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Review Paper

# Genotoxic, Carcinogenic and Reproductive Studies on Aniline: A Mini Review

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***Abstract—*** The presence of certain chemical pollutants in environment plays an important role in altering various biological functions. Anilines are widely used in the preparation of pesticides, herbicides, plants, pharmaceuticals and dyes. The present review aims at highlighting the toxic and detrimental effects of aniline on animal model. We believe that this review will provide valuable information on toxicological profile of aniline which will further help in devising safe guidelines for the usage of aniline in a suitable manner. Aniline has shown increases the methemoglobin level in blood. A derivative of aniline, 3,4 dichloroaniline, has shown to affect the male reproductive system by increasing the frequency of structural and numerical abnormalities in sperms, decreasing sperm count and motility. In female fishes, it, decreased fecundity, caused hormonal disruption and histological changes in the ovaries. In rats, aniline hydrochloride did not show any teratogenic effect but the pregnant rats showed increased spleen weight, decreased RBC count and methemoglobinemia.

***Keywords—*** Aniline, testes, ovaries, hormones, sperm count, reproductive output.

## 1. Introduction

Presence of certain chemical pollutants or contaminants in food, air water or soil plays an important role in altering various biological functions. Daily exposure to them can be very toxic to the health of human beings, animals and plants as well. One of the main groups of anthropogenic environmental contaminants that are commonly present in the environment are aromatic amines. The majority of aromatic amines are cytotoxic or genotoxic to living things [1] and make up 12% of synthetic substances that are thought to be probable carcinogens. [1].

An important family of polluting aromatic amines that poses a substantial threat to the environment is aniline [3,10]. Otto Unverdorben used destructive distillation to isolate aniline for the first time in 1826 from indigo. Pesticides, herbicides, paints, medicines, and dyes are all made using aniline and its derivatives [3,4]. Due to their ongoing use, aniline and its derivatives are continuously discharged into the environment through industrial effluents, unintentional spills, and direct application to the soil [3,5,6]. The soil and aquatic habitats are where aniline is primarily deposited and contaminated [10,11].

Two times in China, significant amounts of aniline were unintentionally spilled, contaminating aquatic habitats and posing a serious risk to human health and the health of other life forms [6,5]. An organic pollutant that is very resistant to abatement, aniline is on the EPAS's priority pollutants list because it is poisonous and persistent [10]. Due to its increasing use worldwide and the possibility of environmental contamination, aniline may continue to constitute a serious hazard to the environment[6,12]. In vitro cell cultures [17], eukaryotic organisms [15] (Brennan et al., 1997), and animal models [13, 14] have all been the subject of few investigations on aniline's harmful effects.

The clinical manifestation of toxicity due to considerable exposure of aniline is fairly well documented. Aniline's early toxicity is typically accompanied by methemoglobin production and erythrocyte destruction [16,2]. Additionally, exposure to aniline causes spleen toxicity, which in rats manifests as haemorrhage, capsular hyperplasia, fibrosis, and a variety of sarcomas [18]. The available literature suggests that aniline causes serious environmental problems, aquatic ecosystem problems and also severe health hazard to human. The present review aims at highlighting the toxic detrimental effects of aniline on animal model. Since aniline is used so widely, it is very likely for us humans and animals to come into it's contact. Hence, more studies about the effects of aniline are of utmost importance.

 

## 2. Methodology

### 2.1 Literature survey strategy

The author followed PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The majority of the time, recommendations are used to publish both systematic reviews and meta analyses. Recommendations are a minimal collection of things based on evidence. The author focused on both experimental and non-experimental studies, using three internet databases, including Google Scholar, PubMed, and Science Direct. Research articles published between 1970 and 2022 were searched for using search engines.

### 2.2 Data extraction

The first studies that were scanned were those that came up in the search engines. Using Microsoft Excel, relevant studies were imported and tallied based on their abstract, goal, and findings.

## 3. Results and Discussion

### 3.1 Studies on the general effects of aniline

In a study conducted by [16] of 5mg and 15mg were orally given to human volunteers. At these doses, no effects of aniline were seen. Doses ranging from 25 to 65 mg caused an increase in methaemoglobin in the blood. He also extended his study in rats, doses of 0, 5, 20, 40, 100, 200, 300, 1000 mg/kg bw aniline were given orally and intravenously. Methaemoglobin levels increased in a dose-dependent manner in the blood of the animals after 1 to 4 hours of treatment. From this study we conclude that aniline causes rise in methaemoglobin. According to a study conducted by [19] p-Chloro aniline (PCA) was given to rats orally at doses 0, 5, 10, 20, 40, 80 mg/kg BW and mice at doses 0,7.5,15,30,60,120 mg/kg BW for a 13 weeks. In both rats and mice, a decrease in the body weight was observed in the treated animals. Also, at dose 80mg/kg bw there was an increase in spleen weight of rats. The methaemoglobin concentration for all dosed rats and mice was significantly greater than control. The leucocyte count and lymphocyte count were markedly increased for rats at 40mg/kg. Higher aniline hydrochloride concentrations caused a noticeable slowdown of the flies' movements to the point where some of them were shaking in the bottom of the vial [20]. Accordingly, a study by [21] exposed male Wistar rats in groups to concentrations of 9.2, 32.4, 96.5, and 274.9 mg aniline/m3 through their noses exclusively over the course of two weeks (days 0–11), with a two-week postexposure period (up to day 28) coming after. This exposure regimen was six hours per day, five days per week. Without causing any clinical symptoms, concentrations up to and including 30 mg/m3 were tolerated. Rats exposed to levels of 90 mg/m3 and higher developed cyanosis (blue colouring of the skin in places that could be seen), whereas rats exposed to levels of 270 mg/m3 also showed tachypnea, laboured breathing patterns, increased salivation, and an ungroomed hair coat. Hb, red blood cell count, and haematocrit all decreased in a dose-dependent manner, whereas reticulocyte counts and erythrocytes with Heinz bodies increased. Besides this, there was also a dose dependent increase in methaemoglobin in blood. Thus, we conclude that high doses of aniline are not safe for any animal model and causes toxicity by the formation of methaemoglobin.

Table.1: Studies on the general effect of aniline

| Model organism | Dosage of Aniline | duration | Inference | Reference |
|---|---|---|---|---|
| Human 17 males 3 females | 5,15,25 mg orally | 3 days | Methaemoglobin increase | Jenkins *et al*., 1972 |
| Rat | 0.93% in water orally | - | Methaemoglobin increase | Jenkins *et al*., 1972 |
| Male and Female Rat. | - | - | Decline in growth rate and food intake. Henz bodies, spleen enlargement | Jenkins *et al*., 1972 |
| Male and Female Rat | 5,10,20,40,80 mg/kg bw orally | 13 weeks | Lesions on kidney, liver, spleen | Chhabra,1990 |
| Male and Female Mice | 7.5, 15, 30,60,120 mg/kg bw orally | 13 weeks | Methaemoglobin increase | Chhabra, 1990 |
| Rat | 2mmol/kg orally | 0.25,0.5,1,3,6,12, 24, 48 hours | Methaemoglobin increases lipid peroxidation increase, congested spleen blood vessels | Khan *et al*., 1997 |
| Male Rat | 10,30,90,270 mg/m3 vapour | 2 weeks | Cyanosis, increased salivation | Pauluhn, 2004 |

### 3.2 Studies on carcinogenic and genotoxic effects of aniline

In one study conducted by [22], aniline hydrochloride was given to lung cells and Chinese Hamster Don cell. This induced sister chromatid exchange without producing chromosomal aberration. Thus, aniline hydrochloride was not found to be clastogenic. Another work by[23] showed that when up to 25g aniline was injected into oocytes in the pupal stage, no evidence of mutagenicity was found in the particular locus test in silk worms. [24] Conducted a study in which male Sprague Dawley rats were orally given 300mg/kg BW aniline. Following the administration, urine was collected during the first 24h. The result of the study showed that aniline did not show mutagenic activity. However urinary metabolites of aniline were mutagenic.in line to this, in a

 

study conducted by [25], Male Swiss mice were given a single intraperitoneal injection of aniline at dosages ranging from 61 to 420 mg/kg bw. The result of the study showed that the amount of sister chromatid exchanges per metaphase rose in a dose-dependent way in the bone marrow that was harvested 25 hours later. [27] studied the genotoxicity of 4-4' methylenebis 2- chloroaniline (MOCA) in hepatocytes of rats, mice and hamster. Exposure of hepatocytes from mouse, rat, and hamster to MOCA csused DNA repair in all species. Another study by[19] 344/N rats of were given by gavage p-Chloroaniline deionized (PCA) water at doses of 0, 2, 6 or 18 mg/kg body weight, 5 days/week for a period of 103 weeks. B6C3Ft mice of both sex were given 0, 3, 10 or 30 mg/kg on the same time. Fibrosis of the spleen rose in all PCA-treated groups. Sarcomas of the spleen occurred. Pheochromocytomas of the adrenal gland have become slightly more common. The incidence of hepatocellular adenomas or carcinomas was higher in dosed animals. The incidence of liver or spleen hemangiosarcomas was similarly higher in the high-dose group. These investigations lead us to the conclusion that aniline is carcinogenic in both rats and mice. Low doses of aniline do not have mutagenic effects, but high dosages result in the development of carcinomas and sarcomas.

Table. 2: Studies on the carcinogenic and genotoxic effects of aniline.

| Model organism | Dosage of aniline | Duration | Inference | Reference |
|---|---|---|---|---|
| Chinese hamster Don and lung cells | - | - | No chromosomal abreactions | Abe and Sasaki, 1977 |
| Pupal oocyte of silk worm | 25µg | - | No mutagenicity | Kawachi *et al.*, 1980 and Tazima, 1980 |
| Male Rat | 300mg/kg bw orally | - | No mutagenicity | Tanaka *et al*., 1980 |
| hepatocytes of Rat, mouse, hamster | - | - | DNA repair | McQueen et al.,1981 |
| Male Rat | 3000, 6000, 12000 ppm | - | No mutagenicity | Haworth *et al*., 1981 |
| Male Mice | 61, 420 mg/kg bw orally | 25 h | SCE rate increase. | Parodi *et al*., 1982b, 1983 |
| V79 cell line | 20mM | - | No mutation at HPRT locus | Fassina *et al.*, 1990 |
| V79 cell line | 60mM | - | Mutation occurred | Fassina *et al.*, 1990 |
| Male and Female Rats | 0,2,6,18 mg/kg bw in water | 103 weeks | Splenic sarcomas | Chaabra *et al*, 1990. |
| Male and Female Mice | 0,3,10,30 mg/kg bw in water | 103 weeks | Hepatocellular carcinomas | Chaabra *et al*, 1990. |

**3.3 Studies on effects of aniline on reproduction**

According to a study by [30], rats given aniline had many big lipid-storing clear cells and a noticeably reduced amount of sterol 3-beta dehydrogenase (a precursor to progesterone). Endoplasmic reticulum levels dropped or disappeared entirely, indicating a severe lack of steroidogenesis-specific enzymes. It suggests that aniline prevents steroidogensis from occurring in the corpora lutea. Thus, it can be concluded that aniline alters the process steriogenesis in rats. In line to this, a work done by [31], pregnant Fischer 344 rats were given, with the help of gavage, aniline hydrochloride (10, 30, or 100 mg/kg/day), on gestational days gestational day 7 through parturition. To Fischer 344 rats, aniline hydrochloride was not teratogenic. Thus, it can be concluded that at low doses, exposure to aniline is not teratogenic. According to a study conducted by [32], reproductive harm of p-Nitroaniline in rats was studied in F0, F1 and F2 generation. Male fertility index and pregnancy rate did not alter in the F1 generation. When the testes and epididymides of the F0 mice were examined histopathologically, no abnormalities that might have affected fertility were found. Thus, it can be concluded that low doses of aniline have no effect on mating, gestation, and lactation. A study was carried by [33] reported the effect of exposure to 3 4 dichloroaniline on certain histological structures in the experimentally raised estuarine mysid Mesopodopsis slabberi fish. For 48 hours, the mysids were subjected to various sublethal concentrations of 3,4-DCA (0.10, 0.30, 0.50, 0.90, 1.00, 1.10, 1.20, 1.30, and 1.40 mg/L). Multiple tissues underwent histological analysis to look for harm in organisms exposed to doses greater than 0.30 mg/L. 3,4-DCA certainly had an impact on gonads, as evidenced by the accumulation of this poisonous chemical and structural abnormalities. Thus, it can be concluded that derivatives of aniline can be detrimental to fish reproductive health. In line to this [34] revealed effects of 3,4-dichloroaniline (3,4-DCA) on rat testicular enzyme activity as a biological marker. Alkaline phosphatase (ALP) and acid phosphatise (ACP) activities in this study considerably increased at a lower concentration of 3,4-DCA and significantly decreased at a greater concentration of 3,4-DCA. Besides this, the activity of LDH (Lactate dehydrogenase) and LDH-X (Lactate dehydrogenase X) reduced significantly, demonstrating that 3,4-DCA can have an impact on how spermatogenic cells function.. According to a study by [35] oral administration of 3,4-Dichloroaniline (3,4-DCA) for 30 days at doses of 13.83, 27.67, and 55.33 mg/kg bw resulted in a significant dose-dependent decrease in the activity of the mitotic index in spermatocytes and altered the chromosomes of spermatocytes. This study showed that aniline caused chromosomal abnormalities in mice. In a study by [36] pregnant rats received in utero dosages of 31g/kg/day and 93g/kg/day from 7 days post coitus till birth. The result of the study showed that administration of high doses of aniline during pregnancy reduced anogenital distance (AGD) in male rat pups. None of the male animals had any gross morphological or spermatogenic abnormalities, according to a histological

 

analysis of the testes using periodic acid-Schiff staining, Ddx4/Vasa and 3-beta-HSD staining specifically for germ cells and Leydig cells, respectively. [37] carried his research even further to look at the potential effects of aniline on female reproductive development. From 7-day post coitus till delivery, pregnant Das received an intrauterine exposure to aniline at dosages of 31 ng/kg/day and 93 ng/kg/day. The overall number of ovarian follicles was lower in the treatment groups, according to immunohistochemical labelling with Amh. According to the expression of the oocyte-specific factor Ybx2, follicle counts in both the aniline treated groups showed a noticeably lower number. When compared to controls in all treatment groups, the number of primordial follicles was roughly reduced to 50% in females treated with aniline. Thus, it can be concluded that aniline reduces follicle count and thus affects fertility. Also, the effects of the aniline derivatives 1,1-naphthylamine (1-NPA), 3,4-dichloroaniline (3,4-DCA), and 4,4′-methylenedianiline (4,4′-MDA) at concentrations of 10.0 and 100.0 mg/L were examined by [38]. All of the tested aniline derivatives were found to lower testosterone (T) levels in H295R cell line. There was also an up-regulation of CYP19A and a down-regulation of StAR or CYP17 genes [38]. Thus, we conclude that aniline causes a disturbance in sex hormone ratio**.** The reproductive response of the *Javanese medaka* fish, exposed to 3,4-DCA, was examined in a study by [39]. The most exposed group (250 g/L) experienced a significant decrease in spawning rate and fertilisation. Females exposed to 250 g/L had extremely low gonadosomatic indexes (GSI). These findings demonstrate that 3,4-DCA affects gonadal tissue and fertility, impairing *Javanese medaka* reproduction. Thus, it can be concluded that aniline causes a reduction in the reproductive output of fish *Javanese medaka.*

**Table.3: Studies on effects of aniline on reproduction**

| Model organism | Dose of aniline | Duration | Inference | Reference |
|---|---|---|---|---|
| Female rat | - | - | Corpora lutea exhibited lipid storing cells. Decrease in sterol 3beta dehydrogenase | Hatakeyama *et al.,* 1971 |
| Female rat | 10,30,100mg/kg bw | Gestational day 7 to parturition | Maternal toxicity | Price *et al.,* 1985 |
| Male and female rat | 0,0.25,1.5,9.0 in corn oil orally | 14 weeks before to mating, during mating, gestation and lactation | Decrease in pregency rate of f0 generation | Nair *et al.,* 1990 |
| Male and female Mysid *Mesopodopsis slabberi* fish | 0.10,0. 30,0.50 ,0.90, 1.10, 1.20, 1.30,1.40 mg/l | 48 h | Lesions and histological damage in gonads | Sardo *et al.,* 2005 |
| Male rat | 39, 81 mg/kg bw orally | - | ALP (alkaline phosphatase) and ACP (acid phosphatise) activities increased significantly at a lower concentration of 3,4-DCA and decreased significantly at a higher concentration of 3,4-DCA | Zhang and Lin, 2009 |
| Male rat | 13.33, 27.67,55.33 mg/kg bw orally | 30 days | Decrease in mitotic index of spermatocytes | Eissa *et al.,* 2012 |
| Male Rat | 31, 93 mg/kg bw | 7 days post coitus till birth | Reduction in AGD of pups | Holm *et al.,* 2015, |
| Female Rat | 31, 93 mg/kg bw | 7 days post coitus till birth | Reduction in AGD of pups | Holm *et al.,* 2016 |
| H295R cell line | 10, 100 mg/l bw | - | up-regulation of CYP19A and a down-regulation of StAR or CYP17 genes. | Bhuiyan *et al.,* 2019 |
| Male zebra fish | 0.024, 0.12, 0.6, or 3.0 mg/L for 3,4-DCA; 0.04, 0.2, 1.0, or 5.0 mg/L for 1-NPA; and 0.2, 1.0, 5.0, or 25 mg/L for 4,4′-MDA | - | reduced testosterone levels and elevated 17-estradiol/testosterone ratios | Bhuiyan *et al.,* 2019 |
| *Javanese medaka* fish | 250g/l | - | slowdown in the development of the female gonads | Ibrahim *et al.,* 2021 |

## 4. Conclusion and Future Scope

The available literature suggests that aniline and its derivatives alter the biological activities of various organisms. Higher doses of aniline cause the formation of methaemoglobin in blood. It also increases the risk of developing carcinomas and sarcomas. It affects the reproductive system of both male and female. In fishes, it has shown to reduce the fecundity and cause histological and

 

morphological alterations of the gonads. In rats, it causes disruption of the hormonal levels, affecting the reproductive output of the animal. It also lowers the sperm count. .in male and gives rise to chromosomal abnormalities. Thus we conclude that aniline and its derivatives cause harm to the reproductive system and general health of animals and man.

**Authors contribution**

The first author, Vaibhavi Ingle carried out the literature review of the general effects of aniline. The second author, Varsha Dhurevy carried out the literature review of the genotoxic and carcinogenic effects of aniline. Rashmi Urkude carried out the literature review of the effects of aniline upon the reproductive system.

**Data availability**

The data that support the findings of this study is freely available at Pubmed and Google scholar. The data set generated during are also available form the corresponding author on reasonable request.

**Conflict of Interest**

No competing interests were disclosed by the author before to this article's publication.

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