An Overview on Toxic Effects of Perfluorooctanoic acid

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Abstract:

Perfluorooctanoic acid (PFOA) is an octanoic acid derivative to which all aliphatic hydrocarbons are substituted by fluorine. PFOA and its salts are commercially used in various industrial processes. The chemical is persistent in the environment and does not undergo biotransformation. It was reported that PFOA is found not only in the serum of occupationally exposed workers but also general populations. Recent studies have suggested that the biological half-life of PFOA in humans is 4.37 years based on study of occupationally exposed workers. It is increasingly suspect that PFOA accumulates and affects human health, although the toxicokinetics of PFOA in humans remain unclear. In experimental animals, PFOA seems low in toxicity. PFOA is well-absorbed following oral and inhalation exposure, and to a lesser extent following dermal exposure. Once absorbed in the body, it distributes predominantly to the liver and plasma, and to a lesser extent the kidney and lungs. PFOA is excreted in both urine and feces. Biological half-life of PFOA is quite different between species and sexes and the difference is due mainly to the difference in renal clearance. In rats, renal clearance of PFOA is regulated by sex hormones, especially testosterone. PFOA is excreted into urine by active tubular secretion, and certain organic anion transporters are thought to be responsible for the secretion. Fecal excretion is also important in the elimination of PFOA. There is evidence that PFOA undergoes enterohepatic circulation resulting in reduced amounts of fecal excretion. Elucidation of the mechanisms of transport in biological systems leads to elimination and detoxification of this chemical in the human body.

Keywords: Toxic Effects of Perfluorooctanoic acid, PFOA.

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Introduction:

Perfluorooctanoic acid (PFOA) is one of the per- and polyfluoroalkyl substances (PFASs), also known as perfluorooctanoate, and is a synthetic, stable perfluorinated carboxylic acid and fluor surfactant (1). It is also formed by the degradation of precursors such as some fluorotelomers (2).

Perfluorooctanoic acid has received much concern as it has been detected in cord blood and breast milk in the general population of industrial countries. In occupational workers, the serum concentration could reach as high as a hundred mg/L (3).

CDC scientists measured PFOA in the serum of 2094 participants of the United States population aged 12 years and older as a part of the National Health and Nutrition Examination Survey (NHANES) during 2003–2004. They found PFOA in the serum of nearly all the people tested with a median of 4 ng/mL, indicating that PFOA exposure is widespread in the U.S. population (4).

Uses of Perfluorooctanoic Acid

Perfluorooctanoic acid has been manufactured since the 1940s in industrial quantities. It is used to make products that resist heat, oil, stains, grease, and water. Its industrial application is as a surfactant in the emulsion polymerization of fluoropolymers. It has been used in the manufacture of such prominent consumer goods as Teflon (5).

Chemical Structure and Physical Properties of Perfluorooctanoic Acid

Perfluorooctanoic acid is a synthetic compound comprised of a linear carbon chain of eight carbons, with each carbon atom bonded to two fluorine atoms, except for the terminal carbon, which is bonded to a carboxylic acid group (-COOH). The formula for PFOA is C7HF15O2. The symmetric arrangement of fluorine atoms around the carbon backbone gives PFOA its characteristic stability and resistance to degradation (6).

Perfluorooctanoic acid has several notable physical properties. It is a colorless, odorless liquid at room temperature with a molecular weight of 414.07 g/mol. PFOA has a relatively high boiling point of approximately 189°C (372°F) and a melting point of around -14°C (7°F). It is sparingly soluble in water, with a solubility of approximately 29 mg/L at 25°C. PFOA is highly stable under normal environmental conditions due to the strength of the carbon-fluorine bonds in its chemical structure. These physical characteristics contribute to its persistence in the environment and its propensity for bioaccumulation in living organisms (7).

Routes of Exposure to Perfluorooctanoic Acid

Perfluorooctanoic acid can enter the human body through various routes of exposure, including inhalation, ingestion via contaminated food and water, and dermal contact. Inhalation of airborne PFOA can occur during industrial processes such as the manufacture or use of products containing PFOA or its precursors. Additionally, PFOA can migrate from consumer products such as food packaging, cookware (especially non-stick coatings), and textiles, potentially leading to inhalation exposure through indoor air contamination (8).

People are most likely exposed to PFOA by drinking contaminated water sources, most water treatment methods are ineffective in removing PFOA. Food is another significant route of exposure to PFOA, as it can be transferred from contaminated packaging or cookware into food during processing, storage, or cooking. Ceramics, particularly those coated with non-stick materials containing PFOA, have been identified as potential sources of exposure when used in cooking or food storage (9).

Dermal exposure to PFOA can occur through direct contact with products containing PFOA or its precursors, as well as through contact with contaminated surfaces or environments. Individuals may come into contact with it through the handling, wearing, or use of such products, leading to dermal absorption. The extent of dermal exposure depends on factors such as the duration and frequency of contact, the concentration of PFOA, and the permeability of the skin (**10**).

Exposure Limits of Perfluorooctanoic Acid

There were no universally agreed-upon exposure limits established specifically for PFOA by organizations such as the Occupational Safety and Health Administration (OSHA) or Environmental Protection Agency (EPA) in the United States. However, some regulatory bodies and expert groups have provided guidelines or recommendations for PFOA exposure based on its potential health risks. For instance, the EPA has issued health advisory levels for PFOA in drinking water. The EPA's lifetime health advisory for combined exposure to PFOA and PFOS in drinking water is 0.07 micrograms per liter (µg/L) (**11**).

Pharmacokinetics of Perfluorooctanoic Acid

- ### Absorption of Perfluorooctanoic Acid

Absorption of PFOA occurs through various routes, including ingestion, inhalation, and dermal contact. Studies have demonstrated that PFOA can be absorbed through the gastrointestinal tract after ingestion of contaminated food or water. Upon inhalation, PFOA can be absorbed directly into the bloodstream through the respiratory epithelium. Additionally, dermal contact with products containing PFOA or contaminated surfaces can lead to absorption through the skin While dermal absorption of PFOA is generally considered to be lower compared to other routes such as ingestion or inhalation, repeated or prolonged exposure to contaminated materials can still contribute to overall body burden (**12**).

- ### Distribution of Perfluorooctanoic Acid

Perfluorooctanoic acid distributes throughout the body following absorption, with a notable affinity for certain tissues and fluids. Studies have shown that PFOA distributes widely, with accumulation observed particularly in the liver and blood plasma. This distribution pattern is attributed to PFOA's strong binding affinity to serum albumin, a major protein in blood plasma. Additionally, PFOA has been detected in other tissues such as the kidneys, lungs, and brain, albeit at lower concentrations compared to the liver (**13**).

- ### Metabolism of Perfluorooctanoic Acid

Perfluorooctanoic acid undergoes limited metabolism in humans, with the compound primarily eliminated unchanged from the body. However, some studies suggest that PFOA can undergo oxidative metabolism in the liver, leading to the formation of metabolites. These metabolites may arise through pathways involving cytochrome P450 enzymes, although the specific metabolic pathways of PFOA in humans are not fully elucidated. The extent of metabolism may vary among individuals and may be influenced by factors such as age, sex, and genetic variability (**14**).

- **Elimination of Perfluorooctanoic Acid**

Perfluorooctanoic acid is primarily eliminated from the body through renal excretion, with a smaller proportion excreted via feces. Studies have shown that PFOA has a relatively long elimination half-life in humans, extending up to several years. This persistence in the body is attributed to PFOA's stability and resistance to metabolic breakdown. Additionally, the extent of elimination may vary depending on factors such as exposure duration, dose, and individual physiological characteristics (**15**).

Molecular Mechanisms of Perfluorooctanoic Acid Toxicity

Although extensively studied, the molecular mechanisms of PFOA-induced toxicity are still uncertain. The structural difference of PFOA makes it unique in toxicity mode. PFOA-induced toxicity is believed to involve multiple mechanisms, including oxidative stress, disruption of cellular signaling pathways, and interference with lipid metabolism and hormone regulation (**3**).

Studies have demonstrated that PFOA exposure can lead to increased production of reactive oxygen species (ROS) and oxidative stress in cells and tissues. ROS can cause damage to cellular components such as proteins, lipids, and DNA, contributing to various pathological conditions. Furthermore, PFOA has been shown to disrupt cellular signaling pathways involved in processes such as cell proliferation, apoptosis, and immune response (**16**).

Toxicity of PFOA in rodents has been linked to the activation of peroxisome proliferator-activated receptor-alpha (PPAR-α), a key regulatory protein in cellular processes. This activation leads to the alteration of gene expression patterns associated with peroxisome proliferation, particularly in organs such as the liver, kidney, and adipose tissue. For example, studies have demonstrated that exposure to PFOA can upregulate the expression of genes involved in peroxisome proliferation in these organs, contributing to the observed toxic effects (**17**).

Another possible underlying molecular mechanism of toxicity of PFOA was investigated with a specific focus on detoxification enzymes, including the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (**18**).

Toxicity of Perfluorooctanoic acid.

Acute toxicity studies have demonstrated adverse effects of PFOA at various dose levels. For instance, in rodent models, liver damage and reproductive dysfunction have been observed at relatively high doses of PFOA, typically ranging from 10 to 100 milligrams per kilogram of body weight administered orally or via other routes of exposure. However, it's important to note that the exact dose-response relationship and threshold for toxicity may vary depending on factors such as the duration of exposure and individual susceptibility (**19**).

Due to its long half-life in the human body, environmental health risks have received an increasing concern (**20**). The human health effects of exposure to low environmental levels of PFOA are unknown. In laboratory animals given large amounts, PFOA can affect growth and development, reproduction, and injure the liver. More research is needed to assess the human health effects of exposure to PFOA (**21**). People most at risk of adverse health impacts are those exposed to high levels of PFOA especially in vulnerable population groups such as children and

the elderly and workers in the perfluorochemical industry who are exposed to greater amounts of PFOA than people in the general population (22).

- **Cardiotoxic Effect of Perfluorooctanoic Acid**

A study by **Anderson-Mahoney et al. (23)** evaluated subjects with prolonged exposure to PFOA in their drinking water and reported a statistically significant greater prevalence of angina, myocardial infarction, and stroke. The increased prevalence of adverse health effects may be due to PFOA.

Perfluorooctanoic acid has been repeatedly found to be positively associated with increased blood cholesterol concentrations in multiple human epidemiological studies. In the majority of these studies, the general pattern observed was a significant increase in the total serum cholesterol or low-density lipoprotein cholesterol associated with increased blood levels of PFOA, while the results reported for high-density lipoprotein cholesterol were inconsistent (24).

- **Hepatotoxic Effect of Perfluorooctanoic Acid**

The liver is an important metabolic organ and studies indicate disruptions in lipid metabolism and liver function upon PFOA exposure, potentially due to the accumulation of lipids in the liver (liver steatosis). In parallel to cholesterol changes, a clear linear association between PFOA serum concentrations and ALT, a marker of hepatocellular injury, was observed in data collected from 69,030 persons (25).

- **Nephrotoxic Effect of Perfluorooctanoic Acid**

Studies indicate that PFOA can significantly impact kidney function through multiple pathways, including the induction of oxidative stress, disruption of mitochondrial function, dysregulation of calcium homeostasis, and promotion of inflammation. Evidence suggests that exposure to PFOA is linked to renal damage, characterized by impaired kidney filtration, and elevated markers of kidney injury (13).

- **Carcinogenic Effect of Perfluorooctanoic Acid**

Studies suggest that exposure of PFOA may be associated with an increased risk of certain types of cancer, including liver and testicular cancer, in both animal models and human populations. The mechanisms underlying PFOA's carcinogenic effects may be due to inducing oxidative stress, disrupt DNA repair mechanisms, and promote cell proliferation, all of which are implicated in cancer development. Furthermore, epidemiological studies have found associations between PFOA exposure and increased cancer incidence in exposed populations, particularly in occupational settings or communities near industrial sites where PFOA contamination has occurred (26).

- **Immunotoxic Effect of Perfluorooctanoic Acid**

Extensive studies, including animal experiments and human epidemiological research, have revealed compelling evidence of PFOA's ability to disrupt immune function. Animal studies consistently demonstrate that PFOA exposure suppresses antibody responses, indicating a

weakening of the immune defense mechanisms. Similarly, human studies have shown associations between PFOA exposure and alterations in immune parameters. These findings collectively suggest that PFOA possesses immunotoxic effects, raising concerns about increased susceptibility to infections and immune-related disorders in exposed populations **(27).**

Perfluorooctanoic acid is believed to modulate immune responses through multiple mechanisms, including inflammation, oxidative stress, and interference with immune cell signaling pathways. Several studies have suggested that PFOA exposure may lead to alterations in cytokine levels and inflammatory responses **(28).**

Furthermore, PFOA-induced oxidative stress has been shown to impact immune cell function and viability. Oxidative stress can impair the function of immune cells such as lymphocytes, macrophages, and dendritic cells, compromising their ability to mount an effective immune response against pathogens. PFOA exposure has also been linked to alterations in immune cell signaling pathways, including those mediated by nuclear receptors such as peroxisome proliferator-activated receptors (PPARs). PFOA can activate PPAR signaling, which plays a crucial role in regulating immune cell differentiation, proliferation, and cytokine production **(18).**

- **Endocrine Disruptor Effect of Perfluorooctanoic Acid**

Research indicates that PFOA can disrupt the function of the endocrine system by interfering with hormone synthesis, secretion, transport, and receptor binding. Animal studies have shown that PFOA exposure can lead to alterations in hormone levels. PFOA exposure has been associated with changes in adrenal hormone levels, including cortisol, which plays a crucial role in stress response and metabolism. Furthermore, PFOA has been linked to disruptions in insulin secretion from the pancreas, potentially contributing to metabolic disturbances and diabetes risk **(29).**

Moreover, PFOA has been implicated in disrupting thyroid hormone balance, which further influences sex hormone regulation **(13)**. PFOA can interfere with the function of thyroid hormones by displacing them from transport proteins or inhibiting enzymes involved in thyroid hormone metabolism. Disruption of thyroid hormone signaling can have widespread effects on various physiological processes, including metabolism, growth, and development **(30)**.

Research suggests associations between increased PFOA exposure and changes in the levels of some key steroidogenic enzymes including gonadal or serum testosterone, testicular receptors for gonadotropin, growth hormone, and semen parameters. This could be explained based on PFOA being endocrine disruptors **(31)**.

- **Neurotoxic Effect of Perfluorooctanoic Acid**

Perfluorooctanoic acid has been implicated in various adverse health effects, including potential impacts on brain function. Research suggests that exposure to PFOA may have neurotoxic effects, affecting brain development and function. Studies have demonstrated associations between PFOA exposure and cognitive impairments, such as decreased memory and learning abilities **(32).** Furthermore, PFOA has been linked to alterations in neurotransmitter

systems, oxidative stress, and inflammation in the brain, which could contribute to neurological dysfunction (33).

- **Respiratory Toxic Effect of Perfluorooctanoic Acid**

Research suggests that exposure to PFOA may contribute to lung-related issues, including respiratory symptoms and impaired lung function. A study by **Darrow et al. (34)** found a positive association between serum PFOA levels and self-reported respiratory symptoms, such as coughing and wheezing, in a community exposed to PFOA-contaminated drinking water. Additionally, animal studies have indicated that PFOA exposure can lead to lung inflammation, oxidative stress, and alterations in lung tissue structure (35).

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