**International Journal of Scientific Research in Biological Sciences**
Vol.**12**, Issue.**2**, pp.**21-31**, April **2025**
E-ISSN: 2347-7520
Available online at: www.isroset.org

Review Article

# Studies of Aniline and it's Derivatives on Various Organ Systems: A Mini Review

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**Received**: 17/Mar/2025; **Accepted**: 04/Apr/2025; **Published**: 30/Apr/2025. | **DOI**: https://doi.org/10.26438/ijsrbs.v12i2.672



***Abstract-*** Certain chemical pollutants in the environment can change a variety of biological processes. Anilines are widely used in the manufacturing of plants, colours, medications, pesticides, and herbicides. This review aims to highlight the destructive, dangerous and altering effects of aniline on various organisms. We believe that this study will provide helpful information regarding aniline's toxicological research, which will help in the formulation of acceptable guidelines for aniline usage.

***Keywords-*** Aniline, reproductive toxicity, neurotoxicity, nephrotoxicity, carcinogens

## 1. Introduction

Numerous industries, including electronics, pharmaceuticals, agriculture, and many more, have benefited greatly from human contributions. The development of industries depends on chemicals. The features and attributes of a material are often what define its usage [1]. Aniline, the main molecule of the family of aromatic amine, is a crucial component of many of these materials. Aniline or its derivatives, including 3,4-dichloroaniline, 4,4′-methylenedianiline, and 1-naphthylamine, are precursors or intermediates in a wide range of rubbers, medications, insecticides, dyes, cosmetics, and adhesive goods [2,3,4,5]. Several anilines have been identified as high-volume production chemicals by a number of countries, including the US and the EU [6,7,8]. In 2016, an estimated 5.6 million tons of aniline were produced globally [5].

Ammonia, phenol, and benzene can all be used to make aniline in an industrial setting. It smells less like rotten fish and more like volatile amines. It has the property of aromatic chemicals and burns with a smoky flame right away. According to [1] this colourless, hydrophilic molecule can also mix with various organic solvents. The production of precursors for the polymer polyurethane is its primary application.

Considered to be among the best thermal insulators, it is utilized in every refrigerator. Additionally, it is used as a pesticide in addition to agricultural chemicals. It starts with the pigments and colours found in aniline. It is utilized in both medicinal and photographic chemicals. Paracetamol, a well-known analgesic drug, is made from aniline. A dye known as O-toluidine is used in forensic science to extract suspected blood.

Anilines are employed as precursors in manufacture of numerous colours and some care articles and could be extracted from a wide range of materials. For example, 1-NPA can be freed from the hairs colour, tattoos, mehendi and make up products [9]. While residual isocyanates in polyurethane adhesive can generate 4,4′-MDA, rubber products can emit 1-NPA and 4,4′-MDA at certain temperatures [10]. Pharmaceuticals may also be a supply of aniline in the environment because aniline is used to create pain killers, fever reducing, allergy controlling, and multivitamins [11]. As breakdown products, these products may be exposed to the environment.

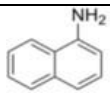
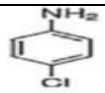
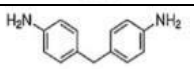
For instance, 1-naphthylamine from inks, pesticides, and herbicides (Guzman Mar *et al*., 2006), 3,4-DCA from pesticides such as diuron, propanil and linuron [4,12,13], and 4,4′-methylenedianiline from rubber and polyurethane compounds [14].

Some anilines are commonly discovered in sediments and rivers around the world, despite the lack of information on their environmental quantities [15,16,4]. Levels of 3,4-DCA

as high as 68.2ng/L were detected in water from the Chattahoochee River and Scope Creek in the United States [17]. 1. In the Zonguldak industrial area of Turkey, NPA was detected in river sediment at an absorption of 186.45 ng/kg [18]. 3,4-dichloroaniline's precursor, diuron, was detected at concentrations as high as 230 ng/L in Korea's main harbours and as high as 1360 ng/L in a port in Jinhae Bay [19].

Studies have been conducted on the toxicological consequences of several anilines due to their diverse sources and environmental detection. The review's objective is to raise awareness of aniline's hazardous and detrimental effects on animal test models. We believe that by providing valuable information regarding aniline's toxicological profile, this analysis will aid in the development of safe guidelines for its appropriate usage.

**Table-1** Aniline's and its derivatives' characteristics:

| Name | Structure | Molar mass (g/mol) | Reference |
|---|---|---|---|
| Aniline |  | 93.13 | (National Institute of Health) |
| 3,4- dichloroaniline |  | 162.013 | (National Institute of Health) |
| 1- Naphthylamine |  | 143.19 | Bhuiyan *et al.*, 2019 |
| 4-chloroaniline |  | 127.57 | Bhuiyan *et al.*, 2019 |
| 4,4'-methylene dianiline |  | 198.269 | Bhuiyan *et al.*, 2019 |

## 2. Materials and Methods

**Literature survey strategy**

The information collected by google scholar, Meta-Analyses, or PRISMA by the writer of the paper. Most of the time, both meta-analyses and systematic reviews are brought out using approval. Recommendations are a small set of evidence-based suggestions. The author used three data platforms - Science Direct Google Scholar, PubMed, and -to concentrate regarding both non-experimental and experimental research. Search engines were put to use to find research information published from 1971 and 2025.

**Data extraction**

The studies that appeared in the search engines were the first to be scanned. Relevant studies were imported into Microsoft Excel and totalled according to their abstract, purpose, and conclusions.

## 3. Results and Discussion

**Studies of aniline on various organ systems:**

**3.1. Study of aniline on nervous system:** [20] Investigated aniline's neurotoxicity and age-dependent effects in male rats. Two of the six rats that were given 1,000 mg/kg of aniline at the age of 4 weeks, exhibited symptoms paralysis of the hind limb or gait which was parallactic in middle of after treatment days 15 and 8. On day 15 following treatment, the white matter of spinal cord in the rats which were administered 750 or 1,000 mg/kg aniline at the age of 4 weeks, displayed spongy change. In addition to mild peripheral nerve degeneration, 3 of the 6 rats given 1000 mg/kg body weight aniline showed some changes revealed alterations in the medulla oblongata and pons spinal trigeminal tracts and facial nerve. [21] Studied that exposure to aniline particularly results in neuron poisoning and a range of neurological symptoms, such as sarcoma, that is typified by fibrosis, splenomegaly, and the formation of tumours. According to the literature that is available, aniline has a neurotoxic effect.

**Table-2** Study of aniline on nervous system

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Rats | 500, 750 or 1,000 mg/kg | 15 days | Signe of paralytic gait or hindlimb paralysis. | Okazaki *et al*., 2001 |
| Rats | - | - | Weakness, lethargy, ataxia, vertigo, nausea, vomiting, and tinnitus fatigue. | Makhdoumi *et al.*, 2019 |

**3.2 Study of aniline on nephric system**- In a study by [22], the nephrotoxic potential of aniline was assessed in vitro and in vivo using Fischer 344 rats. Renal function was evaluated at 48 and 24 hours after rats in the treated group received aniline (1.0, 1.5, or 0.4 mmol/) and rats in the control group received an intraperitoneal injection of saline (2.0 ml/kg). 2. Aniline decreased urine production, raised blood urea nitrogen levels, and prevented lactate and basal-stimulated p-aminohippurate collection by renal cortical at a dosage of 1.0 mmol/kg. At the dosages used in this study, aniline had no discernible effect on renal function. Aniline (10−4 M or above) decreased the base-level buildup of p-aminohippurate in the in vitro assays.

In a study by [23], male Fischer 344 rats were given intraperitoneal injections of aniline, acetyl-p-aminophenol, p-nitroaniline, p-aminophenol, p-chloroaniline, p-chloronitrobenzene, or p-anisidine at a dosage of 1.0 mmol/kg. Rats with p-aminophenol injections showed necrosis of renal tubular epithelial cells and a significant increase in urine and γ-glutamyl transpeptidase and N-acetyl-β-D-glucosaminidase functioning. The tubular epithelial cells in rats responded to p-nitroaniline and p-anisidine by swelling. However, the administration of aniline or its derivatives had no effect on the urine enzymes or renal histology.

The toxicity of the renal cortical slices was assessed by tracking changes in tissue gluconeogenesis capability and lactate dehydrogenase release. None of the anilines enhanced the release of lactate dehydrogenase. 4-iodoaniline 2.0 mM caused the greatest reduction in gluconeogenesis (92%↓), while 4-bromoaniline decreased gluconeogenesis at a dose of (0.1 mM). The most powerful nephric toxicant was 3,5-dibromoaniline, while the least powerful was 3,5-difluoroaniline [24].

A different study was performed in which male Wistar rat's male were used to identify and assess the nephrotoxic hazards of aniline. Group A rats were dosed with 20 mg/kg body weight aniline for a period of 30 days, while B group rats were treated with regular saline water. Blood urea, creatinine, and a few serum pointers of kidney harm all increased in concentration. Other than histological changes such as the shedding of the brush edge of the proximal tubular cells, sodium and potassium contents dropped. Significant degenerative alterations were seen in the distal tubular cells and proximal tubular cells [25].

**Table-3** Study of aniline on nephric system

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Fischer 344 rats | (0.4, 1.0, or 1.5 mmol/kg), | - | Decreased urine production, elevated blood urea nitrogen levels, and prevented renal cortical slices from accumulating p-aminohippurate (PAH) in response to lactate and baseline stimuli. | Rankin *et al.*,1986 |
| Male Fischer 344 rats | 1.0 mmol/kg | - | Necrosis of renal tubular epithelial cells and a considerable increase in the activity of γ-glutamyltranspeptidase (γ-GTP) and N-acetyl-β-D-glucosaminidase (NAG) in the urine were observed. | Yoshida *et al.*,1989. |
| - | - | - | Reduction in gluconeogenesis (92%↓), while 4- bromoaniline decreased gluconeogenesis in the dose of 0.1 mM | Hong *et al*., 2000. |
| Male Wistar rats | 20 mg/kg | 30 days | Creatinine and blood urea and serum indicators of kidney damage all rose in concentration | Ramteke and Dhurvey 2020. |

**3.3 Study of aniline on hepatic system-** [26] conducted a study in which rats were used to examine the effects of administering aniline metabolites, specifically phenylhydroxylamine and p-aminophenol, and human volunteers were utilized to examine the effects of oral aniline administration. Rats fed phenylhydroxylamine or aniline developed splenic enlargement, hemoglobinemia, and Heinz bodies. An oral dose of aniline (20 mg/kg body weight) showed no effect on rats. Five or fifteen milligrams of aniline taken orally did not cause any reaction in twenty human participants. Doses ranging from 25 to 65 mg significantly increased haemoglobin levels in the blood, although no Heinz bodies were observed.

A study found that the liver hydroxylates aniline to make a number of derivatives, few of them, end up in RBCs. The aniline underwent biotransformation in the livers of male albino rats in the concentration of 50mg/kg BW [27].

In a study by [28] mice received dose of 120, 60, 30, 15, 7.5 and 0 mg/kg BW of p-Chloroaniline for 13 weeks, whereas

rats given oral dosage of 5, 40, 20, 10, 80 and 0 mg/kg BW of p-Chloroaniline. In mice and rats, the treated animals' bodyweight decreased. Methemoglobin levels in all of the dosed mice and rats were higher than that in the control.

The male mice's livers showed a collection of lymphocyte buildup, inflammatory cells, large Kupffer cells, proliferation in the bile ducts, and portal vein dilatation after taking 1 to 8th of 3,4DC-A(dichloroaniline) for 35, 29, and 14 noes of day. [29].

Aniline was administered to the male albino rat's reared hepatocytes for a full day at doses of 10, 5.0, 50, 2, 2.5, 1.25, and 0 g/mL. In contrast to the control, aniline significantly decreased catalase, superoxide dismutase, glutathione, and the membrane potential of mitochondria while increasing malondialdehyde and reactive oxygen species in hepatocytes. Aniline reduced cell life and cell death was seen in a dose-dependent fashion. [5].

The liver weight of huge blue F344 (male) rats increased statistically significantly when given a dose of hundred per kg aniline or fifteen mg per kg para-chloroaniline. Additionally, the rats' calcium and cholesterol levels were higher than those of control animals [30].

Furthermore, the addition of aniline caused spectrum aberrations in liver microsomes, oxidative damage from aniline, and hepatocyte death. Aniline exposure over an more duration of time in vivo results in a toxic response in the spleen that includes fibrosis, hyperplasia, tumor growth, and splenomegaly. Due to oxidative DNA damage, iron overload, and accelerated cell proliferation caused by aniline, the spleen may show malignancies [31].

**Table-4** Study of aniline on hepatic system

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Rats | 5 mg and 15 mg | - | Rise in hemoglobin | Jenkins *et al*., 1972. |
| Rats | 50 mg/kg body weight | - | The liver hydroxylates aniline to create a variety of derivatives, few of them become lodged in red -blood cells. | Eyer *et al*., 1980. |
| Rats | 0, 7.5, 15, 30, 60, and 120 mg/kg BW | 13 weeks | All dosed rats and mice had considerably higher haemoglobin levels than the control group. | Chhabra *et al*.,1991. |
| Male Swiss albino mice | - | 14, 30, and 35 days | Showed accumulation of infiltrating lymphocytes, large Kupffer cells, | Sharma *et al*., 2008. |
| - | - | - | Aniline induced apoptosis and reduced cell viability in relation to concentration | Wang *et al*., 2016. |
| Big Blue F344 (male) rats' | 15 mg/kg | - | Liver weight increased statistically considerably, and their calcium and cholesterol levels were significantly higher | Koenig *et al*., 2018. |
| - | - | - | Aniline causes fibrosis, hyperplasia, tumor growth, and splenomegaly. DNA damage, and accelerated cell growth. | Mohurle *et al.*, 2023. |

**3.4 Study of aniline on reproductive system-** According to a study done by [32] the rats which were given aniline caused a marked decrease in sterol 3-beta dehydrogenase and many lipids storing clear cells in their corpora lutea. The endoplasmic reticulum shrank or vanished entirely, indicating a significant reduction in the number of enzymes that perform steroidogenesis. This shows aniline disrupts the corpora lute a's steroidogenesis. Therefore, it may be concluded that aniline changes the rat steroidogenesis.

Accordingly, Fischer 344 rats that were pregnant were dosed with aniline hydrochloride (30, 100 or 10 mg/kg/day) from gestational day 7 to birth in an experiment by [33]. Rats were seen not teratogenic to aniline hydrochloride. Therefore, it may be said that treatment with aniline is not found to be teratogenic at low dosages. In a work of [34] the reproductive toxicity of p-nitroaniline in rats of the F2, F1, and F0 generations was studied. The First generation showed no change in either the male fertility index or the pregnancy rate. Histopathological analysis of the F0 animals' epididymides and testes showed no such alterations that might affect the reproductive capacity. Therefore, this concludes that less aniline levels have no effect on mating, lactation, or gestation.

[35] Conducted an experiment that showed the effect of 3-4 dichloroaniline on histology of gonads in the estuary Mysid

Mesopodopsis slabberi. For a period of 48 hrs, the mysids were exposed to semi lethal concentrations of 3,4-DCA (1.40, 0.10, 1.00 0.30, 0.50, 0.90, 1.20, 1.10, 1.30, and mg/L). Several tissues were examined histologically, and animals given doses more than 0.30 mg/L showed damage. Gonads were obviously impacted by 3,4-DCA, as seen by the buildup of this hazardous material and structural abnormalities. Therefore, it may be said that aniline derivatives may be harmful to fish reproductive health. Accordingly, [36] explained how 3,4-dichloroaniline affected the pointers of enzyme activity of testis in rats. Alkaline phosphatase and acid phosphatase activities in the study significantly enhanced at less 3,4-dichloroaniline dose and became less in higher 3,4-DCA concentration.

In a different study by [37] male Wistar rats were give aniline at dose of 13.33, 27.67,55.33 mg/kg body weight for a duration of 1 month. The result showed a decline in mitotic rate of the spermatocytes.

In another study by [38] female Wistar rats were given 93, 31 mg/kg BW aniline 7 days after intercourse to birth. There was a decline in the distance between the genitals and anus of the pups.

[39] Used H295R cell line and exposed them to 10, 100 mg/l BW aniline. There was an more expression of CYP 19A and a less expression of StAR or CYP 17 genes. The author extended his study in the same year on male zebra fish which was exposed to 0. 024, 0.12, 3.0 0.6 mg/L of 3,4-Dichloroaniline; 5.0 ,0.04, 1.0, 0.2, or 5.0 mg/L of 1-Naphthylamine and 25, 5.0, 1.0, 0.2 mg/L for 4,4'-Methylenedianiline. Decline in the testosterone amount and higher 17-estradiol/testosterone ratios was seen in the results.

In a study by [40] the reproduction activity of the Oryzias (ricefish), fish surrounded to 3,4-DCA was investigated. The spawning rate and fertilization rate became very less in the group that was given to the highest concentration (250 gm/L). The gonad and somatic index GSI were found to be incredibly less in fishes that were put to 250 g/L dose. The outcome proves that 3,4-dichloroaniline hampers Oryzias (ricefish), reproduction by affecting gonadal tissue and fertility. Therefore, aniline reduces the Javanese medaka fish's reproductive capacity.

According to [41] the reproduction system is affected by aniline. It has shown to decrease reproductivity in fishes and affect the gonads' histology. It changes the number of hormones in rats, which impacts the animal's ability to conceive. It also results in chromosomal abnormalities and lowers male sperm counts.

**Table-5** Study of aniline on reproductive system

| Model animal | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Female rat | - | - | The corpus lutea displayed cells that stored lipids. Sterol 3-beta dehydrogenase decreased | Hatakeyama *et al.*, 1971 |
| Female rat | 30,10,100mg/kg bw | From gestational day 7 till birth | Toxicology in mothers and decline in the f0 generation fertility ratio. | Price *et al.*, 1985 |
| Male and female rat | 1.5, 9.0 0,0.25 in oral corn oil | 14 weeks before to mating, during mating, gestation and lactation | | Nair *et al.*,1990 |
| Female and male *Mysid Mesopodopsis slabberi* fish | 1.10, 1.20, 1.30,1.40, 0.10,0.30,0.50 ,0.90, mg/l | 48 h | Damages the ovaries and histological structures | Sardo *et al.*, 2005 |
| Male rat | 81, 39 mg/kg bw orally | - | At a low concentration of 3,4-dicholroaniline, the activities of (alkaline phosphatase) and ACP (acid phosphatase) greatly rose, whereas at a greater concentration, they dramatically decreased. | Zhang and Lin, 2009 |
| Male rat | 27.67,55.33,13.33mg/kg BW orally | 30 days | Reduction in the spermatocytes' mitotic index | Eissa *et al.*,2012 |
| Female rat | 93 ,31mg/kg BW | 7 days post intercourse till birth | Decrease in pups' AGD | Holm *et al.*, 2016 |
| H295R cell line | 100, 10mg/l BW | - | CYP19A up-regulation and StAR or CYP17 gene down-regulation. | Bhuiyan *et al.*, 2019 |

| | | | | |
|---|---|---|---|---|
| *Japanese rice fish (Oryzias latipes)* | 250g/l | | Slowing in the gonadal development | Ibrahim *et al.*, 2021 |
| | | | It has shown to lessen the reproductivity in fishes and affect the gonads' histology. It has shown to lessen the reproductivity in fishes and affect the ovaries and testis histology. this alters the hormonal quantity in animal, that causes an effect on the fertility. | Ingle *et al.*, 2023 |

**3.5 Study of aniline on genes and cancer-** According to a study by [43], no genes alteration, was observed in the silk worm locus test when oocyte at the pupa stage were given about 25µg of aniline.

Aniline hydrochloride was used to lung cells and Chinese hamster don cells. Without any chromosomal abnormalities, sister chromatid exchange was initiated. Aniline hydrochloride was thus found to have no clastogenic action [59]

In a study by [46], 4-chloroaniline was found to be genotoxic to the liver cells of mice, rats, and hamsters. DNA was repaired when MOCA was administered to hepatocytes from hamsters, mice, and rats. Rats were administered p-Chloroaniline deionized (PCA) water by gavage at rates of 6, 2, 0, or 18 mg/kg body weight for five days over a period of 103 weeks in an experiment by [47]. Rats of both sexes received doses of 10 and 30 mg/kg on a comparable schedule. All of the animals treated with PCA showed a marked rise in splenic fibrosis. Additionally, splenic sarcomas were observed.

Pheochromocytomas of the adrenal glands were slightly more common. Medication-treated mice had greater incidences of adenomas or hepatocellular carcinomas. Hepatic or splenic hemangiosarcoma's also increased in the high-dose group. Based on these results, we conclude that aniline causes cancer in both mice and rats. At high concentrations, it leads to the development of sarcomas and carcinomas, but at low dosages, it has no mutagenic effects. Aniline raises the risk of developing sarcomas and carcinomas, claims [41].

Male Sprague Dawley rats were given 300 mg/kg BW of aniline orally in a study by [44]. During the first 24 hours following the treatment, urine was collected. The results of the investigation showed that aniline was not mutagenic. However, urine metabolites of aniline were mutagenic. Male Swiss mice were given a single intraperitoneal injection of aniline at dosages ranging from 61 to 420 mg/kg BW.

The experiments' result proves that the amount of sister chromatids exchange in the bone marrow per metaphase rose [45].

**Table-6** Study of aniline on genes and cancer

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Lung cells and Chinese hamster don cells | - | - | Chromosomal alterations were not seen | Abe and Sasaki, 1977 |
| Silk worm pupal oocyte | 25µg | - | Mutagenicity not observed | Kawachi *et al.*,1980 and Tazima,1980 |
| Male rat | 300mg/kg bw orally | - | Mutagenicity not observed | Tanaka *et al*., 1980 |
| Mouse, hamster, rat hepatocytes | - | - | DNA repair found | McQueen *et al*.,1981 |
| Rat | 12000, 3000,6000, ppm | - | Mutagenicity not seen | Haworth *et al*., 1981 |
| Mice | 420, 61 mg/kg BW orally | 25 h | SCE rate rise | Parodi *et al*., 1982,1983 |
| Mice | 30, 0, 3, 10 mg/kg BW in water | 103 no. of weeks | Carcinomas of hepatic cells and spleen | Chhabra *et al*, 1990 |
| - | - | - | Carcinomas and sarcomas risk | Ingle *et al*., 2023 |

**3.6 Study of aniline on thyroid gland-** The study conducted by [48] For five days, two weeks, four weeks, and thirteen weeks, female F344 rats were given nutritional feed containing 0, 50, 200, 375, 500, or 750 parts per million of 4,4'-methylenebis(N'-dimethyl) aniline (MDA). During study weeks 6 through 13, the 750ppm group's mean body weight

dropped by 5% in comparison to the control. With increasing meal concentrations of MDA and exposure duration, blood TSH rose while serum T4 and T3 levels fell.

Rats given aniline had thyroid gland histopathology that revealed more micro follicles, less colloid secretion, vacuolation in the colloid, a breakdown of the capsular layer, follicular disruption, thyroid follicle fusion, and more interfollicular space than the control group. Rats treated with aniline had significantly lower levels of the thyroid hormones triiodothyronine (T3) and tetraiodothyronine (T4) and higher levels of thyroid stimulating hormone (TSH) when their thyroid glands were analysed hormonal. Upon these findings, it can be said that aniline may have a negative impact on the thyroid gland's structure and function [49].

**Table- 7** Study of aniline on thyroid gland

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Rats | 750,0, 50,200,375,500ppm | 13 WK, 4 WK, 5 days, 2 WK duration | Follicular cell hyperplasia in thyroid gland. TSH elevate and serum T4 and T3 become less with increasing MDA with exposure time | Dodd *et al*., 2012. |
| Rat | - | - | Thyroid follicle fusion, follicular disruption, dissolution of the capsular layer, vacuolation in the colloid, decrease in colloid secretion, and an increase in micro-follicles interfollicular space, elevated thyroid stimulating hormone (TSH) levels, and decreased levels of the thyroid hormones triiodothyronine (T3) and tetraiodothyronine (T4). | Dhurvey *et al*., 2021. |

**3.7 Study of aniline on respiratory system-** Aniline's main effects on the human lung, such as upper respiratory tract irritation and congestion, are both acute (short-term) and chronic (long-term) [50].

Aniline inhalation can irritate the respiratory tract, resulting in coughing or breathing difficulties [51].

**Table-8** Study of aniline on respiratory system

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Humans | - | - | Upper respiratory tract irritation and congestion | US Environment protection agency, 2000. |
| Humans | - | - | Irritation of respiratory tract cough along with breathing difficulties | NIH and Feng *et al*., 2020. |

**3.8 Study of aniline on endocrine system-** It was shown by [52] aniline (aminobenzene) given subcutaneously to rats causes a significant decrease in the blood corticosterone level with a marked enlargement and ivory-white discoloration of the adrenal glands. The sensitivity of the adrenals to stressful stimuli (e.g. vasopressin and insulin) and to exogenous ACTH is also considerably reduced; thus, it seems reasonable to assume that aniline inhibits the production of corticoids by

primarily affecting the adrenocortical cells. The lack of circulating corticoids leads to a compensatory hypersecretion of ACTH, resulting in adrenocortical hyperplasia.

The study used the human adrenal H295R cell line and adult male Danio rerio zebrafish. Tested aniline derivatives all decreased the H295R cell line's testosterone (T) levels. The disruption of sex hormones could be attributed to regulatory alterations in numerous steroidogenic genes, including the decrease in number of gene-regulation of StAR or CYP17 factors and the increase in number of receptors of CYP19A, that was seen in the H295R cells. T levels decreased and E2/T ratios increased in male zebrafish, which showed essentially similar patterns of change. Again, the fish's sex hormone changes might be explained by a down-regulation of key steroidogenic genes such as cyp17 or 3β-hsd, but a slight up-regulation of the cyp19a gene [54].

In a study by [53], aniline at a concentration of 10.0 g/ml was applied for 48 hours to NCI-H295R adrenocortical human cells. Endocrine disruption was found to have anti-prostaglandin and anti-androgenic effects.

**Table-9** Study of aniline on endocrine system

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Rats | - | - | Decrease in the blood corticosterone level with a marked enlargement and ivory-white discoloration of the adrenal glands. | Kovacs *et al*.,1971 |
| NCI-H295R adrenocortical human cells | Concentration of 10.0g/ml | 48 hours | Endocrine disruption was observed as anti-androgenic an anti-prostaglandin effect. | Albert *et al*., 2013 |
| Adult male zebrafish and Human adrenal H295R cell line | - | - | Decreased testosterone (T) levels. down- regulation of key steroidogenic genes like cyp17 or 3β-hsd, although the fish's modest up-regulation of the cyp19a gene may account for the sex hormone changes. | Bhuiyan *et al*., 2019 |

**3.9 Study of aniline on blood-** A study carried out by [56] A 6-hour exposure to 2 ppm aniline resulted in a time-dependent increase in blood Met-Hb in 19 nonsmokers. The highest Met-Hb level in the blood was measured (mean 1.21 ± 0.29 percent, range 0.80–2.07%). Over the course of 24 hours, the mean Met-Hb level (0.65 ± 0.18 %) returned to the baseline level (0.72 ± 0.19 %).

A 6-hour inhalation trial involving exposure to 2 ml aniline/m3 revealed elevated methaemoglobin levels in both healthy male and female subjects. From the baseline level of 0.7% to 1.2% methaemoglobin, the median methaemoglobin augmentation was 0.5% [57].

After study by [58] evaluated the aniline's 96-hour LC50, two sublethal concentrations of aniline (4.19 mg/l and 8.39 mg/l) were selected for acute exposure testing in freshwater feeder fish Channa punctatus. Blood was drawn 24, 48, 72, and 96 hours after exposure to examine the genotoxic, cytotoxic, and haematological effects of sublethal dosages of aniline in C. punctatus. Time and dose-dependent DNA damage increased significantly in the comet and micronuclei assays, with the most damage happening 96 hours after exposure. Analyses using ATR-FTIR and scanning electron microscopy after aniline exposure showed structural anomalies and modifications in the biomolecules of the red blood cells in the group exposed to aniline as compared to the control group, respectively.

In one investigation by [55], thirty male Wistar rats per group received nose-only treatment to mean analytical values of 9.2, 32.4, 96.5, and 274.9 mg aniline/m3. Six hours a day, five days a week, were administered to the rats for two weeks

(days 0–11), after which they were given two weeks (day 28) to recuperate. Serial sacrifices were made for certain experiments on days 28, 14, 11, and 4. The primary causes of toxicity, erythrocytotoxicity and haemoglobin synthesis, were among the changes observed.

A study by [54] investigated the histological, biochemical, and haematological responses of rats to sub chronic exposure to aniline hydrochloride. The male Sprague-Dawley rats were given 600 ppm of AH in their drinking water, while the control rats were given tap water only. At 30, 60, and 90days following treatment, five rats per group were killed. The spleen organ-to-body weight ratio of the AH-treated rats was 56, 61, and 53% higher than that of the controls at days 30, 60, and 90, respectively.

**Table- 10** Study of aniline on blood

| Animal model | Aniline dose | Time period | Inference | Reference |
|---|---|---|---|---|
| Male albino rat | 600 ppm | 90, 30, 60 days | In the AH-treated rats, the spleen's organ-to-body weight ratio was 56, 61, and 53% greater. | Khan *et al*., 1993. |
| Male wistar rats | 274.9, 9.2, 96.5, 32.4 mg aniline/$m^3$ | 6 hours per day, five days per week, for two weeks (days 0–11), and then two weeks after exposure (day 28). | Methemoglobin formation and erythrocyte toxicity. | Pauluhn, 2004. |
| Human | 2 ppm | 6-h exposure | An increase in urine aniline and blood Met-Hb | Kafferlein *et al*., 2014. |
| Fish *Channa punctatus* | 8.39 mg/l and 4.19 mg/l) | 96, 24, 72, 48 h | Studies using ATR-FTIR and scanning electron microscopy revealed structural irregularities and changes in the biomolecules of RBCs from the group exposed to aniline. | Sharma *et al*., 2023. |

## 4. Conclusion

Based on available information, aniline and its derivatives alter the biological behaviour of various organisms. Higher doses of aniline cause the blood to produce methemoglobinemia and excessive reactive oxygen species. It also increases the risk of developing carcinomas and sarcomas. The reproductive systems of both sexes are affected. Aniline reduces the fecundity of the animal. This is mostly due to excessive oxidative stress caused by aniline. Thus, we conclude that aniline and its derivatives are detrimental to biological systems and they should be used with utmost care. Hence, it is important to derive safety guidelines and search for alternative natural substances to use in place of aniline. There is scope for future researchers to study about the mechanisms and precise effects of aniline and it's derivative's toxicity on living organisms.

**Author contributions**

The authors NK and VD conceived the idea, and prepared the protocol. NK did the literature search and that was counter-checked by VD. NK prepared the 1st draft of the manuscript and VD critically edited the article. All of them agreed to the final manuscript.

**Data availability statement**

The research articles used in this systematic review are available for use. Ethical approval Institutional review board approval is not required.

**Declaration of patient consent**

Patient's consent not required as there are no patients in this study.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**Use of artificial intelligence (AI)-assisted technology for manuscript preparation**

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI

**Acknowledgements**

We are grateful to our library colleagues for their assistance with the literature. We are also grateful to our university for their initiatives to support and foster research. We are also grateful for the constant support of Dr. V. T. Dhurvey and Miss. Vaibhavi Ingle.

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