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Glyphosate and Paraquat in Maternal and Fetal Serums in Thai Women

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ABSTRACT

Objectives: This longitudinal study measured the glyphosate and paraquat concentrations found in maternal and umbilical cord serum in 82 pregnant women who gave birth in three provinces of Thailand. Methods: Through questionnaires and biological samples collected at childbirth, factors such as personal characteristics, family members occupation, agricultural activities, and herbicide use in agricultural work were evaluated as predictors of glyphosate and paraquat levels in the pregnant women. Statistical analysis used univariate and binary multiple logistic regression, where the outcome was the probability of exposure to paraquat or glyphosate above the limit of detection associated with occupation and household factors. Results: The glyphosate concentrations in the pregnant women's serum at childbirth (median: 17.5, range: 0.2–189.1 ng/mL) were significantly higher ($P < .007$) than those in the umbilical cord serum (median: 0.2, range: 0.2–94.9 ng/mL). However, the paraquat concentrations in the serum of the pregnant women at childbirth (83% ≤limit of detection [LOD], with maximum of 58.3 ng/mL) were similar to those in the umbilical cord serum (80% <LOD, with maximum of 47.6 ng/mL). Women with glyphosate levels >LOD in serum at childbirth were 11.9 times more likely to report work as an agriculturist ($P < .001$), 3.7 times more likely to live near agricultural areas ($P = .006$), and 5.9 times more likely to have a family member who worked in agriculture ($P < .001$). The only factors affecting paraquat exposures in pregnant women at childbirth were reporting the agricultural activity of digging in farm soil and working in the agricultural fields in the third trimester of pregnancy. Conclusions: These results show that pregnant women who work in agriculture or live in families that work in agriculture have higher exposures to the herbicides glyphosate and paraquat. The potential for long-term health impacts of these prenatal exposures to children should be evaluated, and greater regulation of the sale and use of herbicides should be considered in Thailand.

KEYWORDS
Agricultural activities; glyphosate; maternal and umbilical cord serums; paraquat; pregnant women

Introduction

In Thailand, herbicides are widely used in agriculture to increase produce yields and quality. Data from the Thai Office of Agricultural Economics reported that in 2014 herbicides constituted the largest volume of imported pesticides (106,860 tons out of 134,377 tons of pesticides).[1] They further reported that glyphosate and paraquat were the most commonly imported herbicides.[1] Glyphosate, or *N*-(phosphonomethyl)glycine, has many trade names, such as Gallup, Landmaster, Pondmaster, Ranger, Roundup, Rodeo, and Touchdown.[2] It is a nonselective, systemic, postemergence herbicide that enters the plant through the leaves and disperses throughout, inhibiting an enzyme in the shikimate pathway that is essential for the biosynthesis of aromatic amino acids in plants.[3] It has low oral acute toxicity, with a lethal dose (LD_{50}) of over 4320 mg/kg in rats.[4] People exposed to glyphosate herbicide can develop eye and dermal irritation, oral or nasal irritation, nausea, headache, or asthma if glyphosate is inhaled.[5] Glyphosate was significantly associated with an increase of non-Hodgkin's lymphoma in two case-control studies.[6] Glyphosate was also found to be a teratogen in Wistar rats, producing developmental retardation of the fetal skeleton.[7] Pregnant women who were exposed to glyphosate before conception were found to have an elevated

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risk of late abortion.[8] The US Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC) classified glyphosate as probably carcinogenic to humans (Group 2A).[9,10]

Paraquat (1,1'-Dimethyl-4,4'-bipyridinium dichlori de) is a fast-acting, nonselective herbicide with the common trade name of Gramoxone. Paraquat is banned mainly for health reasons in many countries, such as Sweden, Kuwait, Finland, Austria, Denmark, Slovenia, and Malaysia.[11] It destroys the green part of plants on contact and is often used to eliminate weeds and grasses in agricultural areas and around nonagricultural areas such as airports, power and utility stations, and commercial buildings.[12,13] Dermal contact is considered the major route of exposure, because paraquat is a nonvolatile compound. However, during spraying operations, droplets are produced that could be inhaled.[14] Paraquat is a neurotoxicant and has been associated with the development of Parkinson's disease.[15–17] Organochlorine pesticides are also suspected to play a role in Parkinson's disease.[18] Bartlett et al.[17] showed paraquat uptake in maternal and fetal brains of rhesus monkeys after the injection of ^{11}C-paraquat during pregnancy.[17]

Three agricultural areas, Amnatchareon, Nakhorn Sawan, and Karnjanaburi provinces, were selected for this study to promote research collaboration with the three campuses of Mahidol University. The main crops in these provinces are rice, sugarcane, corn, and vegetables. Most agricultural areas in Thailand use more herbicides than other types of pesticides; however, few data are available about agricultural worker exposure to these pesticides, since no screening tests exists in Thailand. However, Amnatcharoen and Nakhorn Sawan provinces have been in the top 10 provinces for pesticide poisoning cases in the country, usually associated with organophosphate and carbamate insecticides. This study is the first to measure glyphosate and paraquat concentrations in maternal and umbilical cord serums during the normal delivery of pregnant women living in three agricultural areas in Thailand.

Materials and methods

Subjects for a pilot birth cohort were recruited from pregnant women who came for prenatal care at three hospitals in Thailand: Amnatchareon Hospital in Amnatchareon Province in the northeast, Sawanpracharak Hospital in Nakhorn Sawan Province in the lower north, and Paholpolpayuhasena Hospital in Karnjanaburi Province in the west of Thailand, from May to December 2011. To be recruited, the women had to be in their 7th month of pregnancy, 19–35 years of age, not have diabetes or hypertension, and plan to give birth and have follow-up infant care at the recruiting hospital. In total, 113 pregnant women were interviewed and agreed to participate. Of these 113 women, 81 delivered babies in the participating hospitals at full term with normal labor; 19 delivered at other hospitals; 3 delivered preterm by cesarean section; 9 were full-term cesarean; and 1 full-term delivery involved significant complications and was deemed ineligible for follow-up. The 82 subjects for this study included 81 full-term normal birth neonate and 1 full-term cesarean birth neonate.

During their 7th month of pregnancy, the women were interviewed about their general health, diet, and work exposures, including agricultural work, as well as about use of pesticides at home and work. Several questionnaires, each with several sections, constituted the data collection. The questionnaire was based on the type of information collected in previous studies of agricultural workers and modified for the conditions of agriculture and types of pesticide exposures experienced in Thailand. The questionnaires were reviewed by staff at each hospital, then piloted and revised based on comments. One questionnaire collected data on demographics and the mother's general health, whereas another collected birth data. The pesticide exposure questionnaire consisted of six sections; the first section contained 12 items related to pesticide use in the home or outside the home, as well as sources of drinking water. The second section contained 9 items about the woman's work history outside the home. The third section, with 10 items, covered agricultural activities if conducted by the woman. The fourth section, with 3 items, covered agricultural activities conducted by the woman during pregnancy. The fifth section, with 6 items, asked about the agricultural work of family members. The sixth section, with 30 items, collected detailed information only from those who were agricultural workers or had family members who were agricultural workers and included detailed information on the mixing and spraying of pesticides. To summarize, the pesticide exposure questionnaire had 40 items for all subjects and 30 items only for those who were self-identified as agricultural workers or who had family members who were agricultural workers. For comparisons with agriculturists, women with other occupations were used as the control group. The nurses at the prenatal clinics in the three study hospitals were trained to recruit and interview subjects. The maternal and umbilical cord serum was collected during delivery by the delivery nurses and was frozen at −45°C until analysis. This study was reviewed and approved by the Ethics Committee on Human Rights Related to Human Experimentation, Mahidol University, and the University of Massachusetts Lowell Institutional Review Board.

Glyphosate and paraquat dichloride were obtained from Sigma-Aldrich Inc., Singapore. Acetonitrile, trimethylamine, methylene chloride, dichloromethane (all high-performance liquid chromatography [HPLC] grade), and sodium dodecyl sulfate (SDS) (gas chromatography [GC] grade) were purchased from Apex Chemical, Bangkok, Thailand. Other chemicals were of analytical grade. Analysis was performed with an HPLC system (Agilent 1200 Series) with a fluorescence detector for glyphosate and ultraviolet (UV) diode array detector for paraquat. For glyphosate, the serum sample was analyzed on Luna 5 µm C18 (150 × 4.6 mm) column (Phenomenex, Torrance, CA, USA) with guard column at 45°C. The condition of mobile phase is similar to that of Bernal et al.[19] Calibration curves were developed using hospital serum samples of nonsubjects tested for the nonpresence of glyphosate and then spiked with glyphosate to yield final concentrations of 12.5, 25, 50, 100, 150, and 200 ng/mL (n = 3 replicates). For paraquat, the serum sample was analyzed on J' sphere ODS-H80 column (150 mm × 4.6 mm ID, 4 µm) (YMC Co., Ltd., Tokyo, Japan) at 35°C using a flow rate of 1.0 mL/min mobile phase and monitored by UV absorption at 256 nm. The mobile phase consisted of 23% acetonitrile and 0.1 M orthophosphoric acid containing 300 mg/L of SDS. The mobile phase was adjusted to pH 3.0 with triethylamine, followed by filtering with 0.45 µm nylon membrane. Calibration curves were developed using hospital serum samples of nonsubjects tested for the nonpresence of paraquat and then spiked with paraquat to yield final concentrations of 7, 10, 20, 40, 60, 80, and 100 ng/mL (n = 3 replicates).

For sample preparation of glyphosate, the serum sample preparation was similar to that of Bernal et al.[19] by using 250-µL serum samples, and 30 µL of derivatized glyphosate was injected into the HPLC. The serum sample preparation of paraquat was performed following the method of Zou et al.[20] by using 250-µL serum samples, and 40 µl of the pretreated serum was injected into the HPLC. Evaluation of the detection limit was performed following the National Institute for Occupational Safety and Health method.[21] For determination of accuracy and precision, concentrations of hospital serum samples of nonsubjects tested for the nonpresence of the target pesticides were used to prepare concentrations of 50, 100, and 150 ng of glyphosate/mL and 20, 50, and 80 ng of paraquat/mL. Three replicates of each concentration were analyzed on three separate days. The calibration curves for paraquat and glyphosate were linear over the concentration ranges of 7–100 ng of paraquat/mL serum and 12.5–200 ng glyphosate/mL serum with the correlation coefficient of 0.999 and 0.998, respectively. The detection limits for the analysis of paraquat and glyphosate in serum were 0.4 and 0.4 ng/mL, respectively. Values below detection limit for both serum glyphosate and paraquat were used as detection limit divided by 2, since the data were highly skewed.[22] For the glyphosate determination method, the recovery of the method ranged from 94.33% to 99.03% with a relative standard deviation (RSD) of <3% for glyphosate concentrations of 50–150 ng/mL. The recovery of the paraquat determination method ranged from 91.78% to 95.15% with an RSD of <4% for paraquat concentrations of 20, 50, and 80 ng/mL.

The descriptive statistics were calculated using SPSS (SPSS version 18; PASW Statistics Base 18, Bangkok, Thailand). Since exposures were highly skewed due to the large percentage of values below the limit of detection (LOD), concentrations were reported as the median and range. For comparison of the paired mother and cord blood serum concentrations for glyphosate and paraquat, only pairs with both measurements above the LOD levels were used with the Wilcoxon signed-rank test. Binary logistic regression was used to evaluate whether various factors were significantly associated with the probability of having glyphosate or paraquat concentrations over the LOD. Several a priori factors were evaluated for inclusion as potentially significant covariates, such as maternal location/province and educational level of the mother, but these were found not to be significantly associated with the probability of having glyphosate or paraquat concentrations over the LOD. Thus, occupational factors were evaluated in single-factor models and reported as unadjusted odds ratios (ORs). In models examining secondary exposure factors, maternal occupation was included as a covariate in the model to control for the influence of maternal agricultural work on serum levels.

Results

The general characteristics of the 82 pregnant women who gave birth during the study are shown in Table 1. The average age was 26 years old (range: 19–34 years), with most having completed secondary school (41%), although 26% only completed primary school. Of the 82 women, 39% of the women described their occupation as agriculturist/farmer, whereas 21% listed themselves as a housewife, and about 13% were employees or owned their own business (often these are small retail stands with food or other items for sale). Of the 82 pregnant women who gave birth during the study, we were only able to collect cord blood from 75 newborns, all born full term (37–41 weeks).

Table 1. General characteristics of pregnant women ($N = 82$).

Characteristic	*n*	%
Age (years)		
19–24	35	45
25–30	28	36
31–34	15	19
Mean ± SD = 25.68 ± 4.33 (Min = 19, Max = 34)		
Education levels		
Primary school	20	26
Secondary school	32	41
High school or vocational certificate	17	22
Diploma or high vocational certificate	7	9
Bachelor degree or upper degree	2	2
Occupation		
Agriculturist	30	39
Employees	3	4
Own small business	7	9
Housewife	16	21
Government officer	1	1
Other	20	26

The percentage of maternal samples of glyphosate that were at or below the LOD was 46.3%, whereas for cord serum 50.7% were ≤LOD (Table 2). For paraquat, 83.3% of the maternal serum samples were ≤LOD, whereas 79.7% of the cord serums were ≤LOD. Comparison of the glyphosate concentrations in paired serum samples of mother and cord blood that were both >LOD ($n = 36$) found that they were significantly different ($P < .001$), with the mother's serum levels the higher of the two. The paraquat concentrations in paired serum samples of the mother and cord blood that were both >LOD ($n = 8$) were not significantly different ($P = .327$).

With regard to occupational factors predicting glyphosate exposures, the odds of having a detectable level of glyphosate in serum were 11.9 higher than the LOD among women who worked in the fields compared with those who did not. Pregnant women who worked in agricultural fields during the first, second, or third trimester of pregnancy also had significantly elevated ORs (13.5, 7.7, and 12.4, respectively) of having serum levels >LOD compared with those women who never worked in the fields. Likewise, pregnant women who reported picking crops during pregnancy had a significantly elevated OR (5.4), whereas those who reported the agricultural activity of digging in farm soil or controlling weeds during pregnancy did not have elevated ORs (Table 3).

With regard to secondary factors, pregnant women who lived near agricultural fields (<0.5 km) were significantly more likely to have serum glyphosate levels >LOD than those women living far from agricultural fields (ORs of 3.7 [crude] and 4.2 [adjusted for occupation]) (Table 4). Note that there was no significant relationship between home location and agricultural occupation ($\chi^2 = 1.01$, $P = .315$); thus, the adjusted OR does not reflect collinearity or confounding. Those pregnant women who reported a family member who was an agriculturist/farmer living in the same house were significantly more likely to have elevated serum glyphosate than those who did not (OR = 5.9); however, when adjusted for occupation, the OR became nonsignificant, because of the high correlation between having a family member who was a farmer in the same house and maternal occupation as a farmer ($\chi^2 = 17.60$, $P < .001$) (Table 4).

Table 2. Glyphosate and paraquat levels in maternal and umbilical cord serums.

Glyphosate in maternal serum (*n* = 82)		Glyphosate in umbilical cord serum (*n* = 75)	
Concentration (ng/mL)	*n* (%)	Concentration (ng/mL)	*n* (%)
≤LOD	38 (46.3)	≤LOD	38 (50.7)
1–50	25 (30.5)	1–25	22 (28.3)
51–100	10 (12.2)	26–50	9 (12.0)
101–150	6 (7.3)	51–75	4 (5.3)
151–200	3 (3.7)	76–100	2 (2.7)
(Median = 17.5) (Min = 0.2, Max = 189.1)		(Median = 0.2) (Min = 0.2, Max = 94.9)	
Paraquat in maternal serum (*n* = 78)		Paraquat in umbilical cord serum (*n* = 69)	
Concentration (ng/mL)	*n* (%)	Concentration (ng/mL)	*n* (%)
≤LOD	65 (83.3)	≤LOD	55 (79.7)
1–20	6 (7.7)	1–20	4 (5.8)
21–40	6 (7.7)	21–40	6 (8.7)
41–60	1 (1.3)	41–60	4 (5.8)
(Median = 0.2)(Min = 0.2, Max = 58.3)		(Median =0.2) (Min = 0.2, Max = 47.6)	

Table 3. The impact of occupational exposure factors on maternal serum levels using logistic regression for probability of maternal serum concentration >LOD.

	Glyphosate		Paraquat	
Risk factor	*n*	OR (95% CI)	*n*	OR (95% CI)
Occupation agriculturist	30	11.9 (3.6–39.5)*	26	1.3 (0.4–4.3)
Dig in farm soil during pregnancy	14	3.9 (1.0–15.2)	11	6.0 (1.5–24.5)*
Control weeds during pregnancy	5	1.2 (0.2–7.9)	5	1.2 (0.1–11.8)
Pick crops during pregnancy	17	5.4 (1.4–20.8)*	14	2.4 (0.6–9.3)
Work in the field during 1st trimester	19	13.5 (2.8–64.3)*	17	1.8 (0.5–6.8)
Work in the field during 2nd trimester	18	7.7 (2.0–29.8)*	16	2.2 (0.6–8.9)
Work in the field during 3rd trimester	11	12.4 (1.5–102.7)*	9	5.4 (1.2–24.4)*

*Significant at $P < .05$.

Table 4. The impact of secondary exposure factors on maternal serum levels using multiple logistic regression for probability of maternal serum concentration >LOD.

	Glyphosate			Paraquat	
Risk factor	*n*	OR (95% CI)	Adjusted OR (95% CI)**	*n*	OR (95% CI)
Live near agricultural farmland	40	3.7 (1.5–9.2)*	4.2 (1.4–12.3)*	39	0.8 (0.2–2.6)
Family members who work on a farm live in the same house	52	5.9 (2.2–16.1)*	2.8 (0.9–8.7)	47	0.7 (0.2–2.2)

*Significant at $P < .05$.
**Adjusted for maternal occupation as an agriculturist.

With regard to occupational factors predicting paraquat exposures, pregnant women who reported digging in farm soil had significantly elevated odds of having serum paraquat higher than the LOD (OR = 6.0) compared with women who did not (Table 3). Pregnant women who worked in agricultural fields during the third trimester of pregnancy also had a significantly elevated probability of having a serum paraquat >LOD than those who did not (OR = 5.4). The other risk factors examined did not have a significant impact on paraquat serum levels of the pregnant women (occupation, controlling weeds, or picking crops during pregnancy, or working in agricultural fields in the first or second trimester) (Table 3), neither did secondary exposure (home location or having a family member who was farmer living in the home) significantly elevated the risk of having a serum paraquat level >LOD (Table 4).

Discussion

The most striking finding of this study was that glyphosate concentrations over the LOD were significantly more likely to be found in the serum of pregnant women collected at childbirth if their occupation was an agriculturist/farmer or conducted various agricultural tasks or if they lived near agricultural fields sprayed with pesticides (unspecified), when compared with women who had no agricultural exposures. Acquavella et al.[23] measured glyphosate levels in urine among farmers in the United States and found that farmers who had skin contact with pesticides or did not use rubber gloves had significantly higher glyphosate concentrations in their urine.[23] Among those who did not wear rubber gloves, appreciable differences were found in the urinary glyphosate levels between those who repaired equipment during applications or spilled during mixing/loading or application. This supports the notion that dermal contact is an important route of exposure for this herbicide. Mesnage et al.[24] also reported urinary glyphosate in one of the children who lived 1.5 km away from the farm where their father sprayed glyphosate in France. However, in the US study by Acquavella et al.,[23] very few of the spouses (4%) and children (12%) who lived in a home within 1 mile of the sprayed farm fields had measureable urinary glyphosate on the day of spraying, and an even lower percentage had measureable levels on days 1–3 post application.[23] Among the applicators, 60% had measureable glyphosate on the spraying day, with a decrease to 27% on the third day post application. This raises the question of the half-life of glyphosate and how the Thai agricultural women giving birth had measureable levels of glyphosate in their serum. Although these women had regular, repeated exposures to glyphosate, even during their final trimester of pregnancy, it is unlikely that they were exposed in the field on the day prior to giving birth. It is possible that these serum levels were caused by the drift of glyphosate spray, skin contact with the pesticide contaminated family member working in the fields, contamination of the home through clothing (take home exposure), or through poor storage of pesticides near the home.[24,25] Alternatively, little is known about the metabolism and storage of pesticides during pregnancy and the impact on pesticide half-life. The median (range) glyphosate concentrations of maternal and umbilical cord serums in this current study were 17.5 (0.2–189.1) and 0.2 (0.2–94.9) ng/mL, respectively. The maternal serums of glyphosate at birth were significantly higher than those in cord blood serums. It is not known why maternal serum levels were higher than cord serum samples. At this time, only one study has looked at serum levels of pesticides in pregnant and nonpregnant Canadian women who were not agriculturists or living with a spouse who worked with pesticides.[26] They found no detectable levels of glyphosate in the pregnant women before birth or in their cord blood samples. However, 5% (2/39) of the nonpregnant women in that study had measureable glyphosate serum levels (including one with a level of 93.6 ng/mL). Potential exposures in that study were assumed to be through consumption of pesticides associated with genetically modified foods.[26] In our study, we found measureable glyphosate levels (>LOD) in 14.7% of the maternal serum samples of women who were not agriculturists/farmers by occupation. This is concerning, because Arbuckle et al.[27] studied the effect of glyphosate exposures on the risk of miscarriage among women living on farms in Ontario, Canada, and found that women who were exposed to glyphosate before conception (from 3 months before up to conception) had a higher risk of spontaneous abortion.[27]

The 6-fold higher odds of having a paraquat level in the serum >LOD among the pregnant women who reported the agricultural activity of digging in farm soil could be explained by the fact that paraquat degrades slowly under aerobic and anaerobic incubation, and that paraquat has a half-life in soil up to 20 years.[11] Therefore, the use of paraquat herbicide in their fields can result in its accumulation in the soil and exposures during nonspraying periods of agriculture. Exposure to contaminated soil through the hands (dermal exposure) could plausibly lead to higher paraquat concentrations in serum. Van Wendel De Joode et al. showed that dermal contact with paraquat was significantly related to paraquat concentration in urine.[28]

In our study, the paraquat concentration in the serum of pregnant women who were agriculturists or who participated in growing plants, picking crops, or controlling weeds was not different from those who did not engage in these activities. This may be because these women did not use paraquat as an herbicide, but the major source of paraquat exposure was through eating contaminated food and vegetables or only through soil disruption activities. Paraquat residues in foods, namely sorghums, olives, potatoes, and maize, as well as cottons and sunflowers, were found after using paraquat for crop protection.[29] In Thailand, residues of paraquat above the maximum residue limits for dry soybeans (0.1 mg/kg) were found after using paraquat as a preharvest desiccant for mung bean seed.[30] However, paraquat concentrations in many kinds of foods, including corn, rice, cucumber, soybean, fruits, vegetables, meat, milk, and egg, were found to be below the maximum residue limits recommended by Thailand Ministry of Public Health.[31]

The median (range) paraquat concentrations of maternal and umbilical cord serums in this current study were low: 0.2 (0.2–58.3) and 0.2 (0.2–47.6) ng/mL, respectively, with the majority of samples below the LOD. Maternal serum levels for paraquat were not different from the paired cord serum level for those samples >LOD. We do not have an explanation for this, since other case studies have shown paraquat concentrations can cross the placenta, and that cord blood levels were higher than those in maternal blood after a paraquat solution was ingested by a pregnant women.[32,33]

Strength and limitation

This study is the first to measure glyphosate and paraquat concentrations in maternal and cord serums from pregnant women in agricultural areas in Thailand. Future work will investigate the relationship to neonatal and infant neurobehavioral outcomes. Since the number of samples >LOD was limited, comparisons between maternal and cord blood levels may not have enough power to see significant differences for paraquat. Although the sample size was small (N = 82), significant relationships were found between occupational factors and both paraquat and glyphosate exposures. For glyphosate, secondary exposures via living near farmlands that spray pesticides was a significant predictor of glyphosate levels >LOD, even after controlling for maternal occupation as a farmer.

Conclusion

This study suggests that agricultural activities do increase maternal serum levels of both glyphosate and paraquat, even in samples taken on the day of birth. In the case of glyphosate, living near farmland where pesticides are sprayed can also significantly increase the risk of serum levels >LOD at birth. These results suggest that a study evaluating the long-term health of children exposed to herbicides during gestation should be considered. Given that herbicides make up the largest volume of pesticide imports in Thailand, and that imports continue to increase, further regulation of the sale and use of pesticides may help safeguard the health of Thai children.

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