Chapter 1
Introduction to Environmental Harmful Factors

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Abstract In this Chapter, we systematically and comprehensively described various environmental harmful factors. They were classified into four aspects: physical factors, chemical factors, biological factors, and physiological and psychological stress factors. Their classification, modes of presence, toxicity and carcinogenicity, routes of exposure to human and toxic effects on the female reproductive health were introduced. It is expected that the exposure routes could be controlled and eliminated, and the pathogenic mechanism of environmental harmful factors should be investigated and explained to protect female reproductive health.

Keywords Environmental harmful factors · Physical and chemical factors · Biological factors · Physiological and psychological stress factors · Female reproductive health

1.1 Introduction

Various environmental factors are closely related to human health. When some chemicals are adsorbed by plants, they enter food chain and would cause primary threat to human health [1]. The particulate matter (PM), which comes from metals, organic carbon, vehicles, and biomass burning emissions, could lead to oxidative stress and impact human health [2]. Various viruses, such as COVID-19, also threaten human health. All these factors those may have adverse effects are considered as environmental harmful factors. In general, environmental harmful factors include physical factors, chemical factors, and biological factors. However, the term "exposome" includes both external and internal factors as well as human's response to these factors [3]. External environmental factors determine external exposure

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dose; and the internal exposure is dependent on the exposure pathway and the response of human. Finally, environmental factors may cause differential effects on organism due to the additional psychological influence. For example, air pollution is likely to cause greater illness in those with heavier exposure and greater susceptibility [4]. Hence, in this Chapter, we will introduce the environmental harmful factors from the following four aspects: physical factors, chemical factors, biological factors, and physiological and psychological stress factors.

1.2 Physical Harmful Factors

Physical factors mainly include noise, vibration, electromagnetic radiation, and meteorological conditions. These physical factors usually have their definite sources. Except for laser, other factors could all be found in nature. Some of the factors in an appropriate dose would be necessary and non-harmful for human. However, extra strong dose or radiation in other wavelength range would be harmful for human.

1.2.1 Noise

In physics, noise refers to the sound with irregular frequency or intensity. In hygiene, the annoying or unnecessary sounds are considered as noise. According to its source, noise can be divided into natural noise and unnatural noise. Noise mainly affects the auditory system. Short-term exposure to noisy environment may lead to auditory adaptation or fatigue, which belongs to temporary threshold shift and can be recovered after a certain period of time. However, if persons remain in a noisy environment for a prolonged period of time, it will lead to permanent threshold shift, including hearing loss and deafness [5, 6]. Noise-induced hearing loss is more common in work, which could be considered as a kind of occupational disease [7]. Noise can also affect the nervous system, circulatory system, digestive system, and psychology. High levels of traffic noise are not only associated with depression and anxiety disorders, but also related to cardiovascular and metabolic disorders [8–10]. Furthermore, noises are also associated with female reproductive health. A study in China found a link between noise and menstrual disorders in female health workers and nurses [11]. This noise may ultimately affect women's reproductive health. Another experiments show that exposure to modest to high levels of noise significantly decreases the reproductive efficiency of mice by reducing the quantity of pups born and increasing the quantity of stillborn pups [12]. Therefore, it is necessary to set noise standards for environmental and industrial enterprises, to control noise sources and noise propagation, and to perform individual protection and health monitoring against noise.

1.2.2 Vibration

Vibration refers to the repeated motion of a particle or an object in a straight line or arc around an equilibrium position under the action of external forces. It can be divided into local vibration and whole-body vibration. Local vibration is caused by hand contact with vibrating tools or machinery, and can be transmitted through the arm to the whole body. Local vibration will cause vibration damage to fingers, hands, and arms, even induce hand-arm vibration syndrome [13]. Whole-body vibration refers to the vibration that is transmitted to the whole body through the lower limbs or trunk. The situations may cause whole-body vibration, including taking a vehicle, operating agricultural machinery such as tractors, and locating on the platforms such as drilling platforms. Whole-body vibration can increase heart rate, cause dizziness, nausea, and other symptoms, even lead to motion sickness. Experiments on tall buildings confirmed that vibration can cause motion sickness and sopite syndrome (sleepiness) [14, 15]. And long-term whole-body vibration exposure can probably contribute to the disorders of female reproductive organs and disturbances of pregnancy (abortions, stillbirths) [16]. Animal studies further confirmed that vibration is indeed relevant with reproductive health [17]. Eliminating the source of vibration is the fundamental way to prevent vibration hazard.

1.2.3 Ionizing Radiation and Non-ionizing Radiation

Ionizing radiation could cause substances to be ionized. According to the source, it can be divided into natural radiation and artificial radiation. Natural radiation includes cosmic rays and radioactive elements in crustal rocks. Artificial radiation includes x-rays, gamma rays, protons, and so on, which are produced by ray generators. Ionizing radiation exists in nuclear industrial systems, in the production and processing of radioactive elements, production and use of ray generators, and medical processes. Excessive ionizing radiation will affect human health. Radiotherapy used to treat brain tumors may damage the central nervous system, then affect the peripheral immune system [18]. A cohort study has suggested that the occurrence rate of cancer is increased linearly with the increase of radiation exposure [19]. For the health of the fetus, ionizing radiation must be kept away during pregnancy. Gadolinium MRI exposure at any stage of gestation may increase maternal and fetal health risks [20]. Another study shows that occupational exposures of ionizing radiation are positively correlated with spontaneous abortion in female veterinarians [21]. Thus, it is better to avoid radiation by shielding and isolation from the source.

Non-ionizing radiation cannot cause ionization of biological tissues. It belongs to a specific range in the electromagnetic radiation spectra, and mainly includes radiofrequency (RF) radiation, infrared, visible light, ultraviolet, and laser. Since 2011, International Agency for Research on Cancer (IARC) at WHO identified

radiofrequency radiation in the 30–300 GHz range as a "possible" human Group 2B carcinogen [22]. Humans are inevitably exposed in the process of industrial heating, communication, radio positioning, and radar navigation, which can affect the nervous system, reproductive system, blood, and eyes. Animal studies have shown that radiofrequency electromagnetic radiation can lead to learning and memory impairment, decrease the activity of brain antioxidant enzymes, increase the concentration of corticosterone and lipid peroxidation, and cause histopathological aberrations in the hippocampal tissues [23]. Rat assays showed that long-term exposure to radiofrequency electromagnetic radiation from 4G smartphone will diminish male fertility through directly interfering the Spock3-MMP2-BTB pathway in rats [24]. Infrared radiation is generally found in sunlight and strong luminaries (tungsten, neon, infrared searchlight), and it is also present in the process of steel making and welding. Sun, ultraviolet (UV) lamp, welding, smelting, and other processes produce UV. Both infrared and UV radiation can hurt skin and eyes. Solar radiation contains infrared, ultraviolet, and visible light, and they damage human skin [25]. The development of possibly age-related macular degeneration, pterygium, and cataracts may be associated with UV radiation exposure [26]. Therefore, staying away from radiation sources and taking personal precautions are very important to protect human from radiation.

1.2.4 Abnormal Meteorological Conditions

A suitable external environment is important to maintain human health. High temperature directly affects the regulation of body temperature and metabolism and also influences other systems. Heat stroke is a typical disease caused by high temperature. Extreme high temperature appears to increase the incidences of cardiovascular and respiratory disorders [27]. Animal study confirmed that heat stress had a detrimental effect on female fertility in cows [28]. Kawasaki disease (KD) incidence is significantly affected by temperature. It has been found that KD is negatively associated with the temperature from February to May [29]. In addition, low temperature caused by cold environment, high pressure caused by diving, and other low-pressure environments also have impacts on human health. Thus, climate change threatens our living environment and also affects human health.

1.3 Environmental Harmful Chemicals

Many environmental chemical substances are environmental endocrine disruptors (EEDs) or persistent organic pollutants (POPs). The normal functions of the endocrine system of humans can be altered by EEDs. Human are exposed to EEDs due to their occupation, diet, and living environment [30]. POPs are accumulated in the food chain. POPs have the characteristics of long-distance transportation,

persistence, bioaccumulation, and high toxicity [31]. Polycyclic aromatic hydrocarbons (PAHs) and bisphenol A are typical EEDs and POPs.

1.3.1 Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are organic substances consisting more than two fused aromatic rings. The US EPA and the European Food Safety Authority (EFSA) list PAHs in the priority-pollutant lists. PAHs can act as EEDs and cause endocrine disruption on general population. PAHs are classified as known, possibly, or probably carcinogenic to humans (Group 1, 2 A, or 2B) [32].

PAHs are highly mobile and widely distributed in our daily environment. Both natural and anthropogenic processes generate airborne PAHs. The primary airborne PAHs originate from coal/biomass burning [33]. In atmosphere, low-weight PAHs ($\leq$202 g/mol, generally with 2~4 rings) tend to present in vapor phase [34]. The average concentrations of PAHs are higher in fog than in rain [35]. Furthermore, the low-weight PAHs can react with other air pollutants and form toxic compounds [34]. High-weight PAHs ($\geq$252 g/mol, generally with more than four rings) are hardly vaporized and tend to adhere to particulates. Particulate PAHs account for 5%–39.8% of total PAHs [36]. Particulate PAHs mainly deposited to oily substances such as soil [37].

In soil, benzo[b]fluoranthene, pyrene, and fluoranthene are main types of PAHs [38]. In UK, 90% of total PAHs are stored in soil [39], suggesting that soil is the largest reservoir for environmental PAHs. The distribution of PAHs in topsoil is not uniform. In China, the concentration of PAHs in urban topsoil (0.030–23.300 μg/g) is higher than that in rural areas (0.0037–6.250 μg/g) [40]. On the whole, the highest PAHs concentration (1.467 μg/g) was found in Northeast China and the lowest PAHs concentration (0.209 μg/g) was found in West China [41].

In the aquatic environment, PAHs range from 0.03 ng/L to 8,310,000 ng/L in atmosphere and waste water [42]. PAHs are preferentially absorbed onto organic matter and might be re-released into liquid phase [43]. In general, the solubility of PAHs diminishes as the molecular weight increases. High-weight PAHs such as benzo[a]pyrene and chrysene could attach to particulate matter. Thus, the contaminated sediment represents a permanent source of PAHs pollution.

The main ways for the general population to be exposed to PAHs are eating grilled food or breathing air from an open fireplace or smoke. Asian children in polluted areas were exposed to high concentrations of particulate PAHs [44]. Workers in automobile workshop, iron foundries, and aluminum plant have a high risk of exposing PAHs [45].

Many studies have shown that PAHs have genotoxicity, carcinogenicity, mutagenicity, and developmental toxicity. Exposure to PAHs is associated with dysfunction of many organs and diabetes and reproductive disorders [46]. PAHs seem to affect reproductive regulators such as follicle stimulating hormone. PAHs disrupted placental physiology, trophoblast migration, and uterus and cervix [47]. PAHs can

also potentially cause cell damage and induce cytotoxicity and pro-inflammatory responses [48]. Monooxygenase-catalyzed PAH-ligand/AhR activation could add an electrophilic group to PAHs, and generate genotoxic metabolites. Genotoxic metabolites may form adducts with DNA and finally induce DNA damage [49]. However, the toxicological effects of PAHs in most contaminated sites may be underestimated. Nitrogen, sulfur and oxygen (N/S/O)-heterocyclic PAHs, nitrated PAHs (N-PAHs), and oxygenated PAHs (oxy-PAHs) have more potential toxicity but were generally not taken into account [50].

In summary, epidemiological studies have shown that PAHs are harmful to human health. Cellular and molecular biological studies have clarified how PAHs lead to dysfunctions of cells. However, it is difficult to assess the attribution of PAHs to various diseases occurrence and development [51]. Network biology confirmed that PAHs play crucial roles in the occurrence of diseases [52]. With the evolution of new technologies, the disease mechanism induced by PAHs will be clarified.

1.3.2 Bisphenol A

The plastics industry use bisphenol A (2,2-bis [4-hydroxyphenyl] propane, BPA) as monomer in the production of polymer materials (mainly epoxy resins and polycarbonate plastics). BPA is also widely used as raw material for daily necessities [53]. BPA principally through manufacturing and wastewater treatment processes is released into environment. BPA's water phase solubility at 25 °C is 300 mg L^{-1}. At ambient temperature BPA is not volatile, but it can be absorbed into soil, sediments, and solid matrix to form binding residues. In an aerobic environment, BPA could be metabolized by different taxa of algae, fungi, bacteria, and even higher plants. In the absence of oxygen, abiotic processes mediate the conversion and mineralization of BPA [54].

Humans can be exposed to BPA through food, beverages, wastewater, air, dust, and soil [55]. Diet is the main exposure pathway for BPA and its analogues in general population [56]. Breast milk is a source of BPA exposure for infants. BPA enters milk in the milk production process and dairy products, which poses a threat to human health [57].

EEDs affect the reproductive health of male and female [58]. BPA, a poison of ovary, uterus, and prostate, may induce hypomethylation in women and young girls [59]. In placenta, BPA increases inflammation and oxidative stress and decreases cell viability [60]. BPA shows negative effects on implantation and the occurrence of polycystic ovary syndrome. BPA impairs sperm quality, but it is not clear whether it leads to poor reproductive outcomes and sexual dysfunction in men [61]. Moreover, prenatal exposure to BPA might lead to neurobehavioral disorders and adverse behavioral outcomes in children [62].

Exposure to BPA is more likely to suffer from diabetes, general/abdominal obesity, and hypertension [63]. As a metabolic disruptor, BPA causes abnormal epigenetic disorders. BPA impacts DNA methylation, histone demethylation, and

deacetylation of glucose homeostasis-related genes. BPA also impacts glucose and lipid balance, and impairs insulin signal transduction [64]. Finally, BPA induces dysfunction of energy balance control system, leading to obesity and type II diabetes [65].

Exposure to BPA can lead to bone loss. BPA reduces the level of blood calcium, inhibits the secretion of calcitonin, and blocks bone metabolism [66]. Early BPA exposure leads to childhood wheeze/asthma [67], breast cancer, and prostate cancer [68].

Long non-coding RNAs (lncRNAs) could be biomarkers or key regulators of toxicological responses. The expressed profile of lncRNAs is correlated with the toxicity of chemicals [69]. For example, BPA causes hypomethylation of DNA and reduces the expression of Igf2 and H19, one possible mechanism in which BPA induces epigenetic regulation on male fertility [70]. However, much more studies should be further performed to study the roles of lncRNAs as biomarkers or intervention targets in biological regulation.

In addition, other EEDs also threaten human health in all aspects of our lives. For example, neurotoxic pesticides including DDT and chlorpyrifos are widely used in agriculture. Heavy metals such as lead are widely applied in refining, jewelry, mining, batteries, and children's products. Lead has neurological effects and threat health in various ways [71]. Epidemiological evidences should be correlated with the molecular mechanisms obtained in in vitro experiments.

1.4 Biological Harmful Factors

The exposure of biological harmful factors links to poor outcomes like preterm delivery and stillbirth [72]. These factors can be inhaled, ingested, and contacted via ocular and dermal, then threat female health [73]. For instance, it is generally believed that abortion is related to sexually transmitted infections such as *Treponema pallidum*, *Neisseria gonorrhoeae,* and *Chlamydia trachomatis*. Sexually transmitted viruses including human papillomavirus (HPV), human herpes virus (HSV), human cytomegalovirus (HCMV), adeno-associated viruses, and human immunodeficiency virus (HIV) may also link to reproductive alternations [74]. Hence, we review researches that have explored the association between abortion and infection. The pathogens and their relation with abortion were summarized in Table 1.1.

1.4.1 Bacterial Vaginosis

Lactobacillus species bacteria account for a large proportion of the normal genital tract flora in healthy women. Bacterial vaginosis (BV) means other virulent organisms that can replace *lactobacilli* as the main organisms in the vagina. These virulent

Table 1.1 Summary of pathogens and their relation with abortion

	Bacteria	Viruses	Protozoa
Related with abortion	• Bacterial vaginosis (including *Mycoplasma hominis and Ureaplasma urealyticum*) • *Brucellosis* • *Syphilis* • *Coxiella burnetii* • *Mycoplasma genitalium* • *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • *Clostridium sordellii* (*C. perfringens*) • *Listeria monocytogenes*	• Cytomegalovirus • Dengue fever (*Flavivirus)* • HIV • Rubella • Adeno-associated virus • Bocavirus • Hepatitis C • Human papillomavirus • Herpes simplex virus 1 and 2 • Parvovirus B19 • Polyomavirus BK • Hepatitis B	• Malaria (*Plasmodium*) • *Toxoplasma gondii* • *Trypanosoma cruzi* • Schistosoma (*Schistosoma haematobium* and *Schistosoma mansoni*)

organisms have been related with miscarriage and premature delivery, including *Mycoplasma hominis,* group B streptococci, *Gardnerella vaginalis,* group B streptococci, *Staphylococcus aureus,* or *Ureaplasma urealyticum* [75]. Further cohort study includes 759 Belgian pregnant women, 8.4% participants developed BV and did not received treatment. It was found that BV was positively associated with abortion [76].

1.4.2 Virus Infection

1.4.2.1 Human Papillomavirus (HPV) Infection

HPV belongs to sexually transmitted infection. HPV infection is associated with infertility of women. In spontaneous abortion samples, the incidence of HPV infection is three times higher than that of elective abortion [77]. Cervical HPV-infected patients have fewer pregnancies [78]. HPV infection of trophoblasts corrupts the embryo's health by invading the uterine wall. HPV16 also results in trophoblast cell apoptosis, which causes placenta dysfunctions and reduces embryo ability, leading to miscarriage [79].

1.4.2.2 Human Immunodeficiency Virus (HIV) Infection

Negative pregnancy outcomes are related with maternal HIV infection. Pregnant HIV-infected women have a higher risk to spontaneous abortions and stillbirth, and their infants are more frequently born with a low birth weight [80]. HIV infection leads to chronic inflammation with the increased activated innate cells and increases granulocyte-macrophage colony stimulating factor (GM-CSF) [81, 82]. This proinflammatory shift has a link with spontaneous abortion and preterm birth.

1.4.2.3 Other Viruses Infection

In addition, other viral infections are also associated with abortion in women. For instance, syphilis is a bacterial infection, that can be transmitted sexually or via contact with blood of an infected person. Syphilis can cause stillbirth, abortion, and congenital transmission [83]. Cytomegalovirus infection leads to placental dysfunctions and spontaneous abortion [84]. Studies found that Rift Valley fever virus and miscarriage have a link in Sudanese women [85]. Influenza virus may increase the risk of premature delivery in pregnant women [86]. H1N1 influenza virus infection can cause the dysregulation of inflammatory responses, result in pre-term labor, impairment of fetal growth, and fetal mortality [87].

1.4.3 Toxoplasma Infection

The prevalence of toxoplasmosis varies around the world [88]. Alvarado et al. conducted a survey of 326 women with an abortion history, founded that 6.7% of them had been exposed to T. gondii [89]. For IgG against T. gondii, 55% of 100 women were seropositive [90]. The data suggests that there is a higher occurrence of toxoplasma infection if women with abortion.

1.5 Physiological and Psychological Factors

Female health is dependent on physical, mental, and social well-being. Social and economic status, social support, quality of marriage, childbearing age, psychological stress, and unhealthy lifestyle all affect female fertility health [73]. Besides, subfertility, amenorrhea, and poor endometrial development may relate to excessive exercise, calorie restriction, and over diet [91].

1.5.1 Adverse Childhood Experiences

Early life experiences are very important for health throughout the life course. Individual adults who have adverse childhood experiences (ACEs) tend to have more mental and physical health problems and premature mortality [92]. ACEs also potentially affect maternal health outcomes during pregnancy. It is vulnerable to prenatal, perinatal, and postnatal psychosocial health if mothers have adverse childhood experiences. ACEs are associated with mental health risks during pregnancy. These problems include higher depressive symptoms, anxiety, and suicidality [93]. ACEs-related mental and behavioral health conditions are also associated with poorer child health [94]. Women who have ACEs are more susceptible to disease development. ACEs are important hazards for poorer maternal mental and behavioral health during pregnancy [95].

1.5.2 Age

Several other factors are associated with miscarriage. Increasing woman ages reduces conception rates. If both parents are 35 years age or older, the risk of adverse pregnancy outcomes increases. The risk is increased up to 50% if the mother is 42 years old [96]. The developing embryo metabolism might be different, dependent on the age of the mother [97]. Oocytes took from elder women may have higher risk of miscarriage and epigenetic modification [98].

1.5.3 Unhealthy Lifestyle

Infertility is related with body mass index (BMI). It has a similar risk of infertility for overweight (BMI 25–29.9 kg/m^2) and underweight (BMI < 19 kg/m^2). Overweight women have less possibility to ovulate and conceive naturally, and have a higher risk of miscarriage [99]. Obesity results in mitochondrial dysfunction in oocyte, increased granulosa apoptosis, and slower growth and delayed maturation of the oocyte [100].

Regular exercise could prevent diabetes, gestational hypertensive disorders, and fetal growth impairments [101]. However, overexercise could result in negative consequences of conception. Exercise 4 h or more per week for women during the first IVF cycle had a 40% reduction in live births. The risk of implantation failure is tripled, and the risk of miscarriage also became higher.

1.5.4 Double Stress of Work and Life

Psychological stress generally influences female fertility. Positive emotions are associated with an increased chance of having a living baby. When anxiety levels get higher, the chances of stillbirth will increase [102]. Women who worked 16–32 h a week experienced a shorter time to conception than those who worked more than 32 h a week [103]. Long-term stress in women can also lead to changes in the development of the immune systems, endocrine, and immune systems. This results in emotional, social, and cognitive functions impaired, as well as the allostatic load (i.e., chronic physiological damage) increased. Mechanically, stress may affect follicular stimulating hormone and pituitary luteinizing hormone (LH) pulsatility [104]. The reduction in luteal phase progesterone, LH, and serum estradiol concentrations may have associations with higher daily stress levels [105]. Reducing stress levels by therapeutic interventions may help women to return to normal ovulation.

1.5.5 High Altitude or Chronic Hypoxia

It is a great burden to pregnancy at high altitude for both fetuses and mothers. High altitude exposure and chronic hypoxia residence increase the occurrence of neonatal morbidity and pregnancy complications. These adverse outcomes include neurobehavioral disorders in neonates, aberrant organ development, and intrauterine growth restriction [106]. Hypoxia can delay the menarche time of women in high altitude area [107, 108]. When people living at sea-level visited higher altitudes, their menstrual cycle was changed. When the high altitude native population migrates to lower altitude, the menarcheal ages did not change, because their physiology has already adapted to high altitude condition. Besides, hypoxia induces immediate release of catecholamines, including cortisol and gonadotrophins [109]. These changes ultimately delay the follicular maturation, prevent or delay the ovulation, and affect implantation and pregnancy. Hypoxia also leads to the generation of ROS [110]. Excessive ROS has deleterious effects on female reproductive system. Chronic hypoxia reduces NO-dependent vasodilation in myometrial arteries, thus raising uterine vascular resistance, lowering uterine artery blood flow, and leading to hypoxia-related fetal growth restriction [111].

1.5.6 Occupational Exposure

Occupational exposure to reproductive system diseases has important influence on workers. There are many opportunities to be exposed to chemicals and other materials that may be harmful to the reproductive health of men and women. Pesticides and heavy metals on human reproduction have many negative side effects.

Pesticides reduce sperm concentrations by as much as 60% and result in oligozoospermia [112]. Occupational exposure to organic solvents decreases implantation rates [113]. Occupational exposure leads to teratospermia and asthenospermia [114]. Painters may be exposed to lead-based paints; lead may be contacted by crafters who making stained, ceramics, and jewelry; and gardeners may be exposed to pesticides. These contacts possibly reduce fertility. In another survey of 14,614 female workers in China, the female workers who work in the electronics, railway, and medicine and health industries have serious reproductive health problems [115].

In summary, living factors and environment may have influence on fertility, but then can be modified. These factors include age, psychological stress, nutrition, alcohol consumption, cigarette smoking, occupational exposures, exercise, environmental and other behaviors. Since these factors are ultimately under our control, we can subjectively choose our living environment and lifestyle to avoid them.

1.6 Conclusion

In conclusion, physical, chemical, and biological factors act on our bodies in specific and objective ways. Body's responses to subjective factors determine the internal exposure. Combination with psychological responses, these objective and subjective factors decide the final effects on organism. It is expected that the exposure routes could be controlled or eliminated, the pathogenic mechanism of environmental harmful factors could be investigated and explained to protect human reproductive health.

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