Perfluorinated Alkyl Substances: Emerging Insights Into Health Risks

Philippe Grandjean¹ and Richard Clapp²

Abstract
Perfluorinated alkyl substances have been in use for over sixty years. These highly stable substances were at first thought to be virtually inert and of low toxicity. Toxicity information slowly emerged on perfluorooctanoic acid and perfluorooctane sulfonate. More than thirty years ago, early studies reported immunotoxicity and carcinogenicity effects. The substances were discovered in blood samples from exposed workers, then in the general population and in community water supplies near U.S. manufacturing plants. Only recently has research publication on perfluoro-octanoic acid and perfluorooctane sulfonate intensified. While the toxicology database is still far from complete, carcinogenicity and immunotoxicity now appear to be relevant risks at prevalent exposure levels. Existing drinking water limits are based on less complete evidence that was available before 2008 and may be more than 100-fold too high. As risk evaluations assume that untested effects do not require regulatory attention, the greatly underestimated health risks from perfluorooctanoic acid and perfluorooctane sulfonate illustrate the public health implications of assuming the safety of incompletely tested industrial chemicals.

Keywords
carcinogen, exposure limit, immunotoxicant, perfluorinated octanoic acid, perfluorooctane sulfonate, risk assessment

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Introduction

Poly- and perfluorinated alkyl substances (PFASs) have been in use for over sixty years. First manufactured by the 3M Company in Cottage Grove, Minnesota, perfluorooctanoic acid (PFOA) was a primary PFAS product, but perfluorooctane sulfonate (PFOS) and other PFASs were also produced. By about 2000, their global environmental dispersion became publicly known. A phase-out of commercial PFOS production by the end of 2002 was announced by 3M in 2000, and eight major U.S. producers have agreed to phase out PFOA no later than 2015. Recent reports on adverse effects suggest that the toxicity of these substances has long been underestimated.

The PFAS show high thermal, chemical, and biological inertness—properties that make them useful for certain industrial purposes, but persistence may also create an environmental hazard. The strong carbon–fluorine bond renders the PFASs highly persistent in the environment and in the human body. However, the functional group at the end of the perfluorinated carbon chain made the PFASs far from inert. By the 1970s, the physical and chemical properties were well known. Thus, many PFASs can leach through soil to reach the groundwater, while some PFASs may evaporate and disseminate via the atmosphere. Although most of them are oleophobic and do not accumulate in fatty tissues (unlike dioxins and other persistent halogenated compounds), they were later found to bioaccumulate in aquatic and marine food chains, especially PFOS. Thus, as criteria for persistent, bioaccumulative, and toxic chemicals were developed and refined in the 1990s, the PFAS physical and chemical properties should have raised warning signs.

Little was published in scientific journals on PFAS toxicology until the 1980s perhaps because compounds resistant to breakdown were erroneously considered inert. The present overview relies on recent reviews, such as the Agency for Toxic Substances and Disease Registry (ATSDR) draft toxicological profile, a draft risk assessment developed by the U.S. Environmental Protection Agency (EPA), and recent overviews. Our objective is to illustrate the problems that can result from the regulatory assumption that untested chemicals are safe. We focus on PFOS and PFOA as the substances with the best available information to review the emergence of new insight into carcinogenicity and immunotoxicity as potential critical effects. We focus our comments on these two effects because of their long history of scientific study, while recognizing that other adverse health effects have recently been documented. Although mainly relying on published information, we are aware that a major chemical company was fined by the U.S. EPA for failing to comply with the legal requirement of reporting information to the EPA about substantial risk of injury to human health or the environment due to PFAS. A chronology of important events in understanding PFAS’s health risks is provided in Table 1.
Human Exposure to Perfluorinated Compounds

The existence of PFASs in the human body was first suspected in the late 1960s when fluoride in blood samples was found to be partially bound to organic compounds of unknown structure. High concentrations in exposed workers were documented in the 1970s, and specific PFASs were later identified in serum samples from workers at production facilities in accordance with the ready absorption of the compounds in laboratory animals after oral or inhalation exposure.

Multiple sources play a role for exposures of the general population, and human exposures include precursor compounds that may be broken down into PFOA and PFOS. In the Mid-Ohio Valley of the United States, drinking water supplies were contaminated with PFOA in the 1980s from an industrial facility, and aquifers in Minnesota were also contaminated from a production facility.
Concentrations of PFOA in many water samples exceeded 1 μg/L (1000 ng/L), with concentrations of PFOS being almost as high. Other routes of human exposure are primarily from consumer product use, and degradation or improper disposal of PFAS-containing materials, including food wrapping. Analysis of serum samples from the National Health and Nutrition Examination Survey (NHANES) about year 2000 showed that PFOS and PFOA were detectable in all Americans. Median concentrations in serum were about 30 ng/mL (PFOS) and 5 ng/mL (PFOA). The average had decreased eight to ten years later to less than half for PFOS, while PFOA had changed much less. PFASs are transferred through the human placenta and via human milk. Overall, serum concentrations in children tend to be higher than in adults.

Serial analyses of serum samples from former 3M production workers after retirement suggested elimination half-lives for long-chain PFASs to be ~three years (PFOA) and ~five years (PFOS). Declines in serum-PFOA concentrations after elimination of the water contamination suggest a median elimination half-life of 2.3 years, thus confirming the persistence of PFAS in the human body.

Adverse Health Effects

The main evidence on adverse effects in humans comes from observational studies of cohorts of production workers and community studies of subjects exposed either at background levels or through contaminated drinking water. Some studies are hampered by imprecise estimates of long-term PFAS exposures and may for this reason have underestimated the effects. Follow-up studies of workers have largely shown an overall mortality deficit, thus most likely reflecting the presence of a “healthy worker” effect. New evidence has emerged, as a settlement agreement in 2005 established the C8 Health project, where data on approximately 70,000 exposed Ohio and West Virginia residents provided information on drinking water intake, measured and calculated serum-PFOA concentrations, and a variety of possible clinical outcomes. Additional evidence on associations between PFAS exposure and disease parameters in the general population comes from the National Health and Nutrition Examination survey database, which provides national data for exposures to environmental chemicals that can be linked to concurrent health information on the study participants. With regard to experimental toxicity studies, most published reports are based on the rat, which eliminates PFAS much more rapidly than humans and, therefore, is not an ideal species. Even today, chronic toxicity studies in other species are lacking, and a formal cancer bioassay has not yet been completed. In addition, insufficient attention had been paid to exposures during sensitive developmental stages.
Cancer. The rodent cancer bioassay has long served as a key component of carcinogenicity assessment.\textsuperscript{40} Evidence on cancer risks in rodents exposed to PFASs and other peroxisome proliferating substances, which promote rapid cell division, originates from the late 1970s, specifically in regard to pancreatic tumors and hepatocellular carcinomas.\textsuperscript{41–43} For Leydig cell tumors, the first evidence describing the tumor mechanisms was published in 1992,\textsuperscript{44} and further review of cancer mechanisms appeared in the late 1990s.\textsuperscript{45}

The DuPont cancer surveillance system has been monitoring cancer incidence in workers as far back as 1956,\textsuperscript{46} and an internal report showed increased leukemia incidence in employees at a PFOA production plant. As a result of the 3M findings and animal carcinogenicity studies showing increased male reproductive organ cancer, prostate cancer has been monitored in DuPont workers from 1998, although the results have apparently not been released. An updated cancer surveillance report covered the years 1956 to 2002 showed excess kidney cancer (Standardized Incidence Ratio [SIR] = 2.3, 95% confidence interval [CI]: 1.36–3.64), bladder cancer (SIR = 1.93, 95% CI: 1.14–3.06), and myeloid leukemia (SIR = 2.25, 95% CI: 1.03–4.28) in the employees, and an elevated, but not statistically significant, risk of testicular cancer (SIR = 1.46, 95% CI: 0.47–3.41).\textsuperscript{47}

Initially, the most important 3M worker study was Frank Gilliland’s thesis project on retrospective mortality of 2788 male and 749 female production workers during 1947 to 1984. Based on four cases, an excess occurrence of prostate cancer was found (Standardized Mortality Ratio [SMR] = 3.3, 95% CI: 1.02–10.6) in PFOA-exposed workers with greater than ten years of employment.\textsuperscript{34} There were subsequent analyses of cancer in 3M workers after reported further evidence of increased prostate cancer risk but not for other cancers.\textsuperscript{48,49} The key epidemiologic studies are summarized in Table 2. Incomplete follow-up, uncertainties in exposure assessment, and incomplete ascertainment of cancer mortality limit the conclusions that can be drawn from this evidence.

The EPA draft risk assessment of PFOA reviewed the published animal and human epidemiologic studies up to 2005 and concluded that the evidence was “suggestive” of a cancer risk in humans. When reviewing the same evidence a year later, the majority of an expert committee recommended that PFOA be considered “likely to be carcinogenic to humans”.\textsuperscript{50}

This conclusion is supported by the recent C8 Health Project results.\textsuperscript{51} Thus, two different epidemiological approaches\textsuperscript{52,53} support the association between PFOA exposure and both kidney and testicular cancer and suggest associations with prostate and ovarian cancer and non-Hodgkin lymphoma. The C8 Science Panel specifically listed kidney cancer and testicular cancer as having a “probable link” to C8. Although PFOA should therefore be considered a “likely” human carcinogen based on sufficient evidence in experimental animals and limited evidence in human epidemiology studies, current regulations of PFASs are based not on carcinogenicity but on developmental toxicity and changes in liver weight.
Table 2. Summary of Main Cancer Epidemiology Studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Main results</th>
<th>Comments</th>
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<tr>
<td>[34]</td>
<td>2788 male and 749 female workers in PFOA production plant</td>
<td>Male all cause SMR = 0.77 (95% CI: 0.69–0.86); Prostate cancer SMR = 3.3 (95% CI: 1.02–10.6) with 10 + years employment</td>
<td>Likely healthy worker effect; six prostate cancer deaths overall</td>
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<td>[48]</td>
<td>2083 production workers employed at least one year in Alabama PFOS fluoride production plant</td>
<td>All cause SMR = 0.63 (95% CI: 0.53–0.74); bladder cancer SMR = 16.12 (95% CI: 3.32–47.14) in those with high exposure jobs</td>
<td>Likely healthy worker effect; small number of cancer deaths, only three bladder cancer deaths</td>
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<td>[35]</td>
<td>6027 workers who worked in DuPont West Virginia plant between 1948 and 2002</td>
<td>All cause SMR = 67 (95% CI: 62–72); all cancer SMR = 74 (95% CI: 65–84); kidney SMR = 152 (95% CI: 78–265)</td>
<td>Likely healthy worker effect; comparison to other DuPont Region I workers unremarkable</td>
</tr>
<tr>
<td>[49]</td>
<td>3993 workers employed at least a year in Minnesota PFOA plant between 1947 and 1997</td>
<td>All cause SMR = 0.9 (95% CI: 0.7–1.1); prostate cancer SMR = 2.1 (95% CI: 0.4–6.1); moderate/high exposed SMR = 3.2 (95% CI: 1.0–10.3)</td>
<td>Suggestive increased mortality from bladder cancer and cerebrovascular disease</td>
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<tr>
<td>[51]</td>
<td>5791 workers exposed to PFOA in DuPont West Virginia plant</td>
<td>All cause SMR = 0.98 (95% CI: 0.92–1.04); Kidney cancer SMR = 2.66 (95% CI: 1.15–5.24) in most highly exposed quartile</td>
<td>Detailed exposure estimates, additional results with lagged analyses for mesothelioma and chronic renal disease deaths</td>
</tr>
<tr>
<td>[52]</td>
<td>Cancer cases and controls from five West Virginia and Ohio counties diagnosed 1996–2005</td>
<td>Kidney cancer OR = 2.0 (95% CI: 1.0–3.9) for very high exposure category; testis cancer OR = 2.8 (95% CI: 0.8–9.2) for very high exposure category</td>
<td>Community water contamination estimates showed suggestive associations with several types of cancer</td>
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Note. PFOA = Poly- and perfluorinated alkyl substances; PFOS = perfluorooctane sulfonate.
Mechanisms of cancer development are now being explored. Among possible mechanisms, induction of hormone-dependent cancer has been suggested in rodent studies. Developmental exposure to PFOA induces effects that are not necessarily seen in response to exposures during adulthood, as reflected by endocrine disruption effects in humans exposed to PFASs during early development.

**Immunotoxicity.** Among early toxicology studies, immunotoxicity was considered as a main effect in a rhesus monkey study sponsored by 3M, although the report was not published in the open literature. Four monkeys exposed to subacute toxicity from the ammonium PFOA salt showed atrophied thymus, diffuse atrophy of lymphoid follicles of the spleen, and other signs of immunotoxicity. Researchers at the time were well aware of the adverse effects to the “reticuloendothelial system,” and increasing attention was being paid to adverse effects on immune functions. However, these findings did not lead to further exploration of immunotoxic risks associated with PFAS exposure until decades later. Routine parameters, such as spleen microscopy and general clinical chemistry, failed to show any significant effects in non-human primates.

In recent years, immunotoxicity of poly- and perfluorinated compounds has been demonstrated in a wide variety of species and models. In the mouse, PFOA exposure caused decreased spleen and thymus weights, decreased thymocyte and splenocyte counts, decreased immunoglobulin response, and changes in specific populations of lymphocytes in the spleen and thymus. Reduced survival after influenza infection was reported in mice as an apparent effect of PFOS exposure. When injection of sheep erythrocytes was used as antigen exposure in the mouse model, the lowest observed effect level for a deficient antibody response corresponded to average serum concentrations of 92 ng/g and 666 ng/g for male and female mice, respectively. These serum concentrations are similar to or slightly exceed those prevalent in residents exposed to contaminated drinking water. Although a 3M-supported study reported no immunological effects at a high dietary PFOS exposure in the same strain of mice, another study of gestational exposure confirmed that male pups were more sensitive than females and that developmental exposure can result in functional deficits in innate and humoral immunity detectable at adulthood.

In human studies, childhood vaccination responses can be applied as feasible and clinically relevant outcomes because children have received the same antigen doses at the same ages. In the fishing community of the Faroe Islands, PFOS in maternal pregnancy serum showed a strong negative correlations with antibody concentrations in 587 children at age of five, where a doubling in exposure was associated with a difference of −41% (p = .0003) in the diphtheria antibody concentration. Poly- and perfluorinated compounds in the child’s serum at age five showed negative associations with antibody levels at age seven, and a doubling in PFOS and PFOA concentrations was associated with differences in antibody
levels between −24% and −36% (joint effect of −49%, \( p = .001 \)). For doubled concentrations at age five, PFOS and PFOA showed odds ratios between 2.4 and 4.2 for falling below a clinically protective antibody level of 0.1 IU/mL for tetanus and diphtheria at age seven. For doubled concentrations at age five, PFOS and PFOA showed odds ratios between 2.4 and 4.2 for falling below a clinically protective antibody level of 0.1 IU/mL for tetanus and diphtheria at age seven.5 Serum concentrations of both PFASs are similar to, or lower than, those reported from the U.S. population.

A study of ninety-nine Norwegian children at age three found that maternal serum PFOA concentrations were associated with decreased vaccine responses, especially toward rubella vaccine, and increased frequencies of common cold and gastroenteritis.6 In a larger study, PFOS and PFOA concentrations in serum from 1400 pregnant women from the Danish National Birth Cohort were not associated with the hospitalization rate for infectious disease (including such diagnoses as pneumonia or appendicitis) in 363 of the children up to an average age of eight.69 In adults, PFOA exposure was associated with lower serum concentrations of total IgA, IgE (females only), though not total IgG.70 In the exposed Ohio Valley population, elevated serum-PFOA concentrations were associated with reduced antibody titer rise after influenza vaccination.71

Taking into account the likely sensitivity of the various outcome measures as indication of PFAS immunotoxicity, the combined human and experimental evidence is in strong support of adverse effects on immune functions at current exposure levels.

With regard to mechanisms of immunotoxicity, PPAR receptor activation may play a role.7,14 However, experimental evidence suggests independence of PPAR\(\alpha\) for at least some of PFOA’s immunotoxic effects, as shown in PPAR\(\alpha\) knockout models.72 White blood cells from human volunteers showed effects even at the lowest in vitro PFOS concentration applied, that is, 0.1 \(\mu\)g/mL (or 100 ng/mL).73 This level is similar to concentrations seen both in affected male mice62 and in U.S. residents exposed to contaminated drinking water.21,63,64

**Implications for Prevention**

The U.S. EPA first issued a draft risk assessment of PFOA in 2005, but a final, quotable version has yet to appear. While a reference dose is not available, the EPA in 2009 published provisional drinking water health advisories of 0.4 \(\mu\)g/L (400 ng/L) for PFOA and 0.2 \(\mu\)g/L (200 ng/L) for PFOS.4 EPA used calculations of benchmark dose level (BMDL) from experimental toxicology studies and concluded at the time that “[e]pidemiological studies of exposure to PFOA and adverse health outcomes in humans are inconclusive at present.” The same toxicology data published by the end of the last decade were used for derivation of drinking water limits authorized by United States and European union countries as well as the European union Tolerable Daily Intakes for PFOA and PFOS,74 although different default assumptions and uncertainty factors were applied.
BMDL is recommended by the EPA and other regulatory agencies as a basis for calculations of safe levels of exposures.\textsuperscript{75,76} As the BMDL is not a threshold, this lower 95\% confidence limit is applied as a point of departure, and the guidelines proscribe a default tenfold uncertainty factor to be used for calculation of an exposure limit.

Table 3 lists relevant BMDL results in terms of serum concentrations. A sensitive outcome at first appeared to be the increase in liver weight; Leydig cell tumor formation was considered as a dose-dependent outcome and appeared to be less sensitive.\textsuperscript{77} The same was true for immune system toxicity that was generally evaluated by differential leukocyte counts and microscopic examination of lymphoid tissues, sometimes complemented with a cell proliferation test;\textsuperscript{78} functional tests were not conducted. In terms of serum concentrations, the BMDLs were 23\,\mu g/mL serum for PFOA and 35\,\mu g/mL for PFOS.\textsuperscript{22} Expression of the BMDL in terms of the serum concentration is particularly useful, as it facilitates interspecies comparisons by taking into account toxicokinetic differences.

Recent data on mammary gland development in mice suggest that clear effects may result from much lower developmental exposures.\textsuperscript{2} Benchmark dose calculations using a variety of models correspond to a serum concentration of 23 to 25 ng/mL,\textsuperscript{12} that is, one-thousandth of the BMDL based on liver toxicity. Benchmark calculations are not available with regard to immunotoxic

<table>
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<th>BMDL</th>
<th>Outcome parameter</th>
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<tr>
<td>PFOA</td>
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<tr>
<td>[77]</td>
<td>Adult rats with subchronic exposure</td>
<td>23,000 ng/mL</td>
<td>10% increase in liver weight</td>
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<tr>
<td>[2, 12]</td>
<td>Developmental exposure in mice</td>
<td>23–25 ng/mL</td>
<td>10% delay in mammary gland development</td>
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<td>[3]</td>
<td>Prospective human birth cohort study</td>
<td>0.3 ng/mL</td>
<td>5% decrease in serum concentration of specific antibodies</td>
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<td>PFOS</td>
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<tr>
<td>[78, 85]</td>
<td>Adult cynomolgus monkeys with subchronic exposure</td>
<td>35,000 ng/mL</td>
<td>10% change in liver function and thyroid function</td>
</tr>
<tr>
<td>[3]</td>
<td>Prospective human birth cohort study</td>
<td>1.3 ng/mL</td>
<td>5% decrease in serum concentration of specific antibodies</td>
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Note. PFOA = Poly- and perfluorinated alkyl substances; BMDL = benchmark dose level; PFOS = perfluorooctane sulfonate.
effects in mice and cannot easily be estimated from published data\textsuperscript{14} but would likely be orders of magnitude below previously calculated BMDLs.

Using the data from the recent study of immunotoxicity in children\textsuperscript{3} and assuming a linear dose-dependence of the effects, BMDLs were calculated to be approximately 1.3 ng/mL for PFOS and 0.3 ng/mL for PFOA, both in terms of the serum concentration.\textsuperscript{79} Using an uncertainty factor of ten to take into account individual susceptibility, the BMDLs would therefore result in a reference dose serum concentration of about or below 0.1 ng/mL. The experimental data require at least an additional interspecies threefold uncertainty factor for interspecies differences in toxicodynamics.\textsuperscript{76} Thus, using a total uncertainty factor of 30, the reference dose based on mammary gland development in mice would correspond to a serum-PFOA concentration of 0.8 ng/mL. As the experimental studies that the regulatory agencies have relied upon so far correspond to serum concentrations 1000-fold higher, current limits for water concentrations of PFOS and PFOA appear to be too high by at least two orders of magnitude.

For comparison, an approximate limit for drinking water can be estimated by an independent calculation. PFOA concentrations in drinking water and in the serum of residents are highly correlated,\textsuperscript{21,80} and the calculated ratio of 100-fold between the concentrations in the two media could therefore be used to calculate a concentration in drinking water that would correspond to the reference dose expressed in terms of the serum concentration. Assuming no other sources of exposure, a serum concentration of 0.1 ng/mL would correspond to a water concentration of approximately 1 ng/L, or 0.001 μg/L. Although neither of the two sets of calculations in any way represents a formal risk evaluation, it is noteworthy that current limits are generally several 100-fold higher than recent BMDL results would seem to justify.

\section*{Discussion}

The PFASs have been in use for many decades, but their otherwise useful properties unfortunately result in persistence and dissemination in the environment. The toxic properties were initially explored in the 1970s, but the toxicological database has expanded only after environmental dissemination recently became known.

In the United States, the toxic substances control act Toxic Substances Control Act (TSCA) has been in force since the late 1970s but did not require testing of substances, such as PFASs, already in commerce at the time. Perhaps the TSCA even discouraged chemicals producers from testing substances that had already received blanket approval.\textsuperscript{81} The voluntary decision in 2000 to phase-out PFOS production in the United States coincided with the first demonstration of environmental persistence and dissemination of PFASs.
Although comparatively few articles on PFASs were published in scientific journals prior to 2008, our understanding of the toxicity of these compounds has its roots in studies already carried out in the late 1970s. Thus, more than thirty years ago, possible carcinogenicity and immunotoxicity had already been demonstrated in experimental studies, and they were complemented by internal company surveillance of birth defects, mortality, and clinical findings in workers. These reports could have inspired in-depth studies but apparently did not.

As judged from available publications, the early leads were not followed up with the focused research that in today’s perspective would have seemed appropriate. Of note is also the EPA decision to fine a company for violation of the duty to report adverse effects of PFAS and the subsequent court-mandated health studies. Had the first suspicions of health risks from PFAS exposures been explored in systematic research and testing, they could perhaps have triggered earlier and more vigorous efforts to control exposures to workers and to prevent community contamination and global dissemination.

The PFASs therefore provide an example of the “untested-chemical assumption” that the lack of documentation means that no regulatory action is required. In this case, the assumption ignored preliminary evidence on plausible effects and did not inspire further exploration. The present overview suggests that these assumptions resulted in continued PFAS dissemination and exposure limits that may be more than 100-fold too high to adequately protect the general population against adverse health effects. Clearly, the absence of documentation from epidemiological studies should not be considered as a reason to conclude that adverse effects have not and will not occur. Thus, the PFASs represent an example of a failed scientific and regulatory approach and thereby also document the need for better linkage between research and risk assessment to inspire prudent chemicals control policies.

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