, and Direct Black 38. Benzidine-based dyes are manufactured by coupling tetrazotized benzidine with phenols and/or amines. However, the production of benzidine-based dyes has significantly decreased during the last century. Although the National Institute of Occupational Safety and Health (NIOSH) and the Environmental Protection Agency (EPA) documentally listed many potentially available derived dyes; only a few are found in commercial use in the United States and Europe (122). Some of these dyes are mutagenic and/or carcinogenic (123, 124). Benzidine and benzidine congneres can be generated from azo dyes through reduction by intestinal and environmental microorganisms (25, 89) (Table 2). Mutagenicity of benzidine, benzidine analogues, and benzidine-based dyes were reviewed and to be mutagenic

Table 5. List of aromatic amines and azo dyes banned in European Union

Name of Chemical	CAS number
Aminobiphenyl	92-67-1
4-Aminoazobenzene*	60-09-3
Benzidine	92-87-5
4-Chloro-Toluidine	95-69-2
2-Naphthylamine	91-59-8
4-Amino-*2', 3*-dimethylazobenzene*	97-56-93
2-Amino-*4*-nitrotoluene	99-55-8
4-Chloroaniline	106-47-8
4-Cresidine	120-71-8
4, 4'-Diaminoanisole	615-05-4
4, 4'-Diaminodiphenylemethane	101-77-9
3, 3'-Dichlorobenzidine	91-94-1
3, 3'-Dimethoxybenzidine	119-90-4
3, 3'-Dimethybenzidine	119-93-7
3, 3'-Dimethyl-*4, 4'*-Diaminodiphenylmethane	838-88-0
4, 4'-Methylene-bis-*(2*-chloroaniline)	101-80-4
4, 4'-Thiodianiline	139-65-1
2-Aminotoluene	95-53-4
2, 4-Diaminotoluene	95-80-7
2, 4, 5-Trimethylaniline	137-17-7
2-Methoxyaniline	90-04-0
*Azo dyes, Those consumer goods containing azo dyes that, by reductive cleavage of one or more azo groups, may release one or more of the aromatic amines listed in the Table 5 are forbidden. The detectable concentrations of any amine should not exceed 30 ppm in the finished articles or in the dye parts thereof.Source: Pruntern A. and C. Page. 2013. European ban on certain azo dyes. WWW.IFL.COM	

in Salmonella tester strains TA98 and TA100, but require exogenous mammalian activation (S9) (125). IACR classified benzidine and dyes metabolized to benzidine as category 1carcinogens (114).

p-Phenylenediamine was reported to be non-mutagenic (126, 127); but Shahin *et al*. (128-130) reported it to be a weak mutagen. Chung *et al*. (131) studied the mutagenicity of *p*-phenylenediamine and found it to be weakly mutagenic to Salmonella tester strain TA98 with metabolic activation. Burnett *et al.* (132) discovered that an aqueous sdolution of *p*-phenylenediamine was non-mutagenic. *p*-Phenyenediamine prepared solution in DMSO was non-mutagenic; however, upon standing at room temperature for over an hour, this compound in DMSO became mutagenic. Lin and Solodar (127) also reported that *p*-phenylenediamine became mutagenic after it was oxidized. This finding suggests that *p*-phenylenediamine may not be mutagenic but became mutagenic after oxidation (130). Watanabe *et al*. (133) discovered that *p*-phenylenediamine became strongly mutagenic in *Salmonella typhimurium* tester strain TA1538 in the presence of microsomal fraction following oxidation by H_2O_2. However, Shahin *et al*. (134) reported that the hair dye coupler resourcinol, and the oxidation product of *p*-phenylenediamine and resourcinol, hydroxy-*3*-(*p*-amino)anilino-*6,* *N*-(*p*-amino)phenol)benzoquinonemonoimine-*1,4* were found to be non-mutagenic in Salmonella tester strains TA1535, TA1537, TA1538, TA98 and TA100 in the absence or presence of S9. Sulphonation, deamination, or substitution of an ethyl alcohol or an acetyl group for the hydrogen in the amino groups of *p*-phenylenediamine leads to a decrease of mutagenic activity. But *2*- nitro-*p*-phenylenediamine becomes directly mutagen; and *2*-methyl-*p*-pphenylenedamine is mutagen in the presence of S9 mix (119, 131). The *p*-phenylenediamine derivative*, N, N*-dimethyl-*p*-phenylenediamine (DMPD) is mutagenic with metabolic activation (22, 23), which can be released by azo dyes Methyl Orange, Methyl Red, and Methyl Yellow (also known as Butter Yellow, dimethylaminoazobenzene (DAB) (23). DAB is a recognized carcinogen (135, 136). *p*-Phenylenediamine is a monocyclic aromatic amine. A number of monocyclic aromatic amines can be released by azo reduction of azo dyes including *2, 4*-diaminoanisole (137, 138), *2, 4*-diaminotoluene (139), Bismark Brown Y (140), etc. Some monocyclic aromatic amines are mutagenic, which have been reviewed by Chung *et al.* (141). It is suspected that some of those mutagenic monocyclic aromatic amines are also carcinogenic*. p*-Phenylenediamine, *2*-nitro-*p*-phenylenediame and *2*-methyl-*p*-phenylenediamine induced a dose-related increase in chromosomal aberrations in Chinese hamster ovary (CHO) cells in the absence of the S9 mix (131). In other words, these amines are certainly genotoxic.

p-Phenylenediamine is mainly used as a component of engineering polymers and composites, and also is the main aromatic amine used in hair dye formulation (86, 137). Rollison *et al*. (142) reviewed

the literature published 1992-2005 about the personal hair dye use and cancer and discovered at least one well-designed study with exposure assessment that observed associations between personal hair dye use and non-Hodgkin's lymphoma, multiple myeloma, acute leukemia, and bladder cancer, but those associations were not consistently observed across studies. Turesky *et al* (58) reported that hair dye *p*-phenylenediamine can be contaminated with the carcinogenic *4*-aminobiphenyl. Would the reported carcinogenic effects of *p*-phenylenediamine be due to the impurity rather than the *p*-phenylenediamine itself ? Whether *p*-phenylenediamine is a carcinogen remains to be further investigated. However, the Center of Disease Control (CDC) of the United States lists *p*-phenylenediamine as being a contact allergen. Exposure routes are through inhalation, skin absorption, ingestion, and skin/or eye contact. Symptoms include throat irritation (pharynx and larynx), bronchial asthma, and sensitization dermatitis (NIOSH, Registry of Toxic Effects of Chemical Substances (RTECS) entry for *p*-phenylenediamine (PPD)).

Benigni and Passerini (143) studied the structure-activity relationship of carcinogenic compounds and discovered that the gradation of potency of aromatic and arylamines depends on their hydrophobicity and on electronic (reactivity, propensity to be metabolically transformed) and steric properties. Chung and Cerniglia (119) also found that some functional groups within the molecule of these amines affect their genotoxicities. In general, the SO_3 group will increase the solubility and decrease genotoxicity of the compounds. However, Pinherio *et al*. (144) reported that increased hydrophilicity such as sulfonation would be unfavorable for bioelimination in activated sludge systems. On the other hand, halogen groups or NO_2 groups will increase their genotoxicities. What we need is to develop chemicals that are environmentally friendly and with minimum genotoxicities. Another approach is to look for antimutgenic/antigenotoxic chemicals. As an example, Makena and Chung (145) found that various plant polyphenols can decrease the benzidine-induced genotoxicity.

Arylamines are not only important carcinogens but also important chemicals that have been reported to cause a variety of maladies. For example, Sittig (146) reported that acute inhalation exposure to *4*-aminobiphenyl developed cyanosis, headaches, lethargy, urinary burning, and hematuria in humans. Acetaminophen and amphetamine affect central nervous systems. *2*-Naphythylamine (*2*-NA) is considered a hazardous material. High levels of inhalation of *2*-NA can interfere with the ability of the blood to carry oxygen causing headache, fatigue, dizziness, and a blue color to the skin and lips (methemoglobinemia). Higher levels can cause trouble breathing, collapse, and even death. Stasik (147) reported that *4*-choro-*o*-toluidine caused acute toxic effect haemorrhagic cystitis with methemoglobinaemia and haematuria. Further symptoms include dysuria, reduced bladder capacity and pain in the lower abdomen. Some arylamines were reported to cause autoimmune diseases including lupus (148, 149). Adham and Chung (150) discussed the relationship between the arylamines carcinogenesis and lupus and noticed the association between autoimmune diseases and cancer (151, 152). Adam and Chung (150) further found that autoimmune syndromes are common in patients with cancer. It is possible that autoimmunity and arylamine induced cancer may share some the common mechanisms of the etiology. Patient with autoimmune diseases may have a high chance of developing cancer later in their lives. It is prudent to have further investigation on this subject.

Endogenous arylamine such as tryptophan metabolite, serotonin, is reported to be related to anorexia (153) and serotonin syndrome (154). Arylamines may also be related to other diseases as well. Organs, tissue, and species specificity of the arylamines-inducing cancer may be due to their availability (absorption, transport and accumulation, residential time, and the presence of metabolic activation/detoxicification enzymes) for each organ, tissue, and species. It has been reported that triple primary cancers including kidney, urinary bladder, and liver were involved in in dye workers. Are these types of cancer due to the special metabolism of arylamine or due to many enzymes involved in the metabolic activation/detoxification? For example, cytochrome-P450, prostglandin H synthase, *N*-acetyltransferase, glutathione transferase, glucouronyl transferase, sulfotransferase, *o*-acetylase, etc., which have been reported in the metabolic activation of arylamine induced carcinogenesis. The expression and balance of these enzymes are important factors in the onset of cancer.

Dyestuff and chemical industrial workers, pigment and printing workers, textile dye workers, rubber and cable manufacture workers, gas workers, laboratory workers, handlers of certain rodenticides, and workers in the tar and pitch industries were

reported to have a high incidence of bladder cancer because they were frequently exposed to arylamines (155, 156). Other professions such as bus drivers, leather (including shoe) workers, blacksmiths, machine setters, mechanics, and hairdressers are also high risk groups of bladder cancer. Cigarette smokers also were reported to have a triple risk of bladder cancer relative to those who have never smoked (157). Cigarette smoking is also linked with an increased risk of cancers of the lung, larynx, oral cavity, nose and sinuse, pharynx, esophagus, stomach, pancreas, cervix, kidney, ovary, colorectum, and acute myeloid leukemia. Cigarette smoking accounts for at least 30% of all cancer deaths, and 87% of cancer deaths is due to lung cancer. Cigarette smoke was reported to contain some arylamines such as *4*-aminobiphenyl, *2*-naphthlamine (54, 55,158). The decreasing trend of bladder cancer incidence in the developed world suggests that bladder cancer is a preventable disease should arylamines and relevant carcinogenic azo dyes be well regulated.

Exogenous arylamines can contaminate food and water and are present ubiquitously in the environment. Other than occupational exposure, the general public is likely to be exposed through various routes. Therefore, arylamines pose a serious threat to the human health of both occupational groups and the general public. In view of their ubiquity and diseases they cause, arylamines are probably one of the most important groups of compound intimately related to human health and environment. Much more investment in the study of arylamine induced carcinogenesis and other maladies is certainly warranted.

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