



Published in final edited form as:

*Occup Environ Med.* 2021 October ; 78(10): 731–737. doi:10.1136/oemed-2020-107297.

## Occupational Exposure to High-Level Disinfectants and Risk of Miscarriage among Nurses

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### Abstract

**Objectives**—To examine the association of occupational exposure to high-level disinfectants (HLDs) with risk of miscarriage among nurses.

**Methods**—Our study included women who enrolled in the Nurses' Health Study 3 (NHS3) (2010–2020) and had at least one pregnancy during follow up. Occupational exposure to HLDs was self-reported at baseline. Every six months, a follow-up questionnaire was sent to participants

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**Contributors** MD, CCL, and JEC were involved in study concept and design, and critical revision for important intellectual content of the manuscript, and had a primary responsibility for final content; MD analyzed data and drafted the manuscript; and CYJ, JWR, AJG, JMB, SAH, and CMR contributed to data interpretation, manuscript editing and provided expertise in occupational health. All authors were involved in revisions of draft manuscripts and approval of the final manuscript. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

**Competing interests** None declared.

**Ethics approval** The study was approved by the Institutional Review Boards of the Brigham and Women's Hospital (Boston, Massachusetts).

asking for detailed information on pregnancies. We used a discrete-time Cox model to calculate the hazard ratios (HRs) and 95% CIs of miscarriage according to exposure to HLDs.

**Results**—Our study included 2579 nurses with a median of 5.6 years of follow-up (range: 1–9 years), and we documented 768 (19%) cases of miscarriage among 3974 pregnancies. Compared to women with no HLD exposure, the hazard ratios (HRs) of miscarriage were 1.08 (95% CI: 0.87, 1.34) for past users, and 0.84 (95% CI: 0.68, 1.04) for HLD users. Compared to women with no HLD exposure, duration, frequency, and type of HLD and use of exposure controls were not associated with risk of miscarriage. When restricting to pregnancies that occurred within 12 months of HLD use, occupational exposure to unspecified types of HLD was significantly associated with higher risk of miscarriage (HR=1.78; 95% CI: 1.08, 2.93).

**Conclusions**—We observed no associations between occupational use of HLDs and miscarriage; except when we restricted to pregnancies occurring within 12 months of assessed baseline exposure. Given the observational design and limited sample size, results should be interpreted cautiously.

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## INTRODUCTION

High-level disinfectants (HLDs) are commonly used by healthcare professionals to chemically disinfect reusable medical and dental devices. HLDs cleared by the Food and Drug Administration (FDA) include glutaraldehyde, ortho-phthalaldehyde, peracetic acid, hydrogen peroxide, hypochlorous acid, and hypochlorite.<sup>1</sup> HLDs can completely eliminate microorganisms in or on a device, except when there are high numbers of bacterial spores.<sup>2</sup> By oxidizing or interacting with amino acids, proteins, and DNA, HLDs denature proteins, disrupt the cell wall permeability, break DNA, and cause microorganism death.<sup>3</sup>

HLDs are widely used by healthcare workers. In a survey of approximately 1500 nurses, 52% of nurses reported dermal and inhalational exposure to glutaraldehyde, 20% reported regular exposure to glutaraldehyde for over 10 years, and 16% reported exposure to glutaraldehyde during pregnancy.<sup>4</sup> Given the high frequency of occupational exposure to HLDs among nurses and their mechanisms of eliminating microorganisms, the effect of HLDs on health outcomes has long been of interest to researchers. Exposure to HLDs can cause acute health effects including dermatitis, mucous membrane irritation, and skin and respiratory tract irritation.<sup>5</sup> Studies also showed that long-term exposure to HLDs may cause asthma and asthma-like symptoms.<sup>6,7</sup> Despite the reported use of HLDs among pregnant healthcare workers, studies on the reproductive effects of occupational exposure to HLDs remain limited. Two studies among the Finnish population showed that compared to non-exposed participants, occupational exposure to glutaraldehyde during pregnancy was not associated with risk of miscarriage or malformation.<sup>8,9</sup> Another study from our group showed that occupational exposure to HLDs was associated with reduced fecundity among 1739 participants of the Nurses' Health Study 3 (NHS3).<sup>10</sup> Now with additional enrollment and follow-up in the NHS3, we sought to evaluate the relation of occupational exposure to HLDs with risk of miscarriage among the incident pregnancies reported by nurses during follow-up.

## METHOD

### Study Population

NHS3 is an ongoing, internet-based cohort study of nurses in the United States and Canada that started enrolling in 2010.<sup>11</sup> To be eligible for the study, the interested participant had to be either a registered nurse, licensed practical/vocational nurse or nursing student, and born on or after January 1, 1965. Questionnaires were sent to participants to obtain their information on lifestyle, demographic, occupational, and medical characteristics at baseline. Follow-up questionnaires were sent approximately every six months to update the information. In each follow-up questionnaire, participants were asked about their pregnancy and pregnancy intention status. Female nurses who reported that they were currently pregnant on any questionnaire were invited to answer additional questions about their pregnancies between gestational weeks 20 and 25, and approximately 8 weeks after the estimated due date. Given that not all eligible nurses agreed to answer the mid-pregnancy and post-pregnancy questionnaires, all participants were also asked to update their information on all pregnancies taking place after baseline – including outcome, duration, and diagnosis of major complications for each pregnancy – in a Supplementary Reproductive Questionnaire (SRQ) introduced in 2017 and repeated every 30 months thereafter. As of January 2020, 49,515 female nurses had answered the baseline questionnaire. Among these participants, we identified 2475 women who provided information on occupational exposure to HLDs at baseline, were not pregnant at baseline, became pregnant during follow-up, and had reported pregnancy outcome in the SRQ, mid-pregnancy, and/or post-pregnancy questionnaires. These 2475 nurses provided information on 3368 pregnancies during follow-up. The Institutional Review Boards of the Brigham and Women’s Hospital in Boston, Massachusetts approved the study. Completion of the web-based questionnaires was considered implied informed consent.

### Exposure Assessment

The baseline questionnaire collected information on occupational exposure to HLDs. Nurses were asked “In your career, have you ever used disinfectants to disinfect medical instruments, devices or supplies (such as endoscopes, thermometers or other items which cannot be sterilized) by either manual or automatic methods? (This does not include the cleaning of countertops or other surfaces)”. Participants answering yes were asked how long during their career they had been using HLDs, how much total time over an average week in the past month was spent handling HLDs, and to specify types of HLDs used in the past month from the following: glutaraldehyde (e.g., Cidex®, ColdSport®, Endocide®, Glutacide®, Hospex®, Metricide®, Sporicidin®, Wavicide®), ortho-phthalaldehyde (e.g., Cidex OPA®), peracetic acid (e.g., Steris® system), and hydrogen peroxide (e.g., Accell®, Optim®). Women were also asked to report how often they used each of the following exposure controls: local exhaust ventilation (e.g., hood above immersion container, ventilated automated reprocessors), water-resistant gown or outer garment, protective gloves, eye protection (safety goggles or face shield), and respiratory protection (does not include surgical masks) with response options of “always”, “sometimes”, or “never”.

## Outcome Assessment

Pregnancy outcomes included livebirth (singletons or multiple), miscarriage (fetal death <20 gestational weeks), stillbirth (fetal death ≥20 gestational weeks), induced abortion, or tubal (ectopic) pregnancy. Options for gestational lengths were <8, 8–11, 12–19, 20–27, 28–31, 32–36, 37–39, 40–42, and 43+ weeks gestation. Miscarriage was defined as a pregnancy loss at <20 completed weeks gestation, and recurrent miscarriage was defined as miscarriage occurring ≥2 times. The validity of maternal recall of miscarriage has not been assessed in this population; however the sensitivity of reporting a loss when one actually occurred is estimated to be 75%.<sup>1213</sup> Non-cases were all pregnancies that did not end in fetal loss (live births, induced abortions, stillbirth, or tubal/ectopic pregnancies).

## Covariate Assessment

Information on potential confounding variables was assessed on the baseline questionnaire including age, education, race, body weight, height, and smoking status. We also obtained information on other occupational exposures (number of hours worked per week, shift work, and occupational exposure at baseline including ionizing radiation, anesthetic gases, and aerosolized antiviral drugs) and reproductive history variables (gravidity, parity). Body mass index (kg/m<sup>2</sup>) was calculated from self-reported weight. In a previous validation study, self-reported weight was highly correlated with weight measured by a technician among a similar group of nurses (r=0.97).<sup>14</sup> A validation study was conducted among 146 women in the National Collaborative Perinatal Project and showed that the validity of recalled maternal smoking during pregnancy was high (sensitivity=0.86, specificity=0.94).<sup>15</sup>

## Statistical Analysis

We classified women into three categories of occupational exposure to HLDs: never used HLDs, past users, and HLD users at baseline. We further classified occupational exposure to HLDs according to duration (never, < 1 year, 1–5 years, and 6+ years), frequency (never, < 1 hour per week at baseline, ≥1 hour per week at baseline) and type of use (never, baseline occupational exposure to specific HLDs, baseline occupational exposure to unspecified HLDs). We excluded past users for the classification of frequency and type of use. We used discrete-time Cox proportional hazards regression models to examine associations between occupational exposure to HLDs and risk of miscarriage. Given that some participants reported more than one pregnancy, we used a robust sandwich estimate for the standard error of the parameter estimates. We modeled gestational length as a continuous variable and assigned the mean value to each category. As to gestational length <8 and 43+ weeks, we assigned 6 and 43 weeks, respectively. We calculated person-time of non-events at the earliest of tubal pregnancy, induced abortion, or 20 gestational weeks, whichever came first. The regression models included gestational age as the time scale and adjusted for baseline age (continuous), education (licensed practical nurse or registered nurse, bachelor's degree, master's degree or doctoral degree), race/ethnicity (White, Black, Asian, Hispanic, and other races), BMI (<25 kg/m<sup>2</sup>, 25–29.9 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), and smoking status at baseline (yes or no). In sensitivity analyses, we estimated associations of occupational exposure to HLDs and duration of use with risk of first trimester miscarriage (e.g. <12 gestational weeks). We also examined associations of occupational exposure to HLDs and duration of use with

risk of miscarriage restricting the data to pregnancies that occurred within 12 to 24 months of baseline and among nurses who were older than 30 years at baseline. We conducted all analyses using SAS 9.4 (SAS Institute, Inc., Cary, N.C.) and considered a significance level of  $P < 0.05$ .

## RESULTS

Our study included 2579 nurses with a median of 5.6 years of follow-up (range: 1–9 years), and we documented 3974 pregnancies, including 1526 (38%) first pregnancies, 1685 (42%) second pregnancies, and 763 (20%) third or more pregnancies. Of the 3974 pregnancies, we ascertained 768 (19%) cases of miscarriage and 463 (12%) cases of recurrent miscarriage. At baseline, 1901 nurses self-reported never use of occupational HLDs, 262 nurses reported use of HLDs at baseline, and 416 nurses reported past use of HLDs. The mean time between baseline and first pregnancy was 3.1 years. Compared to those who never used HLDs, nurses who used HLDs at baseline were less likely to have advanced nursing degrees, more likely to have  $BMI < 25 \text{ kg/m}^2$ , and more likely to be exposed to other occupational exposures including antineoplastics, radiation, and anesthetic gas (Table 1).

Compared to women who never used HLDs at baseline, the multivariable-adjusted hazard ratios (HRs) of miscarriage were 1.08 (95% CI: 0.87, 1.34) for past users and 0.84 (95% CI: 0.68, 1.04) for HLD users at baseline (Table 2). Duration and frequency of occupational exposure to HLDs was not associated with risk of miscarriage: compared to women who never used HLDs, the HR of miscarriage was 0.87 (95% CI: 0.65, 1.16) for women who used HLDs for 6 years or more and 0.94 (95% CI: 0.64, 1.37) for women who used HLDs for 1 hour per week at baseline. Specific HLDs showed varied associations with risk of miscarriage: compared to never exposed women, the HR was 0.88 (95% CI: 0.64, 1.21) for baseline occupational exposure to glutaraldehyde, 0.40 (95% CI: 0.18, 0.88) for exposure to other specified HLDs, and 0.96 (95% CI: 0.74, 1.25) for baseline occupational exposure to unspecified HLDs. With respect to use of exposure controls, compared to never exposed women, the HR was 0.97 (95% CI: 0.71, 1.34) for baseline occupational exposure to HLDs in the absence of exposure controls and 0.90 (95% CI: 0.61, 1.32) for occupational exposure to HLDs using exposure controls (e.g., local exhaust ventilation, gloves, water resistant gown, eye protection, or respiratory protection).

When restricting to pregnancies that occurred within 12 months of returning the baseline questionnaire ( $n=653$ ), occupational exposure to HLDs at baseline was significantly associated with higher risk of miscarriage. Comparing to never exposed women, the HRs were 1.78 (95% CI: 1.08, 2.93) for participants with unspecified types of HLD use (Table 3). We did not find significant associations between occupational exposure to HLDs and risk of first trimester miscarriage ( $<12$  weeks) (Table 4). No associations of HLD use with risk of recurrent miscarriage was found (Table 5). To better control for confounding of age, we restricted the analyses to nurses who were older than 30 years at baseline or nurses who obtained a bachelor's degree in nursing, and found no significant associations (Supplemental Table 1). In sensitivity analysis, the findings were similar after additionally adjusting for other important occupational exposures, including antineoplastics, ionizing radiation, anesthetic gases. Compared to women who never used HLDs at baseline, the HRs

of miscarriage were 1.08 (95% CI: 0.86, 1.35) for past users and 0.83 (95% CI: 0.67, 1.02) for HLD users at baseline. When restricting to pregnancies that occurred within 12 months of returning the baseline questionnaire, the HR was 1.72 (95% CI: 1.04, 2.84) for HLD users at baseline in comparison to never exposed women.

## DISCUSSION

Our prospective study of 2579 female nurses who contributed 3974 pregnancies during follow-up suggests that occupational exposure to HLDs was not associated with risk of miscarriage or recurrent miscarriage. While the overall results were null, when we restricted our analysis to pregnancies that occurred within 12 months of the baseline questionnaire (to reduce the likelihood of exposure measurement error and increase the likelihood of HLD exposure near or during pregnancy), we found that occupational exposure to HLDs of unspecified type at baseline was significantly associated with risk of miscarriage.

For the past four decades, glutaraldehyde has been the primary chemical used for HLD. In one survey among 4657 healthcare workers, 59% participants reported using glutaraldehyde, followed by peracetic acid (16%) and ortho-phthalaldehyde (15%).<sup>5</sup> Similarly, in our study, glutaraldehyde was the primary HLD used. As to its effects on health, glutaraldehyde has been linked to adverse occupational health effects including dermatitis<sup>16–20</sup> and asthma.<sup>62122</sup> Previous studies have examined associations of glutaraldehyde with reproductive outcomes, and the findings tended to be null. A study in Finland showed that compared to non-exposed participants, occupational exposure to glutaraldehyde alone during pregnancy was not associated with risk of miscarriage.<sup>8</sup> Another study was also conducted in a Finnish population using a case-control design. Cases were nurses who had a miscarriage or a malformed child, and controls consisted of nurses who had a birth without these outcomes. The study showed that exposure to glutaraldehyde in the first trimester of pregnancy was not associated with risks of miscarriage or malformation.<sup>9</sup> Moreover, one recent study conducted among 1739 participants in the NHS3 showed that current glutaraldehyde use was not associated with fecundity, although a significant association was found between exposure to unknown or unspecified types of HLDs and reduced fecundity.<sup>10</sup> In our study, we found that occupational exposure to glutaraldehyde was not associated with risk of miscarriage.

Given the potential side effects of glutaraldehyde on health, three new HLDs were introduced in 1999: ortho-phthalaldehyde, peracetic acid, and hydrogen peroxide. Case reports have shown that occupational exposure to ortho-phthalaldehyde and the combination of hydrogen peroxide and peracetic acid cause work-related asthma and dermatitis.<sup>72324</sup> Hypochlorous acid and hypochlorite are additional FDA-cleared aqueous chlorine-based HLDs more commonly found in bleach. However, few studies have investigated the effects on any of these HLDs on reproductive health, and our study showed that these HLDs were not associated with a higher risk of miscarriage.

In our study, we found a positive association between exposure to unspecific types of HLD use and risk of miscarriage for pregnancies that occurred within 12 months of the baseline questionnaire. This association persisted after further adjustment for additional occupational



exposures. There are several possible explanations for this finding. First, a time window may exist that HLD use had the greatest influence on reproductive health, and within 12 months of HLD use may be the most relevant time window. HLD use has shown to have short-term effects on health by causing dermatitis, mucous membrane irritation, and skin and respiratory tract irritation.<sup>5</sup> And our study may add new evidence of the acute effect of HLD use on reproductive health. Alternatively, the analysis restricted to pregnancies within 12 months of exposure assessment may be less susceptible to misclassification of exposure status over time than the pre-specified primary analysis. Second, the nurses may be unaware of the HLD types they used and reported as unspecified types of HLD. Thus, it is highly likely that these women did not have the knowledge of safe handling of these HLDs and proper use of exposure controls, and we found that 24 out of the 40 women exposed to unspecified HLDs did not use exposure controls. Without effective exposure control, glutaraldehyde may have reproductive toxicity. One study in mice showed that a median lethal dose of potentiated acid glutaraldehyde (5ml/kg/day) reduced maternal weight during pregnancy and increased the number of stunted fetuses.<sup>25</sup> Third, it is also possible that these nurses misinterpreted the question on use of HLD and were in fact reporting exposure to other types of disinfectants such as ethylene oxide and formaldehyde. Population studies have found that exposure to ethylene oxide during pregnancy was significantly associated with higher risk of miscarriage.<sup>82627</sup> One recent meta-analysis showed that maternal formaldehyde exposure was significantly associated with higher risk of miscarriage and all reproductive outcomes combined including miscarriages, congenital malformations, birth weight, and infertility.<sup>28</sup> Last, given our limited sample size among this subgroup of participants, our findings may be due to chance.

Our study has several strengths. First, NHS3 is an open and web-based cohort, which allows new participants to enroll dynamically over time. The information collected using online questionnaires during follow up is immediately updated on daily basis, which allows us to periodically examine similar research questions in a timely manner. Second, our study collected detailed information on occupational exposure to HLDs including duration, frequency, and type of occupational exposure to HLDs, and exposure controls used when handling HLDs. This information allows us to examine whether high-risk occupational HLD exposure (e.g., long duration, high frequency and lacking exposure controls) were associated with risk of miscarriage, which greatly strengthened the scientific rigor of our study. Third, we included multiple pregnancies of the nurses into our study to improve sample size and used Cox models with robust sandwich estimates of standard errors to account for the within-person correlation between pregnancies.

Several limitations also need to be considered. First, occupational exposure to HLDs was self-reported on the baseline questionnaire and some nurses may have misreported their exposure. We were also unable to capture changes in exposure over time; however, we conducted sensitivity analyses to reduce this potential misclassification by limiting our analyses to pregnancies within 12 to 24 months of baseline. Occupational exposure to HLDs was assessed preceding the ascertainment of pregnancy, which minimized the possibility of recall bias. Second, miscarriage was self-reported by questionnaire, and measurement error was inevitable. These measurement errors were most likely to be non-differential and bias the associations towards null. Moreover, a previous study had shown that self-reported

miscarriage had a sensitivity of 74% compared to documented records.<sup>12</sup> Third, the NHS3 is composed of predominantly white nurses, which could limit the generalizability of the findings to other healthcare workers who use HLDs. Fourth, although we adjusted for various confounders, residual confounding and other sources of bias may be present, meaning that we cannot confidently establish a causal relation between occupational exposure to HLDs and miscarriage. Finally, although we had a large sample size overall, the small number of miscarriages among exposed nurses decreased the precision of our estimates.

In conclusion, in this study among 2579 nurses with 3974 pregnancies, we found that occupational exposure to HLDs in nursing may be associated with risk of miscarriage. While the overall results for use of HLDs and risk of miscarriage were null, when we restricted our analysis to pregnancies that occurred within 12 months of exposure assessment on the baseline questionnaire, we found that occupational exposure to unspecified HLDs was significantly associated with risk of miscarriage. Given the observational design and limited sample size, our findings need to be interpreted with caution.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding** This work was supported by contract 200–2013-M-54978 from CDC/NIOSH to the Harvard T. H. Chan School of Public Health. The Nurse's Health Study 3 is supported by grants R24-ES028521 and U01-HL145386–01 from the National Institutes of Health.

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### What this paper adds

#### What is already known about this subject?

The association of occupational exposure to high-level disinfectants (HLDs) with risk of miscarriage among nurses is seldom investigated.

#### What are the new findings?

We observed no associations between occupational use of HLDs and miscarriage among the whole population. When we restricted to pregnancies occurring within 12 months of assessed baseline exposure, occupational exposure to HLDs of unknown type was significantly associated with higher risk of miscarriage.

#### How might this impact on policy or clinical practice in the foreseeable future?

Our study suggests that occupational exposure to HLDs may be associated with an increased risk of miscarriage. However, given the observational design and limited sample size, our findings need to be interpreted with caution.

**Table 1.**

Baseline demographic and occupational characteristics by use of high-level disinfectants (HLDs) of nurses who became pregnant in the Nurses' Health Study 3 (n=2579)

	Use of High-Level Disinfectants?		
	Never (n=1901)	Yes, past user (n=262)	Yes, HLD user at baseline (n=416)
Age, years	29.7 (4.3)	31.5 (4.5)	29.5 (4.1)
Time between baseline and first pregnancy, years	3.2 (1.6)	3.1 (1.6)	3.1 (1.6)
Hours per Week of Nursing Work	32 (11)	33 (12)	35 (10)
Weight status, %			
BMI<25 kg/m <sup>2</sup>	64	65	58
BMI between 25–30 kg/m <sup>2</sup>	22	17	24
BMI ≥ 30 kg/m <sup>2</sup>	14	19	18
Race/ethnicity, %			
White	92	87	90
Black	2	2	2
Asian	3	3	2
Hispanic	3	6	4
Other races	1	2	3
Smoking Status, %			
Never or former smoker	82	78	81
Current smoker	18	22	19
Highest nursing degree, %			
LPN	1	2	4
RN	16	17	16
BSN	59	47	63
MS or PhD	24	34	17
Nulligravidity*, %	44	55	50
Nulliparity <sup>#</sup> , %	33	43	34
Typical work schedule, %			
Days only	53	70	51
Evenings only	5	6	4
Nights only	18	9	19
Rotating with nights	18	12	23
Rotating no nights	5	4	4
Other occupational exposures, %			
Antineoplastics	11	5	19
Radiation	2	3	10
Aerosol drugs	1	0.4	1
Anesthetic gas	7	17	15

Abbreviations: BMI, body mass index; B.S.N., bachelor of science in nursing; L.P.N., licensed practical nurse; R.N., registered nurse; M.S., master's of science; Ph.D., doctor of philosophy.

Values are means (SD) or percentages.

\* Nulligravidity is defined as never having experienced pregnancies.

# Nulliparity is defined as never having completed a pregnancy beyond 20 weeks.

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**Table 2.**

Hazard ratios (HR) of miscarriage associated with use of high-level disinfectant (HLDs) among 2579 nurses who reported being pregnant after baseline.

	Miscarriage/Total Pregnancies	Unadjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
Ever used HLDs?			
Never	563/2960	1.0 (REF)	1.0 (REF)
Yes	189/1014	0.98 (0.83, 1.15)	0.94 (0.80, 1.11)
Ever used HLDs?			
Never	563/2960	1.0 (REF)	1.0 (REF)
Yes, past user	91/410	1.17 (0.94, 1.46)	1.08 (0.87, 1.34)
Yes, HLD user at baseline	98/604	0.85 (0.68, 1.05)	0.84 (0.68, 1.04)
Duration of HLD use?			
Never used HLDs	563/2960	1.0 (REF)	1.0 (REF)
<1 year	43/199	1.13 (0.83, 1.55)	1.13 (0.84, 1.53)
1–5 years	106/622	0.90 (0.72, 1.11)	0.91 (0.74, 1.12)
6+ years	40/193	1.08 (0.80, 1.44)	0.87 (0.65, 1.16)
Frequency of HLD use in past month at baseline?			
Never used HLDs	563/2960	1.0 (REF)	1.0 (REF)
< 1 hour per week at baseline	71/459	0.81 (0.64, 1.03)	0.81 (0.64, 1.03)
1 hour per week at baseline	27/145	0.96 (0.65, 1.41)	0.94 (0.64, 1.37)
Type of HLD used at baseline?			
Never used HLDs	563/2960	1.0 (REF)	1.0 (REF)
Baseline HLD use, glutaraldehyde	43/257	0.87 (0.63, 1.19)	0.88 (0.64, 1.21)
Baseline HLD use, other types <sup>&amp;</sup>	8/99	0.42 (0.20, 0.86)	0.40 (0.18, 0.88)
Baseline HLD use, unspecified types	47/248	1.00 (0.76, 1.32)	0.96 (0.74, 1.25)
Protective equipment used			
Never used HLDs	563/2960	1.0 (REF)	1.0 (REF)
Baseline HLD use, no exposure controls	32/155	1.10 (0.79, 1.54)	0.97 (0.71, 1.34)
Baseline HLD use, with only glove protection	37/283	0.68 (0.49, 0.95)	0.72 (0.52, 1.01)
Baseline HLD use, with glove and other types of exposure controls <sup>*</sup>	29/166	0.90 (0.62, 1.32)	0.90 (0.61, 1.32)

Cox model adjusted for age (continuous), age at pregnancy (continuous), education (licensed practical nurse or registered nurse, bachelor's degree, master or doctoral degree), race (White, Black, Asian, Hispanic, and other races), BMI (<25 kg/m<sup>2</sup>, 25–<30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), and smoking status (yes, no).

<sup>&</sup>Other specific HLDs included ortho-phthaldehyde, peracetic acid, and hydrogen peroxide.

<sup>\*</sup>Other exposure controls included ventilation, water resistant gown, eye protection, and respiratory protection.



**Table 3.**

Hazard ratios of miscarriage associated with use of high-level disinfectants (HLDs) for pregnancies that occurred within 12 and 24 months of the baseline questionnaire.

	Pregnancies within 12 months of baseline questionnaire (n=653)		Pregnancies within 24 months of baseline questionnaire (n=1404)	
	Miscarriages/ Total Pregnancies	Multivariable-adjusted HR (95% CI)	Miscarriages/ Total Pregnancies	Multivariable-adjusted HR (95% CI)
Ever used HLDs?				
Never	114/468	1.0 (REF)	238/1021	1.0 (REF)
Yes, past user	19/70	1.09 (0.70, 1.71)	39/152	1.01 (0.73, 1.41)
Yes, HLD user at baseline	34/115	1.44 (0.98, 2.11)	53/231	1.04 (0.77, 1.41)
Duration of HLD use?				
Never	114/468	1.0 (REF)	238/1021	1.0 (REF)
< 1 year	8/33	1.17 (0.55, 2.49)	14/69	0.91 (0.53, 1.56)
1–5 years	33/115	1.33 (0.92, 1.94)	54/233	1.05 (0.78, 1.41)
6+ years	12/37	1.27 (0.73, 2.19)	24/81	1.08 (0.73, 1.58)
Type of HLD used at baseline?				
Never used HLDs	114/468	1.00 (REF)	238/1021	1.00 (REF)
Baseline HLD use, glutaraldehyde	16/52	1.50 (0.90, 2.48)	22/95	1.02 (0.65, 1.61)
Baseline HLD use, other types <sup>&amp;</sup>	3/21	0.68 (0.16, 2.90)	3/33	0.40 (0.09, 1.67)
Baseline HLD use, unspecified types	15/42	1.78 (1.08, 2.93)	28/103	1.29 (0.90, 1.84)
Protective equipment used				
Never used HLDs	114/468	1.00 (REF)	238/1021	1.00 (REF)
Baseline HLD use, no exposure controls	11/32	1.58 (0.88, 2.82)	19/72	1.16 (0.76, 1.77)
Baseline HLD use, with only glove protection	15/56	1.29 (0.75, 2.23)	20/103	0.89 (0.57, 1.41)
Baseline HLD use, with glove and other types of exposure controls <sup>*</sup>	8/27	1.66 (0.79, 3.50)	14/56	1.17 (0.65, 2.12)

Cox model adjusted for age (continuous), age at pregnancy (continuous), education (licensed practical nurse or registered nurse, bachelor's degree, master or doctoral degree), race (White, Black, Asian, Hispanic, and other races), BMI (<25 kg/m<sup>2</sup>, 25–30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), and smoking status (yes, no).

<sup>&</sup>Other specific HLDs included ortho-phthaldehyde, peracetic acid, and hydrogen peroxide.

<sup>\*</sup>Other exposure controls included ventilation, water resistant gown, eye protection, and respiratory protection.

**Table 4.**

Hazard ratios of early miscarriage (<12 weeks) associated with use of high-level disinfectants (HLDs) among 2579 nurses who reported being pregnant after baseline.

	Miscarriages/ Total Pregnancies	Multivariable-adjusted HR (95% CI)
Ever used HLD?		
Never	521/2960	1.0 (REF)
Yes, past user	80/410	1.02 (0.80, 1.30)
Yes, HLD user at baseline	93/604	0.87 (0.70, 1.08)
Duration of HLD use?		
Never	521/2960	1.0 (REF)
< 1 year	39/199	1.09 (0.79, 1.52)
1–5 years	101/622	0.94 (0.76, 1.17)
6+ years	33/193	0.77 (0.56, 1.07)
Type of HLD used at baseline?		
Never used HLDs	521/2960	1.00 (REF)
Baseline HLD use, glutaraldehyde	42/257	0.93 (0.68, 1.28)
Baseline HLD use, other types <sup>de</sup>	8/99	0.43 (0.19, 0.96)
Baseline HLD use, unspecified types	43/248	0.95 (0.72, 1.25)
Protective equipment used		
Never used HLDs	521/2960	1.00 (REF)
Baseline HLD use, no exposure controls	30/155	0.99 (0.70, 1.39)
Baseline HLD use, with only glove protection	36/283	0.76 (0.55, 1.06)
Baseline HLD use, with glove and other types of exposure controls*	27/166	0.90 (0.60, 1.35)

Cox model adjusted for age (continuous), age at pregnancy (continuous), education (licensed practical nurse or registered nurse, bachelor's degree, master or doctoral degree), race (White, Black, Asian, Hispanic, and other races), BMI (<25 kg/m<sup>2</sup>, 25–30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), and smoking status (yes, no).

**Table 5.**

Hazard ratios of recurrent miscarriage (occurred  $\geq 2$  times) associated with use of high-level disinfectants (HLDs) among 2579 nurses who reported being pregnant after baseline.

	Recurrent miscarriages/ Total Pregnancies	Multivariable-adjusted HR (95% CI)
Ever used HLD?		
Never	355/2960	1.0 (REF)
Yes, past user	52/410	0.99 (0.73, 1.34)
Yes, HLD user at baseline	56/604	0.79 (0.59, 1.06)
Duration of HLD use?		
Never	355/2960	1.0 (REF)
< 1 year	24/199	0.98 (0.63, 1.52)
1–5 years	65/622	0.91 (0.69, 1.20)
6+ years	19/193	0.68 (0.45, 1.05)
Type of HLD used at baseline?		
Never used HLDs	355/2960	1.00 (REF)
Baseline HLD use, glutaraldehyde	21/257	0.69 (0.42, 1.16)
Baseline HLD use, other types <sup>de</sup>	6/99	0.56 (0.23, 1.36)
Baseline HLD use, unspecified types	29/248	0.96 (0.69, 1.35)
Protective equipment used		
Never used HLDs	355/2960	1.00 (REF)
Baseline HLD use, no exposure controls	21/155	1.05 (0.71, 1.56)
Baseline HLD use, with only glove protection	18/283	0.57 (0.34, 0.94)
Baseline HLD use, with glove and other types of exposure controls*	17/166	0.89 (0.52, 1.51)

Cox model adjusted for age (continuous), age at pregnancy (continuous), education (licensed practical nurse or registered nurse, bachelor's degree, master or doctoral degree), race (White, Black, Asian, Hispanic, and other races), BMI (<25 kg/m<sup>2</sup>, 25–30 kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>), and smoking status (yes, no).