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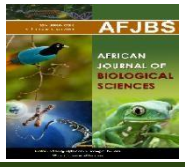

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The pathological and toxicological effects due to chronic exposure to polyfluoroalkyl substances (PFAS) in albino rat: a comprehensive review

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Abstract: There is growing worry about the enduring and potential health effects of per- and polyfluoroalkyl substances (PFAS), a class of synthetic compounds that have contaminated the environment extensively. PFAS are a type of organofluorine compounds that are frequently used in many commercial products such as non-stick cookware, food packaging and fire-fighting foam. Exposure of humans to PFAS in the workplace and community has been linked to several health issues, such as hepatotoxicity, developmental and reproductive toxicity, endocrine disruption, immunological toxicity and carcinogenicity. Although there is data indicating that PFAS are not directly mutagenic, numerous different routes of carcinogenicity have been suggested. This review presents a comprehensive overview of these compounds, including their chemical structure and the many toxicological and pathological effects seen in a rat model following chronic exposure, as rats are frequently employed as animal models to investigate these impacts because to their physiological resemblances to humans. This study aims to enhance comprehension of the health hazards linked to prolonged exposure to PFAS. The results could have consequences for environmental regulations, assessments of human health risks, and the formulation of strategies to reduce PFAS exposure and its related health impacts.

Keywords: PFAS, chronic exposure, albino rats, pathological effects, toxicological effects, hepatotoxicity, endocrine disruption, immunotoxicity, carcinogenicity

Introduction: Per- and poly-fluoroalkyl substances (PFAS) are a large group of man-made fluorinated organic compounds with at least one fully (per-) or partially (poly-) fluorinated carbon chain attached to different functional groups. They possess remarkable physicochemical properties that have been sought and irreplaceable in thousands of industrial and consumer applications since the 1950s (**Berhanu et al 2023)**.

There are over 4700 members of PFAS compounds that may have been on the global market, despite this high diversity, all PFAS are alike in that they contain strong carbon-fluorine bond, a defining feature of PFAS, makes them extremely resistant to environmental and metabolic degradation. (**Cousins et al 2020)**

PFAS have very useful chemical and physical properties are due to their molecular structure. The highly fluorinated portion of the PFAS molecule makes them both lipophobic and hydrophobic and not degrade through normal chemical, physical, or biological processes. (**Gaines 2023)**

The distinctive characteristics of PFAS, such as their resistance to heat, stains, and water, are attributed to their chemical structure. These features are highly desired by both industry and consumers. The carbon-fluorine bond, renowned to be one of the shortest and strongest bonds, plays a crucial role in PFAS compounds, enhancing their stability, impeding degradation and bioaccumulation. (**Teaf et al 2019)**

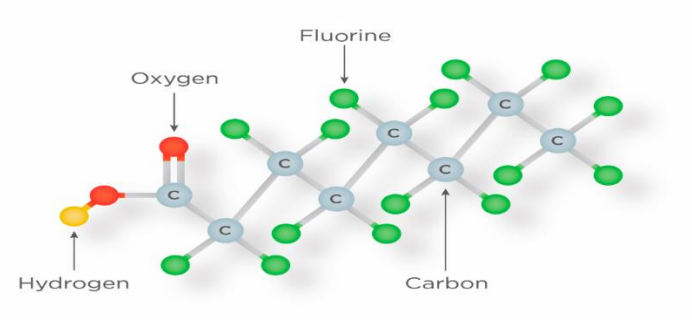
PFAS accumulate in the environment and living organisms, raising concerns about potential health effects from chronic exposure. (**Panieri et al 2022)** Rats are often used as animal models to study these effects due to their physiological similarities to humans. This review will explore the current understanding of PFAS and their chronic exposure effects in rats.

2. Chemical structure of PFAS:

Substituted fluorine atoms in place of hydrogen atoms on a carbon chain define the chemical structure of PFAS (Per- and Polyfluoroalkyl Substances as showed in fig (1). This structure is commonly known as a perfluoroalkyl moiety, which is a functional group consisting of a carbon chain where all hydrogen atoms have been substituted with fluorine atoms. (**Gaines et al 2023)**

The general description of PFAS is based on molecular structure alone and serves as a starting point to guide the identification of PFAS. The definition does not include any minimal or maximal chain length requirements, or any other considerations beyond chemistry. (**Gaines et al 2023)**

PFAS can be classified into various categories according to their molecular structure, including linear and branched PFAS, as well as their functional groups, such as carboxylic acids and sulfonic acids. The PFAS family tree serves as a valuable tool for categorising the wide array of PFAS molecules, which can be further classified into subclasses, groups, and subgroups according to their chemical features and behavior. (**Teymourian et al 2021)**



Fig(1): **PFAS chemical composition (Source: 3M)**

3. PFAS Exposure and Accumulation in Rats:

A. Exposure routes: Common exposure sources to PFAS include food, drinking water, occupational circumstances, and products in commerce (e.g., carpeting, clothing, paper products). (**Teaf et al 2019)**

B. Absorption: PFAS can be absorbed orally through ingestion of contaminated food, drinking water, inhalation of household dust and dermally through contact with products containing it. Once absorbed by the body, it can enter serum, breast milk, liver and kidney and PFAS have a tendency to build up in various tissues based on their unique characteristics. .Animal studies show that after PFAS exposure, the highest concentration is found in the main target organ, the kidney, followed by the liver and lungs. (**DeWitt 2015)**

C. Metabolism and excretion: PFAS is not metabolized in the body and is excreted mainly from the kidney without biotransformation or through feces . PFOA is reabsorbed into the kidneys. (**Liu et al 2023)**

D. PFAS half-lives: The elimination half-lives of PFAS can range from days to years, depending on the structure of PFAS compound, species, age and sex of animals as shown in table (1). The protracted persistence of these substances enhances their capacity for bioaccumulation.

species	Rat		Mice		Angus steer	Monkey		Human	
	M	**F**	**M**	**F**		**M**	**F**	**M**	**F**
PFOA	5.6 days	1.9 hours	22 days	16 days	19 hours	21 days	33 days	3.3 years	2.3 years
PFOS	38 days	62 days	43 days	38 days	114 hours	132 days	110 days	3.4 years	6.7 years

Table (1) showing half-lives of some PFAS (**DeWitt 2015)**

E.Bioaccumulation and tissue distribution: PFAS tend to accumulate in different tissues depending on their specific properties. Liver, kidneys, blood serum, and adipose tissue are often found with the highest concentrations. (**Pérez et al 2013)**

4. Chronic Exposure Effects in Rats:

PFAS possess a vast of toxic effects, including developmental toxicity, genotoxicity, carcinogenicity, hepatotoxicity, reproductive toxicity, immunotoxicity, cytotoxicity, neurotoxicity, and hormonal toxicity. (**Wee and Aris 2023)**

A. Hepatotoxicity: PFAS exposure has been related to a series of metabolic diseases, such as obesity, dyslipidemia and insulin resistance, which leads to nonalcoholic fatty liver disease (NAFLD), which is characterized by hepatic lipid accumulation without excess alcohol consumption consequently leading to hepatomegaly, altered liver enzyme levels. (**Weng et al 2020)** PFAs exposure has been associated with carcinogenic effect in several tissues, including hepatic, pancreatic, testicular and breast tissues. Several different regulatory agencies and researchers have reviewed the carcinogenicity of PFAs, with contradictory conclusions, especially regarding epidemiological findings on kidney cancer and testicular neoplasm. (**Qu et al 2023)**The exact mechanisms PFAS-induced hepatotoxicity are yet not fully understood but is expected to include oxidative stress, mitochondrial dysfunction, Inflammation and disruption of lipid metabolism. (**Naderi et al 2023)**

B.Endocrine disruption: Certain PFAS can interfere with hormone regulation, leading to i mbalances in thyroid hormone levels and other endocrine pathways. Perfluorooctanoic acid (PFOA) is known to be one of endocrine disrupting chemicals (EDCs) that may disrupt the hypothalamic-pituitary-thyroid (HPT) axis and thyroid hormone action.(**Sohn et al 2020)**PFOA was found to cause hypertrophy or hyperplasia of thyroid follicular cells in rats and showed decrease in total and free thyroxine (T4) concentrations. (**Sohn et al 2020)**

C.Developmental and reproductive toxicity: Exposure during critical developmental win dows can lead to adverse effects on offspring, including reduced birth weight, delayed pube rty, and impaired fertility. PFAS are suggested to have negative impact on strcture and function of rat testis, a study on rat found that the seminiferous tubule lumen in the PFOA-induced rats was narrowed, and the seminiferous epithelium was thinned. The arrangement of spermatogenic cells was disordered, and numerous immature spermatogenic cells fell off into the seminiferous tubule lumen. At the same time, sertoli cells and stromal cells were vacuolated. (**Zhang et al 2023)** The levels of Follicle stimulating hormone (FSH) in male rats were significantly increased after exposure to PFOA, but the levels of Testosterone (T) were decreased. (**Zhang et al 2023)** however the estrogenic activity or possibly estradiol (E2) levels may be part of the mode of action for PFOA. In male rats provided 13.6 mg/kg/d PFOA in their diet, serum E2 levels were elevated. (**White et al 2011)** The impairment of male reproductive function due to PFOA binding to estrogen receptors , oxidative damage to the body, disruption of spermatogenesis by inducing developmental impairment and testicular oxidative stress (**Liu et al 2015)**

D.Immunotoxicity: PFAS exposure can suppress the immune system, making rats more su sceptible to infections and diseases. Epidemiological research has repeatedly demonstrated that exposure to PFAS is linked to decreased antibody synthesis in reaction to vaccines, especially in children getting the tetanus and diphtheria vaccinations. (**Bline et al 2024)** (**van Larebeke et al 2023)** Both adults and children have shown this immunosuppressive impact; the data basis for children is larger. Furthermore, investigations on experimental animals and humans have connected PFAS exposure to a higher risk of gastrointestinal and respiratory tract diseases, especially in children whose mothers exposed PFAS in utero. (**van Larebeke et al 2023)** PFAS have the potential to disrupt the regulation of the immune system by affecting several aspects of the immune regulatory network. This includes the cellular and humoral response, the survival and maturation of immune cells, as well as the synthesis of cytokines involved in immune function. (**Garvey et al 2023)** PFAS can cause allergy and autoimmune illnesses and impair the body's ability to fight infections. Animal experiments have demonstrated that exposure to PFAS can lead to reduced weights of the spleen and thymus, decreased numbers of thymocytes and splenocytes, diminished immunoglobulin response, and alterations in particular lymphocyte populations in the spleen and thymus . (**Garvey et al 2023)**

E.Carcinogenicity: Some studies suggest an association between PFAS exposure and increased tumor development in specific organs, including liver, testicles, and mammary glands. Multiple epidemiological studies have repeatedly demonstrated a positive correlation between exposure to PFAS and an elevated susceptibility to specific forms of cancer, such as kidney, testicular, and pancreatic cancer (**Durham et al 2023)** (**Winquist et al 2023)**. The International Agency for Research on Cancer (IARC) has categorised PFOA as "carcinogenic to humans" (Group 1) due to substantial evidence demonstrating its ability to induce cancer in laboratory animals and strong data indicating that it possesses several fundamental characteristics of a carcinogen (**Temkin et al 2020)**. IARC has classed PFOS as a Group 2B carcinogen, meaning it is "possibly carcinogenic to humans." This classification is based on compelling evidence that PFOS exhibits certain characteristics of a carcinogen in individuals who are exposed to it, as well as limited evidence suggesting that it can induce cancer in laboratory animals. (**Temkin et al 2020)** Based on mechanistic understanding, PFAS can potentially promote the development of cancer by modifying the way genes are expressed and causing alterations in the epigenome. This can impact various signalling pathways in different types of cells. (**Boyd et al 2022)**Activating peroxisome proliferator-activated receptors (PPARs) is a plausible explanation for the various biological effects of PFAS, including its propensity to cause cancer. (**Boyd et al 2022)**

5. Obstacles and Prospects:

Extrapolating rat data to humans: While rat models give useful insights, changes in physiology and metabolism must be taken into account when interpreting data and determining human health concerns.Human exposure to intricate combinations of PFAS necessitates investigation to comprehend the cumulative impacts of these substances.

Identifying vulnerable populations: Specific demographics, including pregnant women, babies, and those with pre-existing diseases, may exhibit heightened susceptibility to the impacts of PFAS exposure.

6. Conclusion:

In conclusion, studying PFAS and how long-term exposure affects rats is very important for learning about possible health risks in humans. Strong evidence suggests links to a number of negative outcomes, but more study is needed to fully understand the complex mechanisms of action, the long-term effects, and how these findings affect humans. For creating good risk management plans and keeping the people healthy, this information is necessary.

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