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Nonylphenol Toxicity: Exposure, Mode of Action, Toxic Effects

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ABSTRACT

Nonylphenol (NPL) is concerned as a substance that may disrupt human endocrine systems. NPL is extensively prevalent in the environment which could disrupt the nervous system, immune system, reproduction. Its high hydrophobicity, makes NPL can withstand environmental conditions for an extended period particularly those in soil. Determining NPL risk depends up on the exposure circumstances including exposure pathways, exposure time, and exposure concentrations. It's critical to comprehend these concerns to evaluate the risk for human. NPL contaminates the environment through soil, and wastewater effluents causing its toxicity. Hence, determining origin, fate and harmful impact of NPL, besides elimination of it appears to be a top priority. NPL can be treated using microbiological and physicochemical techniques. Meanwhile, the fact that microbial techniques are environmentally friendly makes them popular. This review shows NPL toxicity, fate, and the ways for elimination from the environment.

Keywords: Endocrine disruptor, Nonylphenol, Organ toxicity, Toxic effects.

INTRODUCTION

Recently, environmental pollution has been arising as the main issue, because of increased urbanization, widespread industrialization, and population growth (Liu *et al.*, 2021). Strong estrogenic activity is exhibited by a highly diverse range of compounds known as endocrine disruptors (EDCs) (Gingrich *et al.*, 2020). Over the lifespan, EDCs can cause disease by interfering with normal hormonal signalling and endocrine functioning (Kassotis *et al.*, 2020). Many different substances are included in EDCs, including bisphenol S (BPS), triclosan (TCL), nonylphenol (NPL), and bisphenol A (BPA). Kahn *et al.* (2020) reported that EDCs are extensively present in a variety of industries and are present in medical supplies, food, and food packaging that results in environmental contamination. EDCs have the ability to negatively impact ecosystems, aquatic life, and human activity, even while they are applicable. The detrimental effects of exposure to these exogenous substances on endocrine processes and functions have been proven by numerous reports (Kaur *et al.*, 2020 b). Surfactants are a type of phospholipid layer substance that can penetrate the bronchioles of the lung and small air passages. In these areas, they serve a variety of protective functions, including preventing the airways from collapsing (Olayiwola and Dejam, 2020). And, surfactants are compounds that act in decreasing surface tension in industrial products by acting as detergents,

dispersions, and wetting agents (Nagarnaik and Boulanger, 2011). In the food and agricultural sectors, alkylphenol ethoxylates (APEOs) are among the surfactants that are most frequently used (Mahalakshmi *et al.,* 2020). The most widely used APEOs, making over 80% of all applications, are nonylphenol ethoxylates (NPEOs) (He *et al.,* 2020). However, the application, the effective elimination of NPEOs from the environment is critical. Conventional techniques are unable to eliminate NPEOs from the environment and generate alternative compounds, such as nonylphenol (NPL) (He *et al.,* 2020). Due to its toxicity to organisms, bioaccumulation in biotas, and persistence in environmental areas, NPL is one of the primary EDCs that has recently gained substantial attention. There are several applications for this non-ionic surfactant. NPL is a xenobiotic chemical, poorly soluble and has very hydrophobic phenol ring and possess on the para position nine-carbon chain. NPL causes water contamination due to high usage (Tang *et al.,* 2020), and its level can vary from 644 mg/L in water to 1350 mg/L in wastewater (Medvedeva *et al.,* 2017). This chemical compound is prevalent in both household and industrial wastewater and is stable in the environment. Studies have shown a correlation between the incidence of specific diseases and occupational exposure to NPL (Snijder *et al.,* 2012).

Even though exposure from employment, the public is exposed to NPL through inhalation, digestion, and cutaneous contact because it is more enduring in the environment, among which the primary pathway is digestion. In terms of digestive exposure, NPL can reach humans through the food chain when they bioaccumulate from contaminated environments. Furthermore, the widespread use of NPEOs in food packaging materials results in the transfer of NPL into food (Loyo-Rosales *et al.,* 2004). It has been found that NPL is present in a wide variety of foods. NPL a hormone-disrupting chemicals with estrogenic nature that is persistent in the environment, has negative effects on both people and wildlife. Several Evidence that shows how hazardous NPL to the neurological system, reproductive functions, and developmental processes. Even though NPL exposure has been linked to chronic liver damage (Mukherjee *et al.,* 2022). Many adverse impacts were documented on exposure to NPL like hepatotoxicity (Abd-Elkareem *et al.,* 2018), nephrotoxicity (Kotb *et al.,* 2018), testicular damage (Sayed and Ismail, 2017), neurotoxicity (Ton *et al.,* 2006), genotoxicity (Al-Sharif, 2012), social behaviour disturbance (Xia *et al.,* 2010), hemotoxicity (Madhu and Pooja, 2015), thyrotoxicosis (Naderi *et al.,* 2015), immunosuppression (Sharma, 2015). Moreover, NPL has been demonstrated to cause DNA fragmentation, apoptosis, and the reactive oxygen species (ROS) generation and antioxidant enzymatic system depletion (Sayed and Soliman, 2018).

a. Chemical structure

Nonylphenol (NPL) is the end product of the breakdown of ethoxylated alkylphenols (APEOs) in an environment (Fig. 1), which is composed of a phenol ring and a nine-carbon chain on the para-position and accounts for approximately 80% of the APEOs. This environmentally stable chemical is present in both household and commercial effluent (Gong *et al.,* 2009 and Gong and Han, 2006).

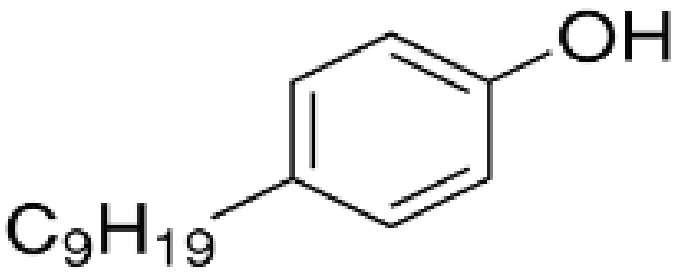

Fig1. Chemical structure of NPL (Tothova *et al.,* 2009).

b. Chemical and Physical properties of NPL

Anaerobic breakdown of the ethoxylated alkylphenols (APEO) results in the formation of NPL. When compared to aerobic conditions, the creation of NPL is enhanced four to eight times in the absence of oxygen. Under aerobic conditions, the APEO break down into either low-molecular-weight ethoxylates by the loss of ethylene oxide (EO) units or carboxylated ethoxylates, which finally end in water and CO2. According to reports, ethoxylated alkylphenol derivatives are more hazardous and persistent than their parent compounds. They can also cause natural hormones to be disrupted by interfering with the oestrogen receptor and cause physiological disturbance (Renner, 1997). Additionally, Hesselsoe *et al.* (2001) found that, NPL half-life in the soil was 3 to 6 days under aerobic conditions.

The chemical formula of NPL is C15H24O, with M.M. equal to 220 g mol-1. Under ambient circumstances, it is a viscous liquid that dissolves in common organic solvents like acetonitrile and methanol and is marginally soluble in water (4.90 mg L-1 at 25 °C). It has a density of 0.6 g mL-1 at 20 ºC, a melting point of -10 °C, a boiling point of 304 °C, and a vapor pressure of 1.33 Pa (20 °C). With a pKa of 10, 7, it functions as a weak acid in aqueous solution. NPL is very harmful to aquatic creatures, persistent, and somewhat bio accumulative (Tothova *et al.,* 2009).

c. Mode of action.

Natural or artificial substances known as "endocrine disrupting chemicals" (EDCs) could interact with the endocrine system, which can lead to a variety of health issues in both humans and animals (Lee *et al.,* 2013). The harm that EDCs cause to humans, animals, and microorganisms is a topic of significant concern in today's developed world (Aly *et al.,* 2012). Estrogen recipient agonists, or EDCs, interfere with hormone synthesis, release, metabolism, and storage while also changing how they normally work (Dobrzyńska, 2014). One of the most common substances that disrupts hormones is APEOs. The class of EDCs known as non-ionic surfactants may pose a risk. These substances find widespread application in the manufacturing of various detergents, cleansers, and emulsifiers (Gong *et al.,* 2009). NPL can bind to estrogen receptors and shares a structural resemblance with estrogen. Research has demonstrated that NPL can cause reproductive disorders in animals, including disturbance in spermatogenesis and ovarian development (Di *et al.,* 2018). Because of NPL binds to estrogen receptor binding sites, it can compete with 17β-estradiol (E2) and disrupt the body's endocrine system, which is why it has hazardous effects (Yadetie *et al.,* 1999). Furthermore, NPL is referred to as a potent mitochondrial uncoupler since it could increase the proton permeability of the mitochondrial membrane and interfere with ATP synthesis (Bragadin *et al.,* 1999).

d. Sources and environmental exposure

Industrial detergents including insecticides, cosmetics, additives, plastics, polyvinyl chloride pipes, food processing industries, packaging, paint, and other agricultural items are frequently made using NPL (Zhao *et al.,* 2015). NPL is also widely employed in many other sectors, such as modifiers for phenolic resin, gasoline additives, and rubber antioxidants (Soares *et al.,* 2008). As represented in Fig.2, Numerous environmental sectors, including the air, soil, sediments, and water, are known to have NPL deposits (Cao *et al.*, 2019). A concentration of 28.6µg/L of NPL was found in Chinese river and lake water, while a significantly greater amount of NPL was found in surface water from Spain, with a concentration of 644µg/L (Fu *et al.*, 2007).

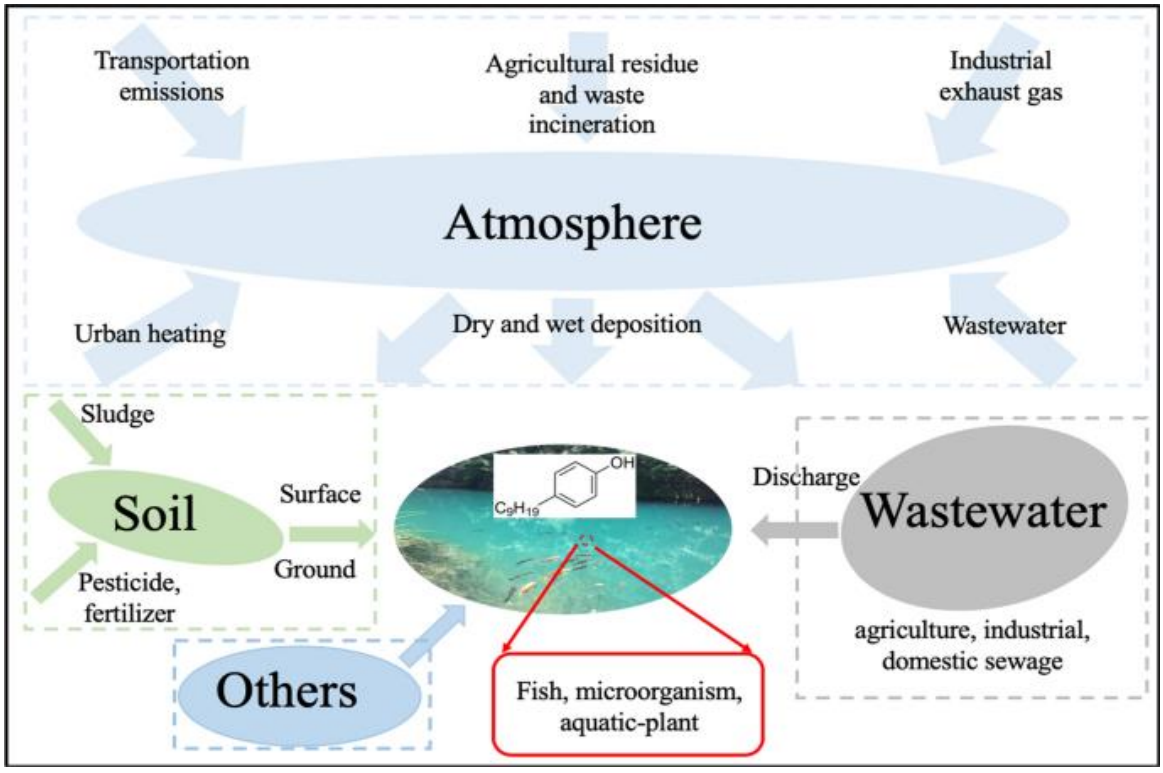

Fig.2. Sources of NPL exposure in water ecosystems. Nonylphenol enters the water ecosystem via water and agricultural sources, wastewater treatment plant effluents, agricultural runoff, and groundwater discharge from air, soil (Hong *et al.,* 2020).

e. Industrial uses

The primary class of non-ionic surfactants, NPLs are widely employed in human care items such as paints, cleaners, detergents, hair dyes, hair dyes, insecticide formulations, and many other synthetic goods. Additionally, it is present in polyvinyl chloride (PVC), which taints the water that passes via PVC pipes (Rivero *et al.,* 2008).

f. Toxicokinetic profile of NPL

Absorption, bioavailability, and metabolism of NPL

Industrial effluents and community wastewater treatment plants are the two main ways that NPL enters the environment (van den Berg *et al.,* 2003). Adipose tissue can harbour accumulations of NPL, due to the lipophilic characteristic. Therefore, it can enter the food chain. Routes of exposure with NPL include absorption, eye contact, skin contact, ingestion, and inhalation. The target organs for NPL

include skin, eyes, gastro/intestinal tract, respiratory system, liver, brain, thyroid, pancreas, kidney, bladder, female (ovary, endometrium, breast cancer, and foetus), and male (sperm, epididymis, testis, Sertoli cell). Human plasma samples from healthy individuals were found to contain 0.2–0.3 ng/ml of NPL (Kawaguchi *et al.,* 2004). Moreover, the initial absorption of NPL through the gastrointestinal tract is likely substantial and rapid (Daidoji *et al.,* 2006). The two primary metabolic routes that are probably implicated include glucuronide and sulphate conjugation, as well as the significant NPL first pass metabolism that is ingested through the alimentary tract (Inoue *et al.,* 2016). NPL is mostly excreted in the urine and stool and is widely dispersed throughout the body, with fat containing the largest quantity (Careghini *et al.,* 2015). Additional research revealed that NPL can alter the metabolism of steroid hormones, which could increase its harm to reproduction (Ying *et al.,* 2012).

q. Nonylphenol toxicodynamic profile

Through several methods, NPL can have a negative impact on many tissues and organs. The central neurological, endocrine, immunological, and reproductive systems of both people and animals can be adversely affected by NPL (Ho and Watanabe, 2018).

q.i. Hepatotoxicity

The liver serves as the primary organ in the body's detoxification process, metabolism, and production of energy-producing macromolecules for several vital processes (Djordjevic *et al.,* 2011). Therefore, when assessing the impact of specific xenobiotics, hepatotoxicity is a crucial endpoint. To determine the effects of chemical exposure on specific organs, clinical chemistry and histological examinations are frequently employed techniques (Mossa *et al.,* 2012). NPL increased serum alkaline phosphatase (ALP) level and hepatic (HO-1 and Gadd45b) genes expression in compared with the control group (Kazemi *et al.,* 2016). The livers of both male and female fish subjected to 100 µg/l of NPL showed considerably lower levels of SOD and CAT, and microscopic examination of the liver tissues revealed distinct changes in fish exposed to NPL (Shirdel *et al.,* 2020). Increased amounts of ALP, AST, and ALT were observed, indicating that NPL had a significant effect on liver enzymes. When considered collectively, Mirror carp fish's hepatic tissue's histological changes suggested oxidative stress (Rahman *et al.,* 2022).

Liver cells have been shown to contain a particular estrogen receptor, and the relationship between the hormone and the responses of the cells has been identified. NPL is commonly metabolized by microsomal UDP glucuronosyltransferase (Doerge *et al.,* 2002). Exposure to NPL+ high sucrose-high fat diet (HSHFD) enhances expression of Sterol regulatory element binding protein 1(SREBP1), fatty acid synthase (FAS). Enzymes and lipid production are regulated by SREBP1, a crucial liver transcription factor (e.g., fatty acid synthase) catalysing numerous steps in the fatty acid and also triglyceride synthesis and elevated the plasma levels of triglyceride (TG), and total cholesterol (TC) (Yu *et al.,* 2018).

NPL induced haemolytic anaemia, leucocytosis, azotemia, hyponatremia, and hyperkalemia. Also, significantly elevated levels of AST, ALT, and LDH, ammonia, creatinine, cholesterol, TNF-alpha, and MDA were reported. Furthermore, splenic lymphoid depletion coupled with hepatic structural injury (Mohamed *et al.,* 2019).

q. ii. Nephrotoxicity

As the kidney is regarded as a vital organ responsible for reabsorption of substances and then elimination outside the body through urine (Al-Jassim *et al.,* 2016). In the kidney, NPL causes tubular epithelial degradation, congestion region, infiltration of mononuclear cells, and necrotic lesions (Woo *et al.,* 2007). Bisphenol A (BPA) and NPL may harm the kidneys. by increment

in serum levels of creatinine and blood urea nitrogen (Shi *et al.*, 2021).

It was discovered that 4-NPL poisoning may result in cell death and debris accumulation, which may obstruct the renal tubular system, resulting in an accumulation of fluid within the glomerulus. 4-NPL has an impact on the structure of the renal tubules; it causes a noticeable reduction in the tubular brush border's thickness, which results in renal fluid stasis and renal tubule lumen dilatation. On the other hand, anomalies in the renal tubular structure may interfere with the body's natural fluid absorption, which could result in proteinuria, it is thought that 4-NPL-induced nephrotoxicity causes glomerular cell loss in catfish (Kotb *et al.,* 2018).

q. iii. Reproductive toxicity

NPL exhibits moderate estrogenic action. The suppression of estrogen binding to the ER by NPL causes hormonal problems by interfering with the body's natural hormone production, release, transport, metabolism, binding, action, and elimination (Kwack *et al.,* 2002). The administration of NPL in rats resulted in deleterious effects on antioxidant enzymes, spermatogenic cells of the male reproductive system, apoptotic and anti-apoptotic proteins, steroidogenic testicular enzymes, hormonal and sperm parameters, and testicular morphological integrity (Ijaz *et al.,* 2021).

In the testes, undifferentiated male germ cells called spermatogonia go through spermatogenesis to become sperm. Exposure to bisphenol A (BPA) and NPL, two EDCs, is thought to have negative effects on sexual development and fertility. As spermatogonia is one example of early germ-cell development damaged by EDC exposure, this can lead to male infertility (Karmakar *et al.,* 2017).

NPL produced histological lesions in the testis of juvenile Caspian brown trout during smolting, and it also altered the plasma levels of sex hormones, gonadotropins, phosphorus, and the estradiol to testosterone ratio. Both sex of smolts exposed to NPL had considerably higher plasma levels of estradiol due to NPL. In both genders, exposure to NPL reduced levels of testosterone and FSH. It has also increment in LH levels in females but did not show change in levels of LH in male fish (Shirdel *et al.,* 2020).

Research has shown that long-term exposure to NPL reduces testicular size, lowers blood levels of testosterone, reduces the number of sperm in the epididymis, lowers the activity of antioxidant enzymes in epididymal sperms, disrupts testicular structure, causes testis cancer, reduces the seminiferous tubules diameter, lumen, and epithelial thickness, causes cryptorchidism, increases Sertoli cell apoptosis, and causes Sertoli cells hypertrophy (Tan *et al.,* 2003 and Cardinali *et al.,* 2004). Some prior research examined the impact of NPL on freshwater and marine organisms during reproduction and early stages of embryonic development (Arslan *et al.,* 2007). In fish, lab animals, and humans, the main route of NPL is metabolism by cytochrome P450 enzymes followed by glucuronidation. NPL has the ability to cause oxidative stress by generating ROS), which include superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). According to reports, the formation of ROS can upset the equilibrium between pro- and antioxidants, damage cellular components, and ultimately cause cell death. Because sperm's plasma membrane is high in polyunsaturated fatty acids, ROS can damage it and cause sperm loss and DNA breakage. Due to its detrimental effects on spermatogenesis and sperm quality, NPL may be the cause of male infertility (Kourouma *et al.,* 2015).

Testicular abnormalities caused by NPL exposure include a decrease in the number of sperm in the head of the epididymis, a drop in testosterone levels, a decrease in the proportion of motile sperm, and the modification of a particular form of testicular proteinases. Moreover, aberrant

semen analyses are seen in around 25% of male infertility patients (Pflieger-Bruss *et al.,* 2004 and Working, 1988). Exposure to NPL reduced the developmental capability of oocytes and increased the number of atresia follicles. According to transcriptomic research, exposure to NPL changed the expression of over 800 genes in oocytes, including several biological pathways. An analysis of the subcellular structure revealed that NPL exposure resulted in chromosomal misalignment and disturbed meiotic spindle architecture. Furthermore, it was shown that exposure to NPLs resulted in abnormal mitochondrial distribution and reduced membrane potential. Reactive oxygen species (ROS) accumulated as a result of NPL exposure, leading to oxidative stress and early apoptosis (Xu *et al.,* 2020).

q. iv. Neurotoxicity

NPL induced oxidative stress that leads to neural stem cells to undergo apoptosis, which increases cytotoxicity and raises the possibility that NPL influences CNS neurogenesis (Mao *et al.,* 2008). It has been suggested that the NPL contributes to the pathogenesis of neuropsychiatric disorders either directly or indirectly (Jie *et al.,* 2010). Following ingestion, the blood brain barrier (BBB) is eventually penetrated by NPL as it is distributed throughout the central nervous system by the circulation (Arukwe *et al.,* 2000). The lipophilic properties of NPL leads to storage of NPL in different tissues high in fat content such as the brain (Geens *et al.,* 2012). NPL decreased the activity of the acetylcholine esterase (AchE), monoamine oxidase (MAO) and Na+/K+-ATPase and alteration of antioxidant enzymes in an article shows that NPL similar to other endocrine disruptors, raises the possibility of exposure to environmental factors causing changes in neurochemical, and histopathological states (Tabassum *et al.,* 2017). NPL has a variety of effects on how brain tissue develops, primarily through interfering with cell ion channels, influencing how cells use energy, decreasing the neurotransmitters production and release, impairing neurotransmitter receptor's function, and eventually influencing the growth and differentiation of neurons. But as of right now, the majority of research has been done on animals like rats (Chitra *et al.,* 2002 and Mao *et al.,* 2010). By triggering inflammatory factors, NPL can result in brain inflammation. In certain pathological circumstances, the production of pro-inflammatory cytokines increases, resulting in CNS damage (Aydoğan *et al.,* 2008).

1. Remediation.

To remove NPL from the environment and water supplies, numerous techniques have been tried. Adsorption is a widely utilized method for removing NPL because it is easy to apply, affordable, and readily available. However, secondary contamination in water can result from complexes being adsorbed into a solid phase. The degradation process is a well-liked and intriguing way for eliminating NPL among many physical, chemical, and biological utilized procedures because of its special qualities, which include simplicity, ease of operation, affordability, speed, and high selectivity (Kaur *et al.,* 2020a; Liang *et al.,* 2020). Many physicochemical remediation techniques have been used to clean up NPL-polluted environment.

CONCLUSION

NPL differs from more conventional pollutants such as heavy metals and nutrients. Among the many harmful effect endpoints of NPL toxicity are acute death, toxicity to growth and development, estrogenic effect, endocrine interference, and other toxicities. There is a lack of reliable reporting of NPL toxicity and there is currently no standard or relevant

study to measure the environmental risk and toxicity of NPL.

ABBREVIATIONS

AchE	Acetylcholine esterase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APEOs	Alkylphenol ethoxylates
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BPA	Bisphenol A
BPS	Bisphenol S
CAT	Catalase
CNS	Central nervous system
DNA	Deoxy nucleic acid
E2	17β-estradiol
EDCs	Endocrine disruptors chemicals
EO	Ethylene oxide
ER	Estrogen- receptor
FAS	Fatty acid synthase
FSH	Follicular stimulating hormone
H_2O_2	Hydrogen peroxide
HSHFD	High sucrose-high fat diet
LDH	Lactate dehydrogenase
LH	Lutelizing hormone
MAO	Monoamine oxidase
MDA	Malondialdehyde
NPEOs	Nonylphenol ethoxylates
NPL	Nonylphenol
O_2^-	Speroxide anion
PVC	Polyvinyl chloride
ROS	Reactive oxygen species
SOD	Super oxide dismutase
SREBP1	Sterol regulatory element binding protein1
TC	Total cholesterol
TCL	Triclosan
TG	Tri-glyceride
TNF-alpha	Tumor necrosis factor
UDP	Uridine di phosphate

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