Contaminants in Vaginal Tampons: A Systematic Literature Review (SLR)

Final Report

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VERSION 5.0

Protocol Prepared for FDA CDRH

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Table of Contents

Abbreviations

Abbreviation	Term
As	Arsenic
Ba	Barium
BBzP	Butyl benzyl phthalate
BMI	Body mass index
BPA	Bisphenol A
BPB	Bisphenol B
BPF	Bisphenol F
BPAF	Bisphenol AF
BPAP	Bisphenol AP
BPP	Bisphenol P
BPS	Bisphenol S
BPZ	Bisphenol Z
BuP	Butyl-paraben
BzP	Benzyl-paraben
Ca	Calcium
Cd	Cadmium
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMC	Carboxymethyl cellulose
Co	Cobalt
Cr	Chromium
CRP	C-reactive protein
Cu	Copper
DBP	Dibutyl phthalate
DCHP	dicyclohexyl phthalate
DEP	Diethyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DIBP	di-iso-butyl phthalate
DMP	Dimethyl phthalate
DNHP	di-n-hexyl phthalate
DOP	di-n-octyl phthalate
EDCs	Endocrine-disrupting chemicals
EI	Electron ionization
EtP	Ethyl-paraben
EU	Europe
FDA	U.S Food & Drug Administration
Fe	Iron
FHP	Female hygiene product
GM	Geometric mean
GSD	Geometric standard deviation
HeP	Heptyl-paraben
HIV	Human immunodeficiency virus
Hg	Mercury

Abbreviation	Term
HPV	Human papilloma virus
IQR	Interquartile range
KQ	Key question
LOD	Limit of detection
MDL	Method detection limit
MEP	Mono-ethyl phthalate
Mn	Manganese
MnBP	Mono-n-butyl phthalate
MS	Mass spectrometer
NA	Not applicable
NHANES	National Health and Nutrition Exam Survey
NHLBI	National Health, Lung and Blood Institute
Ni	Nickel
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
OUS	Outside the United States
Pb	Lead
PICOTS	Population, Intervention, Comparison, Outcome(s), Timing and Setting
PON1A	Human serum paraoxonase 1 arylestarase
PON1P	Human serum paraoxonase 1 paraoxonase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PrP	Propyl-paraben
RCT	Randomized Controlled Trial
SD	Standard deviation
Se	selenium
SE	Standard error
SLR	Systematic Literature Review
Sr	Strontium
TBARS	Thiobarbituric acid reactive substances
TCC	Triclocarban
TSS	Toxic shock syndrome
UK	United Kingdom
US	United States
V	Vanadium
VOC	Volatile organic compounds
Zn	Zinc

Background and Objectives for Systematic Review

Background

FDA is assessing the available literature regarding potential additives, chemicals, and contaminants found in vaginal tampons. FDA requested a systematic literature review (SLR) assessing the literature for metals and to help address related questions surrounding additives, chemicals, contaminants in tampons, absorption of these substances during tampon use, and potential health impact of these substances with vaginal tampon use.

Objective

The purpose of this SLR was to summarize the evidence regarding potential contaminants in vaginal tampons and to assess vaginal tampon safety.

Key Questions (KQs)

KQ1: What is the existing published evidence on the prevalence, levels, and types of tampon-related contaminants as well as respective biomarkers potentially found in individuals using vaginal tampons?

a. If available, how do these findings differ from normal/expected values?

KQ2: What health outcomes are described in the literature associated with vaginal tampon use (except toxic shock syndrome), and did the authors report if these outcomes differ from expected rates?

KQ3: What does the literature describe in terms of laboratory testing of vaginal tampons with regard to the level of contaminants/chemicals and potential associations with tampon materials or other variables, if any?

Methods

The evidence synthesis for contaminants in tampons will follow established best methods used in SLR research.[1-3]

Study Eligibility

The table below summarizes the population, intervention, comparison, outcome(s), timing, and setting (PICOTS) inclusion and exclusion criteria that defined study eligibility.

Table 1. Eligibility of Studies

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	All people who menstruate and were eligible to participate in studies investigating vaginal tampons without age restrictions *In the case of laboratory studies, we included literature investigating samples of tampons.	Not applicable
Intervention/ Exposure	Vaginal tampons are defined as a method of absorbing menstrual flow during a period, designed to be inserted in the vagina with or without an applicator, meant to be used one time, and discarded.	Any method of collecting menstrual flow during a period that is not vaginal tampons
Comparison	No restrictions	Not applicable
Outcome(s)	1) Health outcomes (such as those related to chronic conditions: cardiovascular, endocrine, neurological, reproductive, reactions, symptoms, organ/system specific adverse events, etc.) 2) Biomarkers identified in human samples (e.g., elicited by absorption of chemicals, metals, additives, and other contaminants stratified by systemic circulating biomarkers and those found within the vaginal microenvironment) 3) Laboratory findings based on testing of tampons (not human samples) (e.g., chemicals, metals, additives, particles, contaminants, etc)	Outcomes not related to health or related only to toxic shock syndrome (TSS)
Timing	All time points	NA
Setting	US	OUS
Study Design	RCTs Cohort studies (prospective/retrospective) Case-control studies Cross-sectional studies Case series Case reports SLRs (with and without meta-analyses) Laboratory studies	Expert Opinions Commentary pieces Narrative/non-systematic review Animal studies Letters to editors/correspondence Conference abstracts
Language	Articles published in English	Non-English language articles

PICOTS	Inclusion Criteria	Exclusion Criteria
Publication dates	January 2004 to August 2024	For any included SLRs, ≥80% of the included studies in the SLR must have been published within this date range.

Abbreviations: NA: not applicable; RCT: randomized controlled trial; OUS: Outside the US; US: United States

ICA planned to present the findings stratified by subgroups of interest where data are available. The subgroups may include:

- Brand of tampons (when specified)
- Naturally derived materials vs synthetic materials (organic vs non-organic tampons)
- Biomarker presentation (systemic circulatory vs. localized tissue/microenvironment)
- Type of additive/contaminant
- Age of participants
- Race/ethnicity of participants

Literature Searches

ICA searched Embase and Pubmed/MEDLINE for studies published from January 2004 to August 2024, on August 9, 2024. The search strategies for each database and yield are presented in Appendix A.

Study Selection

ICA implemented single-screening of titles and abstracts for eligibility based on the criteria defined in h. One ICA reviewer independently screened all titles and abstracts of citations retrieved from literature searches and the full-text reports of titles and abstracts deemed potentially relevant after the abstract screening. All screening was done using DistillerSR, and EndNote was used to track citations. ICA noted the reasons for full-text exclusions according to the eligibility criteria as a benchmark.

ICA identified two relevant published SLRs for this topic.[4,5]. However, both SLRs included other interventions in addition to tampons. Therefore, ICA hand-searched the list of studies included in the SLRs to verify if our electronic search strategies captured all relevant primary studies. After assessment according to our eligibility criteria (available in Table 1), ICA verified that our search strategy captured all relevant studies previously identified by the two SLRs that are within the scope of this review.[4,5] Not all studies included in the relevant published SLRs were within the scope of this review.

Data Extraction and Management

One ICA reviewer abstracted the data from the primary studies into data extraction forms. ICA presented the data of interest in a customized evidence table designed to capture all elements relevant to the KQs. The table includes study design characteristics, population characteristics (including age, race/ethnicity, and comorbidities), descriptions of the intervention/exposure (including the brands of devices and materials, exposure details such as the number of tampons used/cycle), outcome definitions, enrolled and analyzed sample sizes, study design features, and results.

Assessment of Methodological Quality/ Strength of Evidence and Applicability

ICA narratively described the overall quality of the evidence considering the predominant study designs and the studies' funding sources.

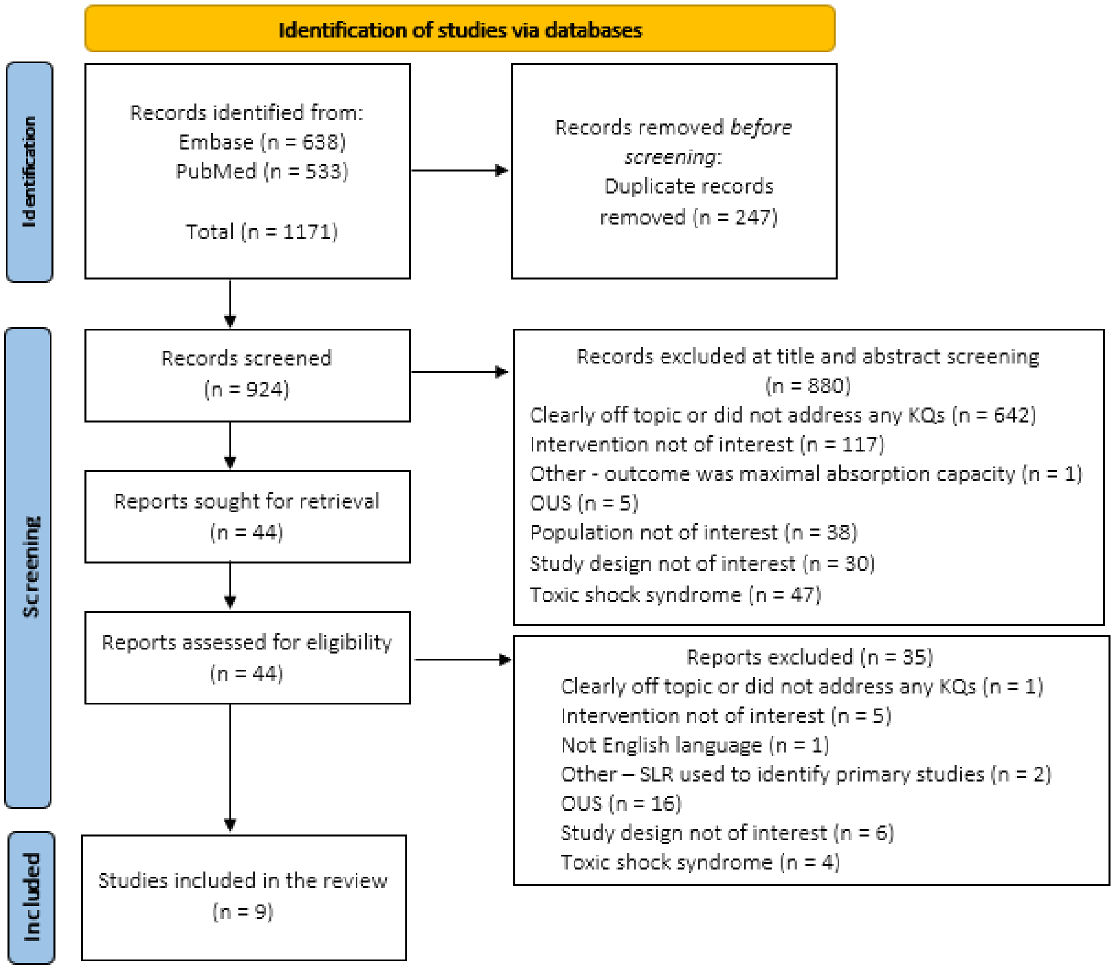
Data Synthesis

ICA summarized eligible studies narratively and used tables to consolidate the studies' characteristics and relevant outcomes. The characteristics of the study population included sample size, age, sex, race/ethnicity, and comorbidities. ICA summarized the study design, objective, funding source(s), comparators, and the duration of follow-up. ICA also captured relevant characteristics related to the intervention of interest, such as the brand of tampons and types of materials. When available, ICA captured the characteristics of the comparison(s) group. Regarding the outcomes of interest, ICA captured detailed information as available (including the type of additive/contaminant and biomarker presentation (systemic circulatory vs localized tissue/microenvironment)). This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines.[6]

Results

Electronic database searches were conducted on August 9, 2024. A total of 1,171 unique records were identified. Among them, 247 were duplicates and were excluded. After de-duplication, 924 records were screened for eligibility, and 880 were excluded because they were irrelevant to this review. Of the 44 records retrieved and screened in full-text, 35 studies were excluded for the following reasons: study conducted OUS (n = 16), study design not of interest (n = 6), intervention not of interest (n = 5), study published in another language (n = 1), study did not address any KQs (n =1), studies pertained to toxic shock syndrome (n = 4), and studies were relevant SLRs (used to identify primary studies of interest) (n = 2). Therefore, 9 studies were relevant to this review. Appendix B includes an evidence table of the study characteristics and outcomes. A list of excluded studies and the reasons for their exclusion can be found in Appendix C.

Figure 1. Literature Flow Figure



Characteristics of Included Studies

Of the nine studies included in this review, four were bench studies/laboratory experiments assessing vaginal tampons[7-10] and five were clinical studies assessing human samples.[11-15] Within the clinical studies, one had an experimental design,[11] two studies were cross-sectional,[12,14] one study was a prospective cohort,[13] and one study was a case series.[15]

Within bench/lab-based studies, the largest sample size contained 60 samples,[7] and the smallest, 22 samples.[9] One study did not report the sample size analyzed.[10] Within the clinical studies, other than the two-patient case series[15], the largest sample size included 851 women,[12] and the smallest included 25 women who provided 100 urine samples.[11]

Within the clinical studies, the mean age of participants ranged between 23[11] and 34 years.[12] One study[14] reported the proportion of women in age ranges: 29% of White, 24% of Black, and 42% of Mexican American women were between 20 – 29 years, 33% of White and 32% of Black and Mexican American women were between 30 – 39 years, while 38% of White, 34% of Black, and 26% of Mexican American women were aged between 40 – 49 years.

Among studies that reported race/ethnicity (n = 5),[11-15] White/Caucasian women composed the majority of samples (ranging between 100%[15] and 44%[11]). Black/African American women were reported in four studies,[11-14] and the proportions ranged between 24.0%[11] and 8.55%.[13] One study reported Asian American women, and the proportion was 32.0%.[11] Mexican American or other Hispanic ethnicity was reported in two studies,[12,14] and the proportions were 24.4% of Mexican Americans in Branch et al., 2015[14] 22.5% of Mexican Americans and 4.1% of other Hispanic ethnicity were reported in Ding et al., 2020.[12] Lastly, five studies reported participants' comorbidities.[11-15] These were: smoking status,[11,13] obesity (reported as body mass index (BMI)),[12-14] and body composition, also reported as BMI.[15]

Regarding device characteristics, nine studies did not provide details about the brand/manufacturer.[7-15] Three studies mentioned the number of brands analyzed but did not provide information on which brands were assessed.[7,9,10] Six studies did not report on the materials composing the tampons.[9,11-15] The level of detail in the description of materials also varied across studies. We identified the following tampon compositions: 100% cotton tampons,[7,8,10] a blend of cotton and rayon,[10] a blend of cotton, rayon, and viscose,[7] a blend of cotton, rayon, polyester, polypropylene, polyethylene,[8] a blend of cotton, rayon, polyester, polyethylene,[8] and a blend of rayon, polyester, and polyethylene,[8] and avec fiber (plastic tampon).[8] One study classified the tampons as organic and non-organic[7], and Lin et al., 2020 cited that they analyzed 17 brands (NR) and five store brands (NR). The authors stated that two samples contained organic material in their composition, and 20 were non-organic. There is no additional information reported regarding the device material for the remaining nine samples.[9] The remaining studies did not report whether the tampons were organic. Table 2 summarizes the included studies per KQ.

Table 2. Summary of Included Studies

Outcome	Number of Studies Reporting	References
KQ1: contaminants and biomarkers found in individuals	4	11-14
KQ2: health outcomes associated with vaginal tampon use	1	15
KQ3: laboratory testing of vaginal tampons	4	7-10

Key Question 1

KQ1: What is the existing published evidence on the prevalence, levels, and types of tampon-related contaminants as well as respective biomarkers potentially found in individuals using vaginal tampons?

a. If available, how do these findings differ from normal/expected values?

Four studies provided information to help answer this key question.[1,11-14]

Types of contaminants

The same author assessed volatile organic compounds (VOCs) in two studies.[11,12] In the first study, VOCs were assessed in whole blood samples of participants aged 20-49 years who completed questionnaires about feminine hygiene products in the National Health and Nutritional Examination Survey (NHANES) during 2001 - 2004.[12] Later, the same authors conducted an experimental study design, assessing VOCs in 100 urine samples of 25 women aged 20 to 49 years recruited in a University setting.[11] VOCs identified in human samples were: hexane,[11] n-Nonane,[11] hexanal,[11] nonanal,[11] benzene,[11] toluene,[11,12] p-Isopropyltoluene,[11] 2-Butanone,[11] methyl isobutyl ketone,[11] bromodichloromethane,[12] chloroform,[12] dibromochloromethane,[12] 1,4-Dichlorobenzene,[12] ethylbenzene,[12] and m-/p/xylene.[12]

One study investigated metal concentrations in blood samples of healthy, regularly menstruating women who self-reported menstrual cycle lengths (21 to 35 days) in the past six months and were enrolled in a prospective cohort study (BioCycle).[13] The metals investigated were cadmium, lead, and mercury. Lastly, one study cross-sectionally measured phthalate metabolites in urine samples of participants aged 20 – 49 years who had self-reported feminine hygiene product (FHP) use in the NHANES between 2001 and 2004 and had urinary measurements.[14] These metabolites were mono-ethyl phthalate (MEP) and mono-m-butyl phthalate (MNBP).

Levels of contaminants

In the experimental study conducted by Ding et al., 2022,[11], the authors reported the effects estimates of associations between the use of menstrual products and VOC concentrations in urine samples. The reference group for their analysis was the individuals who reported using pads or liners. Statistically significant associations between the use of tampons and VOC concentrations were reported for 2-Butanone (β: 1.58 log ng/g, 95% CI: 0.16, 3.00, p = 0.03) and methyl isobutyl ketone (β: 0.63 log ng/g, 95% CI: 0.03, 1.22, p = 0.04), meaning that women who used tampons during their period had statistically significantly higher urinary concentrations of these VOCs compared to those who used pads/liners only. The analyses were controlled for race, study visits, background VOC exposure, and the use of other FHPs. Background VOC exposure was defined as whether or not the participant was involved in one of the VOC exposure-related activities. This information was captured through questionnaires right after urine sample collection (samples were collected seven days before menstruation, three days after the first day of menstruation or at the end of heavy bleeding, seven days after the first day of menstruation or the end of heavy bleeding, and seven days after a period ends). The questions used to identify VOC exposure-related activities included paint or gasoline use (e.g., storage of items at home, recent fill-ups); source of drinking water (from a private well); use of deodorizers at home (e.g., mothballs, moth crystals, toilet deodorizers); use of natural gas for cooking or baking; spending time at a swimming pool or hot tub or a steam room; use of dry cleaning solvents or visiting a dry cleaning shop or wearing clothes that had been dry cleaned; use of fingernail polish or visit a nail salon. The analyses did not include women who used both tampons and pads/liners. The authors discussed in this study that the mean values reported for tampons and sanitary pads were consistent with other studies conducted for VOC measurements in sanitary pads.

In the NHANES cross-sectional analysis,[12] the authors reported the adjusted percent change in VOC concentrations in blood samples for women who reported using tampons in the past month. None of the VOCs analyzed were associated with the use of tampons. The models were adjusted for age at the time of interview, race/ethnicity, educational attainment, income-to-poverty ratio, BMI, pregnancy status, and menopausal status.

Singh et al., 2019[13] reported the metal concentration levels in blood samples for tampon and non-tampon users as geometric means (GM) and geometric standard deviations (GSD). Cadmium concentrations were 0.26 (1.90) vs. 0.33 (1.90) µg/L, lead concentrations were 0.85 (1.53) vs. 1.01 (1.62) µg/dL, and mercury concentrations were 1.08 (2.75) vs. 1.01 (2.47) µg/L for tampon users vs non-tampon users, respectively. None of the adjusted linear regression models to estimate the association between tampon use and metal exposure were statistically significant. Models were adjusted for age, BMI, smoking, education, race, parity, physical activity, birth control use, and marital status. For mercury, the authors further adjusted the model for fish consumption. This study did not provide evidence of normal/expected values for metal concentrations.

Branch et al., 2015[14] assessed the association between tampon use and phthalate metabolite concentrations, with non-tampon users as the reference group. Both MEP and MNBP concentrations were not associated with tampon use. The minimally adjusted model was adjusted for creatinine only, and the fully adjusted models were additionally controlled for age, race/ethnicity, BMI, and educational attainment.

Types of biomarkers

One study reported oxidative and inflammatory biomarker concentrations in blood samples.[13] The biomarkers reported were thiobarbituric acid-reactive substances (TBARS),[13] human serum paraoxonase 1 arylesterase (PON1A),[13] human serum paraoxonase 1 paraoxonase (PON1P),[13] isoprostane,[13] and C-reactive protein (CRP).[13]

Levels of biomarkers

Singh et al., 2019[13] reported biomarker concentrations assessed in blood samples as GM (GSD) among tampon and non-tampon users. TBARS concentrations were 0.85 (1.27) vs. 0.85 (1.25) nmol/mL, PON1A concentrations were 113.12 (1.24) vs. 111.39 (1.22) µmol/min/L, PON1P concentrations were 179.35 (1.84) vs. 212.90 (1.83) µmol/min/L, isoprostane concentrations were 47.80 (1.37) vs. 46.11 (1.45) pg/ml and, CRP concentrations were 1.32 (6.48) vs. 3.17 (13.60) mg/L, for users vs. non-users, respectively. Linear regression models estimated the associations between tampon use and these oxidative stress and inflammation biomarkers, where non-tampon users were the reference group. These models were conducted for different stages of menstrual periods (classified as menses, early follicular phase, menstruating week, cycle, and cycle expect menstruating week). None of the associations between tampon use and these biomarkers were statistically significant when compared to non-tampon users. The models were adjusted for age, BMI, smoking, education, race, parity, physical activity, birth control use, and marital status.

None of the studies informed about how their findings differ from normal or expected values. We did not conduct subgroup analyses, as the studies did not present their findings stratified by the characteristics of interest for this review. Additional details are summarized in Table 3; additional information about these studies can be found in Appendix B.

Table 3. Summary of Contaminants and Biomarkers Identified in Individuals

Reference Study Design	Intervention details	Sample size	Outcome N (%)
Ding et al., 2022[11] Non-randomized, repeated measures, experimental study; measurements in urine sample	Device type/brand: NR Device material: NR Exposure details: Use of tampons, pads, or panty liners, n (%): 24 (100) Use of tampons or pads during period, n (%): Tampon only: 5 (22.7) Both tampon and pad: 4 (18.2) Duration of menstrual bleeding (median, IQR): 5 (5 – 7) days Duration of heavy bleeding (median, IQR): 2 (2 – 3) days	N = 25; 100 samples collected	Effect estimates of associations between the use of menstrual products and specific gravity-adjusted VOC concentrations for tampons were reported as (β, 95% CI and p-value) with pads or liners only as the reference group: Hexane: 0.56 (-0.84, 2.00) log ng/g, p = 0.43 n-Nonane: -1.52 (-7.03, 3.98) log ng/g, p = 0.59 Hexanal: 1.28 (-0.71, 3.27) log ng/g, p = 0.21 Nonanal: -0.16 (-0.78, 0.46) log ng/g, p = 0.61 Benzene: -0.23 (-1.58, 1.12) log ng/g, p = 0.74 Toluene: -0.52 (-2.18, 1.14) log ng/g, p = 0.54 p-Isopropyltoluene: -0.06 (-1.32, 1.23) log ng/g, p = 0.93 2-Butanone: 1.58 (0.16, 3.00) log ng/g, p = 0.03 Methyl isobutyl ketone: 0.63 (0.03, 1.22) log ng/g, p = 0.04 *Analyses were controlled for race, study visits, background VOC exposure, and use of other FHPs. Women who used both tampons and pads/liners were not included in the analysis Median (IQR), [Max] VOC concentrations Hexane: 1.3 (0.5, 4.3) [491.9] ng/mL n-Nonane: 0.01 (<LOD, 0.05) [1.2] ng/mL Hexanal: 0.2 (0.1, 0.3) [0.9] ng/mL Nonanal: 0.1 (0.04, 0.2) [1.3] ng/mL Benzene:0.02 (<LOD, 0.04) [3.0] ng/mL Toluene: 0.07 (0.03, 0.2) [3.4], ng/mL p-Isopropyltoluene: 0.02 (<LOD, 0.06) [0.2] 2-Butanone: 2.0 (0.9, 4.2) [37.2] ng/mL Methyl isobutyl ketone: 0.1 (0.07, 0.3) [1.8] ng/mL
Ding et al., 2020[12]	Device type/brand: NR Device material: NR	Total sample: 2,432; 851 (35%) reported tampon use	Adjusted % change (95% CI) in VOC concentrations in tampons in the past month compared to never users:

Reference Study Design	Intervention details	Sample size	Outcome N (%)
Cross-sectional analysis of NHANES data	Exposure details (use of tampon in the past month), %: White: 53% Black: 36% Mexican American: 25% Other Hispanic: 29% Other race/ethnicity: 33%		Bromodichloromethane, (n = 756): -6.8 (-26.0, 17.5) Chloroform, (n = 704): -9.5 (-28.5, 14.7) Dibromochloromethane, (n = 763): -6.0 (-25.8, 19.0) 1,4-Dichlorobenzene, (n = 758): -16.9 (-333, 3.5) Ethylbenzene, (n = 784): 5.7 (-7.2, 20.4) Toluene, (n = 822): 5.4 (-13.8, 29.0) m-/p-xylene, (n = 827): 9.8 (-2.4, 23.6) *models were adjusted for age at interview, race/ethnicity, educational attainment, income-to-poverty ratio, BMI, pregnancy status, and menopausal status
Singh et al., 2019[13] Prospective cohort (BioCycle study)	Device type/brand: NR Device material: NR Exposure details: Median (IQR): 4 (3 – 5) tampons/cycle	Tampon users: 158 Non-tampon users: 97	Metal concentrations [µg/L in blood], as GM (GSD) Cadmium: users: 0.26 (1.90), non-users: 0.33 (1.90) Mercury users: 1.08 (2.75), non-users: 1.01 (2.47) Metal concentrations [µg/dL], as GM (GSD) Lead users: 0.85 (1.53), non-users: 1.01 (1.62) Biomarker concentrations, as GM (GSD) TBARS [nmol/mL]: 0.85 (1.27), non-users: 0.85 (1.25) PON1A [µmol/min/L]: 113.12 (1.24), non-users: 111.39 (1.22) PON1P [µmol/min/L]: 179.35 (1.84), non-users: 212.90 (1.83) Isoprostane [pg/ml]: 47.80 (1.37), non-users: 46.11 (1.45) CRP [mg/L]: 1.32 (6.48), non-users: 3.17 (13.60) Linear regression models to estimate the association between tampon use and metal exposure, oxidative stress, and inflammation biomarkers, expressed as (exp(β) of the ratio of the expected GM for those who used tampons over those who did not, 95% CI Cadmium (µg/L): 0.94 (0.78, 1.14) Lead (µg/dL): 0.91 (0.80, 1.05) Mercury (µg/L): 1.24 (0.92, 1.67) TBARS (nmol/mL) Menses: 0.99 (0.94, 1.05) Early-follicular phase: 1.01 (0.95, 1.06) Menstruating week: 1.00 (0.95, 1.05) Cycle: 1.00 (0.95, 1.05) Cycle except menstruating week: 1.04 (0.99, 1.08) PON1A (µmol/min/L) Menses: 1.03 (0.99, 1.08) Early-follicular phase: 1.00 (0.96, 1.04) Menstruating week: 1.00 (0.96, 1.04) Cycle: 1.00 (0.97, 1.03) Cycle except menstruating week: 1.00 (0.97, 1.03) PON1P (µmol/min/L)

Reference Study Design	Intervention details	Sample size	Outcome N (%)
			Menses: 1.02 (0.91, 1.15) Early-follicular phase: 1.02 (0.91, 1.14) Menstruating week: 1.01 (0.91, 1.12) Cycle: 0.95 (0.89, 1.02) Cycle except menstruating week: 0.96 (0.90, 1.03) Isoprostane (pg/ml) Menses: 1.04 (0.95, 1.14) Early-follicular phase: 1.05 (0.96, 1.15) Menstruating week: 1.05 (0.96, 1.14) Cycle: 1.03 (0.96, 1.11) Cycle except menstruating week: 1.02 (0.95, 1.09) CRP (mg/L) Menses: 1.06 (0.85, 1.32) Early-follicular phase: 0.93 (0.75, 1.16) Menstruating week: 0.98 (0.80, 1.20) Cycle: 0.94 (0.76, 1.15) Cycle except menstruating week: 0.90 (0.73, 1.11) *models were adjusted for age, BMI, smoking, education, race, parity, physical activity, birth control use, and marital status. For mercury, the model was additionally adjusted for fish consumption
Branch et al., 2015[14] Cross-sectional study	Device type/brand: NR Device material: NR Exposure details (tampon use in the past month, %): White: 55 Black: 31 Mexican American: 22	Total sample: 739 White: 396 Black: 163 Mexican American: 180	Associations of tampon use and phthalate metabolite concentrations (ng/ml), expressed as % change (95% CI) MEP Unadjusted (n = 739): -6.4 (-24.9, 16.6) Adjusted (n = 731): 6.1 (-16.0, 35.5) MnBP Unadjusted (n = 739): 2.4 (-11.8, 18.9) Adjusted (n = 731): 4.1 (-11.0, 21.9) *The reference group is non-users of tampons. *MEP and MnBP were natural log-transformed *both models adjusted for urinary creatinine. Adjusted models additionally controlled for age, race/ethnicity, BMI, and educational attainment

Abbreviations: BMI: body mass index; CI: confidence interval; CMC: caboxymethyl cellulose; CRP: c-reactive protein; FHP: female hygiene product; GM: geometric mean; GSD: geometric standard deviation; IQR: interquartile range; MEP: mono-ethyl phthalate; MNBP: mono-n-butyl phthalate; NR: not reported; NS: not significant; PON1A: human serum paraoxonase 1 arylestarase; PON1P: human serum paraoxonase 1 paraoxonase; SD: standard deviation; SE: standard error; TBARS: thiobarbituric acid reactive substances; VOC: volatile organic compounds

Key Question 2

KQ2: What health outcomes are described in the literature associated with vaginal tampon use (except toxic shock syndrome), and do the authors report if these outcomes differ from expected rates?

One study provided evidence for this KQ.[15] Gaudiani et al., 2011[15] reported a case series of two women who experienced vaginal ulcerations due to daily tampon use over an extended time period. Both women had a severe case of anorexia nervosa and were below their ideal body weight. These patients had complaints of vaginal bleeding due to endometrial atrophy and used tampons daily to manage the vaginal bleeding. The daily use of tampons led to vaginal ulceration and persistent vaginal bleeding. The cessation of daily tampons and the initiation of conjugated estrogen vaginal cream resolved the vaginal bleeding.

Given that the only study reporting adverse events was a case series, we could not assess how these outcomes differed from expected rates. Additional details pertaining to this KQ are summarized in Table 4 and in Appendix B.

Table 4. Summary of Health Outcomes Associated with Vaginal Tampon Use

Reference Study Design	Intervention details	Sample size	Outcome N (%)
Gaudiani et al., 2011[15] Case series	Device type/brand: NR Device material: NR Exposure details: daily tampon use	2	Vaginal ulcerations: 2 In both cases, outpatient providers had presumed that months of daily vaginal bleeding were due to endometrial atrophy, but bleeding persisted despite varying doses of systemic hormonal therapies. Ultimately, the history of daily tampon use was elicited during both patients' inpatient hospitalizations, and a speculum and pelvic examination revealed traumatic vaginal ulcerations in the setting of the atrophic vaginal mucosa. Cessation of tampon use and initiation of conjugated estrogen vaginal cream resolved the vaginal bleeding.

Abbreviations: NR: not reported

Key Question 3

KQ3: What does the literature describe in terms of laboratory testing of vaginal tampons with regard to the level of contaminants/chemicals and potential associations with tampon materials or other variables, if any?

We identified four studies that conducted experiments with tampon materials.[7-10]

Contaminants and chemicals identified

Studies pertaining to this KQ investigated a variety of contaminants and chemicals in tampon samples. We identified studies investigating metals,[7] phthalates,[8] parabens,[8] bisphenols,[8] triclocarban (TCC),[8] VOCs,[9] and dioxins.[10]

Methods used to identify contaminants and tampons

In Shearston et al., 2024,[7] the researchers acid-digested tampon samples (0.2 – 0.3 g of a tampon) in a microwave digestion system (MARS 6, CEM Corporation, USA). Each sample included portions of the inner absorbent core and, when present, the non-woven outer covering from random areas of the tampon. The non-mercury metals in the tampon digest were measured using a PerkinElmer NexION 350S Inductively Coupled Plasma Mass Spectrometry with dynamic reaction cell (ICP-DRC-MS). To measure mercury, the authors used an Agilent 8900 ICP-MS equipped with an Agilent SPS 4 autosampler system.

Gao et al., 2020[8] phthalates in tampons were measured using a gas chromatography (Agilent Technologies 7890A) system coupled with a mass spectrometer (Agilent Technologies, 5975C). Parabens, bisphenols, and TCC were measured using modular high-performance liquid chromatography (Shimadzu Prominence, Shimadzu Corporation, Kyoto, Japan) coupled with API 3200 electrospray triple quadrupole mass spectrometer (ESI-MS; Applied Systems, Foster City, CA).

Lin et al., 2020[9] measured VOCs using purge and trap methods. The researchers measured the weight of a whole tampon, placed it in a 40 ml vial, added 5 ml of LC-MS grade deionized water (MilliporeSigma, Burlington, Massachusetts, USA), capped the vial, heated it to 40C for 10 minutes. The samples were maintained at 40C and purged with 400 ml of N_2 for 20 minutes to sample VOCs. Then each absorbent tube was injected with internal standards (fluorobenzene, *p*-bromo-fluorobenzene, and 1,2-dichlorobenzene-d_4) and analyzed using a short-path automated thermal desorption system (ATD, Scientific Instrument Services, Inc. Ringoes, New Jersey, USA) coupled to a gas chromatography-mass spectrometer (GC-MS, model 6890/5973, Agilent Technologies, Santa Clara, CA) equipped with a cryotrap/focuser (1140C to focus, 250C to inject). The chromatographic separation was performed using a DB-VRX capillary column (60 m x 0.22 mm, 1.4 µm film thickness) with helium as the carrier gas and a temperature program that started at 45C (10 min hold), ramped at 8C/min to 140C (10 min hold), and finally ramped at 30C/min to 225C (hold for 13 min). The mass spectrometer (MS) detector, transfer line, electron ionization (EI) ion source, and quadrupole temperatures were set at 250, 300, 230, and 150C, respectively. The MS was operated in full scan mode from 27 – 270C atomic mass unit. Peak areas were extracted by a ChemStation macro program (G1701BA Version B.01.00, Agilent, Santa Clara, USA), adjusted for internal standards and transferred to a spreadsheet. The sum of target VOCs was designated as total target VOCs. The authors investigated the larger non-target peaks in a subset of products using the MS fragmentation pattern and elution time. They provided a tentative identification of chemicals in their match quality values in the NIST 98 spectral library exceeded 90%. Their masses were not quantified. The authors analyzed for 98 target VOCs.

Archer et al., 2005[10] investigated dioxins and furan levels. After removing the outer wrappers and applicators, they prepared their samples by cutting them into strips. All samples were spiked with 15 of the 17 2,3,7,8-chlorine-containing C13 congeners (ranging from 10 to 20 pg per extract) for direct isotope dilution analyses. All tampons were Soxhlet extracted during an 18-24h period using a 1:1 hexane: methylene chloride solvent mixture. Each extract was subjected to a cleanup process measured using multilayered silica gel and alumina columns. Some extracts needed additional carbon cleanup procedures as well. All sample extracts were analyzed via gas chromatography/high-resolution mass spectrometry using a Micromass AutoSpec Ultima high-resolution mass spectrometer at 10,000 mass resolution. As data were confirmed and quantified using direct isotope dilution, only the 17, 2,3,7,8-chlorine-containing dioxin and furan concentrations were calculated from these analyses.

Potential associations with tampon materials or other variables

Shearston et al., 2024[7] reported metal(loid) content in combined tampon samples (containing portions of the inner absorbent core and, if present, the non-woven outer covering from random areas of the tampons) after microwave-acid digestion (a total of 60 samples, representing 14 brands without brand/product name specification). Metals detected above the method detection limit (MDL) were arsenic, barium, calcium, cadmium, cobalt, copper, iron, manganese, nickel, lead, selenium, strontium, vanadium, and zinc. Chromium and mercury had values below the MDL when the samples were analyzed as a group (60 samples), but the authors report that in (5/60), 8.3% of the samples detected mercury, and (6/60), 10% of the samples detected chromium above the MDL.

One study investigated the concentrations of phthalates in tampons and in other FHPs.[8] In this study, different materials/blends of tampon compositions were analyzed separately, and the authors reported the mean value of all 12 brands/samples as a "tampon group". Moreover, the brands were not reported. From the nine phthalates investigated, the authors were able to detect mean concentrations of the following ones: dimethyl phthalate (DMP) (412 ng/g), diethyl phthalate (DEP) (192 ng/g), di-iso-butyl phthalate (DIBP) (128 ng/g), dibutyl phthalate (DBP) (378 ng/g), and Di(2-ethylhexyl) phthalate (DEHP) (744 ng/g). Butyl benzyl phthalate (BBzP) was identified but the concentrations were below the limit of detection. Dicyclohexyl phthalate (DCHP), di-n-hexyl phthalate (DNHP), and di-n-octyl phthalate (DOP) were not detected.

Parabens were investigated by Gao et al., 2020[8]. The authors reported mean concentrations of methyl-paraben (MeP) (18.2 ng/g), ethyl-paraben (EtP) (27.6 ng/g), propyl-paraben (PrP) (2.01 ng/g), butyl-paraben (BuP) (0.06 ng/g). Concentrations of benzyl-paraben (BzP) and heptyl-paraben (HeP) were below the detection limit.

Gao et al., 2020[8] measured the concentrations of bisphenols in tampons. The authors reported concentrations for bisphenol F (BPF) (5.60 ng/g), bisphenol A (BPA) (0.87 ng/g), bisphenol S (BPS) (0.02 ng/g). Bisphenol P (BPP) and bisphenol Z (BPZ) were below the detection limit. The concentrations of bisphenol AP (BPAP), bisphenol AF (BPAF), and bisphenol B (BPB) were not detected. This study also reported on the concentration of triclocarban (TCC) (0.05 ng/g).[8]

The dermal detection doses of phthalates, parabens, bisphenols, and TCC were also presented in Gao et al., 2020.[8] The individual values are presented in Table 5.

Lin et al., 2020[9] analyzed the composition of VOCs in tampons and other FHPs. The authors reported including tampons of major brands and store brands, but they did not identify or list the actual brands of tampons or store brands within their publications. The authors reported concentrations of the following VOC classes identified in tampons: aldehydes, alkanes, aromatics, halohydrocarbons, terpenes, ketones, esters, and other VOCs.

One study assessed the concentration of dioxins in seven brands of tampons (brands NR) with varying compositions of rayon/cotton (details NR).[10] They reported that most detected quantities of dioxins were at or near the detection limit values.

Organic vs non-organic subgroup

Two studies presented stratified analyses by type of material (organic vs. non-organic).[7,9] In Shearston et al., 2024[7] the organic tampons were composed of 100% cotton, while non-organic ones were composed of rayon or a mixture of cotton, rayon, and viscose. The median metal concentrations of barium, cadmium, cobalt, lead, and zinc were lower in organic tampons when compared to non-organic. The median metal concentrations of arsenic, calcium, chromium, iron, manganese, strontium, and vanadium were higher in organic tampons when compared to non-organic. Lin et al., 2020[9] reported the mean concentrations of VOCs for organic and non-organic tampons, and the definition of organic as tampons that were labeled as "organic" or "all-natural" (the composition of tampons was not reported). Organic tampons had statistically significantly higher concentrations of n-Decane ($p = 0.009$) than non-organic tampons. The differences in concentrations of halohrydrocarbon, terpenes, butanal, octanal, o-isopropyl toluene, limonene, and ethylbenzene between organic and non-organic tampons were not statistically significant, and the values were not reported. This study calculated the hazard ratio for non-cancer health effects of tampons and other FHPs. The hazard ratio for tampons was below 0.1, and the authors indicated a negligible potential for non-cancer health effects. The hazard ratio calculated for cancer risk fell below 10^{-6}, a commonly used and protective reference level.

Other reported subgroups

Two studies reported their findings stratified as store-brand vs name-brand.[7,9] However, the name of the brands was not disclosed. We also identified subgroup analysis for metal concentrations by place of purchase (Europe/UK vs US) and by plastic vs. no or cardboard applicator.[7]

Additional details pertaining to this KQ are summarized in Table 5, and additional information on the included studies can be found in Appendix B.

Table 5. Summary of Outcomes Derived from Laboratory Testing in Tampons

Reference	Intervention details	Sample size	Outcome N (%)
Shearston et al., 2024[7]	**Device type/brand:** 14 brands analyzed; names NR **Device material:** 16 non-organic (rayon or mixture of cotton, rayon, and viscose); 15 organic (100% cotton); 1 NR **Method of analysis:** Non-mercury metals in the tampon digest was assessed using a PerkinElmer NexION 350S Inductively Coupled Plasma Mass Spectrometry with dynamic reaction cell (ICP-DRC-MS). For Hg, Agilent 8900 ICP-MS equipped with an Agilent SPS 4 autosampler system.	n = 60 samples (representing 30 unique tampons and 24 unique brand-product line-absorbency combinations)	Metal concentrations (ng/g) in tampon samples, reported as GM (GSD) [As]: 2.56 (2.02) [Ba]: 1,100 (4.60) [Ca]: 39,000 (2.17) [Cd]: 6.74 (2.67) [Co]: 19.8 (2.17) [Cr]: < MDL (NA) [Cu]: 78.9 (2.00) [Fe]: 3,099 (2.68) [Hg]: < MDL (NA) [Mn]: 296 (2.38) [Ni]: 80.1 (1.44) [Pb]: 120 (2.24) [Se]: 28.5 (6.04) [Sr]: 190 (2.74) [V]: 6.37 (2.71) [Zn]: 52,000 (1.93) Effect estimates and 95% CIs from metal-specific mixed median quantile regression models evaluating the relationship between select tampon characteristics and metal concentrations (ng/g): Organic (n = 14) vs non-organic* (n = 44) [As]: 4.53 (2.32, 6.75) [Ba]: -1,346.22 (-2,028.06, -664.37) [Ca]: 78,980.41 (55,0.16.32, 102,944.5) [Cd]: -9.93 (-13.62, -6.23) [Co]: -22.53 (-27.24, -17.82) [Cr]: 18.98 (1.59, 36.36) [Cu]: -15.02 (-57.07, 27.03) [Fe]: 14,152.14 (10,017.3, 18,286.98) [Hg]: 0.01 (-0.47, 0.48) [Mn]: 213.91 (43.97, 383.84) [Ni]: -4.51 (-28.33, 19.31) [Pb]: -155.46 (-191.38, -119.55) [Se]: 0.71 (-146.2, 147.61) [Sr]: 612.72 (2.88, 1,222.55) [V]: 26.03 (9.92, 42.15) [Zn]: -48,605.46 (-63.500.14, -33.710.77) Purchased in EU/UK (n = 8) vs US* (n = 52) [As]: 0.82 (-2.97, 4.62) [Ba]: 1,621.01 (-3,669.28, 6,911.31)

Reference	Intervention details	Sample size	Outcome N (%)
			[Ca]: 22,983.52 (-60,802.61, 106,769.6) [Cd]: -8.17 (-12.78, -3.56) [Co]: -17.22 (-25.76, -8.68) [Cr]: -0.65 (-11.86, 10.55) [Cu]: 50.22 (-423.06, 523.5) [Fe]: 2,104.58 (-7,308.49, 11,517.65) [Hg]: -0.4 (-1.3, 0.5) [Mn]: -62.7 (-513.32, 387.91) [Ni]: 25.48 (-24.73, 75.7) [Pb]: -133.14 (-177.35, -88.94) [Se]: 81.67 (-281.53, 444.87) [Sr]: 89.73 (-114.27, 293.72) [V]: 4.00 (-8.8, 16.8) [Zn]: -45,440.21 (-60.499.03, -30.381.39) Plastic (n = 46) vs no or cardboard applicator* (n = 14) [As]: 0.12 (-2.21, 2.44) [Ba]: 276.28 (-2,598, 3,150.56) [Ca]: -13,715.6 (-59.954.51, 32,523.31) [Cd]: 2.81 (-4.48, 10.1) [Co]: 2.45 (-28.84, 33.74) [Cr]: 5.81 (-2.76, 14.39) [Cu]: -17.12 (-182.72, 148.49) [Fe]: -1,589 (-6,614.45, 3,435.75) [Hg]: -0.02 (-1.42, 1.39) [Mn]: -55.35 (-268.46, 157.76) [Ni]: -10.16 (-44.43, 24.12) [Pb]: 71.23 (-20.06, 162.51) [Se]: -320.29 (-697.01, 56.43) [Sr]: -49.34 (-210.52, 111.84) [V]: -4.11 (-14.62, 6.4) [Zn]: 24,738.98 (-381.54, 49,859.51) Store-brand (n = 11) vs name brand* (n = 49) [As]: -0.86 (-3.04, 1.31) [Ba]: 2,503.34 (-945.84, 5,952.51) [Ca]: -27,120.2 (-56.811.56, 2,571.15) [Cd]: -4.86 (-12.01, 2.29) [Co]: -0.93 (-56.55, 54.7) [Cr]: 2.15 (-14.13, 18.44) [Cu]: 81.26 (15.68, 146.85) [Fe]: -608.85 (-6,306.63, 5,088.93) [Hg]: -0.26 (-1.11, 0.6) [Mn]: -206.76 (-438.46, 24.94) [Ni]: 50.1 (21.97, 78.23) [Pb]: -23.45 (-148.22, 11.32)

Reference	Intervention details	Sample size	Outcome N (%)
			[Se]: 454.39 (23.54, 885.23) [Sr]: 40.62 (-134.46, 215.71) [V]: 0.92 (-11.59, 13.44) [Zn]:-21,721.58 (-42,772.55, -670.61) *Reference groups
Gao et al., 2020[8]	**Device type/brand:** NR **Device material:** Cotton: n = 4 Cotton, rayon, polyester polypropylene, polyethylene: n = 3 Rayon, cotton fiber, polyester, polyethylene: n = 2 Rayon, polyester, polyethylene, polyester: n = 1 Avec fiber (plastic tampon): n = 2 **Method of analysis:** Solvents used for extraction and instrumental analysis included methanol, hexane, methyl-*tert*-butyl-ether, dichloromethane, acetone, and water. Phthalates were determined using an Agilent Technologies 7890A gas chromatography system coupled with an Agilent Technologies 5975C mass spectrometer. Parabens, bisphenols, and TCC were determined using a Shimadzu Prominence modular high-performance liquid chromatography system (Shimadzu Corporation, Kyoto, Japan) coupled with an API 3200 electrospray triple quadrupole mass spectrometer (ESI-MS/MS; Applied Biosystems, Foster City, CA).	12	Concentrations of phthalates (ng/g), reported as mean, median, and range DMP: 412, 214, 141-1650 DEP: 192, 190, 127-262 DIBP: 128, 99.2, 57.9 - 326 DBP: 378, 125, 72.0 – 2,240 BBzP: < LOD DEHP: 744, 267, 64.1 – 4,680 DCHP: not detected DNHP: not detected DOP: not detected $\sum_9$ Phtalate: 1850, 1130, 621 – 6160 Concentrations of parabens (ng/g), reported as mean, median, and range MeP: 18.2, 15.3, 0.01 – 5.85 EtP: 27.6, 25.2, 0.02 – 89.9 PrP: 2.01, 0.46, < LOD – 12.8 BuP: 0.06, < LOD – 0.48 BzP: < LOD HeP: < LOD ∑6 Paraben: 47.9, 42.7, 0.04 – 162 Concentrations of bisphenols and TCC (ng/g), reported as mean, median, and range BPF: 5.60, 4.82, < LOD – 15.4 BPA: 0.87, 0.70, < LOD – 2.46 BPP: < LOD BPS: 0.02, < LOD, < LOD – 0.22 BPZ: < LOD ∑6Bisphenol: 6.49, 5.56, < LOD – 15.6 TCC: 0.05, < LOD, < LOD – 0.44 BPAP: not detected BPAF: not detected BPB: not detected Dermal absorption doses (ng/kg-bw/day) of phthalates, reported as median and maximum DMP: 4.940, 38.03 DEP: 4.384, 6.051 DIBP: 2.288, 7.518 DBP: 2.885, 51.67 BBzP: < 0.001, < 0.001

Reference	Intervention details	Sample size	Outcome N (%)
	The daily exposure doses via dermal absorption were calculated using the equation: DED = C1 x M1 x N x A/BW Where DED is the daily exposure dose (µg/kg-bw/day), C1: is the measured concentration of phthalates, parabens, bisphenols, and TCC; M1 is the weight (g) of the tampons; N is the number of tampons used per day; A is the transdermal absorption rate, and BW is the average body weight of women.		DEHP: 0.308, 5.400 Total: 1.309, 7.105 Dermal absorption doses (ng/kg-bw/day) of parabens, reported as median and maximum MeP: 0.176, 0.676 EtP: 0.291, 1.037 PrP: 0.005, 0.148 BuP: < 0.001, 0.006 BzP: < 0.001, < 0.001 HeP: < 0.001, < 0.001 Total: 0.493, 1.866 Dermal absorption doses (ng/kg-bw/day) of bisphenols and TCC, reported as median and maximum BPF: 0.056, 0.177 BPA: 0.008, 0.028BPB: < 0.001, < 0.001 BPS: < 0.001, 0.003 BPZ: < 0.001, < 0.001 Total: 0.064, 0.180 TCC: < 0.001, < 0.001
Lin et al., 2020[9]	**Device type/brand:** n = 17 brands (NR); n = 5 store brands (NR); regular-sized **Device material:** Organic: n = 2 Non-organic: n = 20 **Method of analysis:** analyses used a short-path automated thermal desorption system (ATD, Scientific Instrument Services, Inc., Ringoes, New Jersey, USA) coupled to a gas chromatography – mass spectrometer (GC-MS, Model 6890/5973, Agilent Technologies, Santa Clara, California, USA) equipped with a cryotrap/focuser (-140C to focus, 250C to inject)	22	Reported as median, mean (SD), range in ng/g Aldehydes: 52, 56 (31), 13 - 138 Alkanes: 28, 138 (506), 6.9 - 2402 Aromatics: 3.7, 5.0 (4.9), 0.9 - 23 Halohydrocarbons: 1.9, 2.4 (2.1), 0.1 – 7.2 Terpenes: 3.5, 67 (292), 0.5 - 1374 Ketones: 1.4, 3.5 (4.9), < MDL - 23 Esters: 0.4, 0.8 (1.0), < MDL – 3.1 Mean and median concentrations (ng/g) of VOC compared between store brand (no, n = 17/yes, n = 5) tampons Halohydrocarbon: NS (values NR) Terpenes: no = 5.3 (86), yes = 1.4 (1.5), p = 0.03 Butanal: no = 1.0 (0.9), yes = 2.8 (3.3), p = 0.03 Octanal: no = 3.4 (8.7), yes = 1.5 (2.0), p = 0.03 p-isopropyl toluene: no = 0.3 (1.5), yes = 0.1 (0.1), p = 0.03 Limonene: no = 5.0 (85), yes = 1.1 (1.5), p = 0.05 n-Decane: NS (values NR) Chloroform: no = 1.0 (1.6), yes = 1.8 (3.5), p = 0.08 Ethylbenzene: no = 0.1 (0.2), yes = 0.4 (0.4), p = 0.08

Reference	Intervention details	Sample size	Outcome N (%)
			Mean and median concentrations (ng/g) of VOC compared between "organic" (no, n = 20/yes, n = 2) tampons Halohydrocarbon: no = 1.9 (2.6), yes = 0.3 (0.3), p = 0.05 Terpenes: NS (values NR) Butanal: NS (values NR) Octanal: NS (values NR) p-isopropyl toluene: NS (values NR) Limonene: NS (values NR) n-Decane: no = 2.3 (101), yes = 0.2 (0.2), p = 0.009 Chloroform: no = 1.4 (2.2), yes = < MDL, p = 0.08 Ethylbenzene: NS (values NR)
Archer et al., 2005[10]	**Device type/brand:** Seven brands (NR) **Device material:** Varying % in the composition of rayon-cotton (quantification NR) **Method of analysis:** Gas Chromatography/High-Resolution Mass Spectrometry using a Micromass Autospec ultima high-resolution mass spectrometer at 10,000 mass resolution	NR	Most detected quantities of dioxins were at or near detection limit values. (results presented in Figures)

Abbreviations: As: Arsenic; Ba: Barium; BBzP: butyl benzyl phthalate; BPA: bisphenol A; BPB: Bisphenol B; BPF: Bisphenol F; BPAF: Bisphenol AF; BPAP: Bisphenol AP; BPP: Bisphenol P; BPS: Bisphenol S; BPZ: Bisphenol Z; BuP: Butyl-paraben; BzP: benzyl-paraben; Ca: calcium; Cd: cadmium; CI: confidence interval; CMC: Caboxymethyl cellulose; Co:Cobalt; Cr: Chromium; Cu: Copper; DBP: dibutyl phthalate; DCHP: dicyclohexyl phthalate; DEHP: Di(2-ethylhexyl) phthalate; DEP:; DIBP: di-iso-butyl phthalate; DMP: dimethyl phthalate; DNHP: di-n-hexyl phthalate; DOP: di-n-octyl phthalate; EtP: ethyl-paraben; EU: Europe; Fe: Iron; GM: geometric mean; GSD: geometric standard deviation; HeP:Heptyl-paraben; Hg: Mercury; LOD: limit of detection; MDL: method detection limit; MeP: mono-ethyl phthalate; Mn: Manganese; NA: not applicable; Ni: Nicklel; NR: not reported; NS: not significant; Pb: Lead; PrP: propyl-paraben SD: standard deviation; Se: selenium; Sr: strontium; TCC: triclocarban; UK: United Kingdom; V: Vanadium; VOC: volatile organic compounds; Zn: zinc

Discussion

During the review process, ICA identified a few challenges worth mentioning. Tampon brands, manufacturers, and materials composing the tampons assessed were not described in detail. This impeded ICA from analyzing contaminants as intended or stratifying the results per brand, type of materials, and relevant participants' characteristics. Tampons of different brands were commonly pooled as one "tampon" group. In terms of participants' characteristics, there was an overall lack of description, including details regarding their menstrual cycles, overall hygiene practices, comorbidities, lifestyle, and sociodemographic characteristics, which would be informative to this review. ICA did not come across literature comparing contaminant exposures in the vaginal microenvironment vs. systemic circulation.

ICA also noted a few methodological aspects in the studies analyzed that are worth discussing. For KQ1, the experiment conducted by Ding et al. 2022[11] had a relatively small sample size (n = 25), the sample was recruited by convenience, and the study authors mentioned that urine concentrations may not be the optimal biomarker to assess VOC concentrations. Despite the large sample sizes in two cross-sectional studies[12,14], the cross-sectional design does not allow us to infer causality. Moreover, the exposure in these studies could be subject to recall bias, as tampon use was self-reported in questionnaires. A prospective cohort, the BioCycle study,[13] compared exposure to contaminants between tampon and non-tampon users (that included people using other menstrual products). The sample size was relatively small, and exposure was self-reported and subject to recall bias. While the prospective observational design is more robust, it is also subject to residual confounding.

The body of evidence that we identified to address KQ2 to date demonstrated that it is unlikely that vaginal tampon use is associated with harmful health outcomes. The vaginal ulcerations reported in the case series[15] appear to be related to the daily tampon use, as they were resolved when tampon use was stopped. However, tampons are not designed for daily use outside the menstrual cycle. The patients in this study had other health conditions that likely led them to use tampons daily.

KQ3 summarized contaminants and chemicals identified in tampon samples analyzed in laboratory settings. This evidence revealed the presence of metals, phthalates, parabens, bisphenols, VOCs, dioxins, and TCC. In some instances, contaminants were below detection limits. Many associations were explored; most did not reach statistical significance based on the evidence assessed. Overall, studies failed to report on the normal/expected levels of these contaminants, limiting the interpretation of findings. Nonetheless, Shearston et al.2024[7] identified the following toxic metals in microwave-acid digested tampons: lead, cadmium, and arsenic. Notably, the prospective cohort[13] reported lead, mercury, and cadmium concentrations in blood samples of tampon and non-tampon users. Their linear regression models were not statistically significant for blood metals, demonstrating that tampon use was not associated with metal concentrations in this cohort of participants.

In conclusion, additional studies are needed to illuminate the relationships between vaginal tampon use and exposure to contaminants.

Evidence Assessment and Critique

Seven studies declared their funding sources,[7,9,11-14,16] two studies did not report whether funding was received.[8,15] Seven studies reported not having conflicts of interest with the conduction of studies,[7-9,11-14] and two studies did not report on conflicts of interest.[10,15] Five provided clinical outcomes while four were laboratory assessments of tampon samples. Within the clinical studies, one had an experimental design, two studies (20.0%) were cross-sectional, one was a prospective cohort, and one was a case series. Only three studies (30.0%)[12-14] had sample sizes with more than 100 individuals, and the largest sample had 851 tampon users[12]. Within the experimental laboratory analyses of tampons, the largest sample size was 60, and the smaller contained 22 samples. Moreover, the study with the largest sample size did not have the statistical power to detect differences between tampon brands (and these were not disclosed). ICA rates this group of studies as low quality, given that one study was a prospective cohort, and most studies had samples < 100 individuals.

Appendix A: Literature Search Strategy

Literature searches were conducted on August 9, 2024, using two electronic biomedical databases (PubMed and Embase). Tables A1 and A2 depict search strategies from PubMed and EMBASE, respectively. The search strategy was generated using the intervention and condition of interest. The search strategy also utilized Boolean operators, medical subject heading [MeSH], and Emtree thesaurus terms. The literature search between 2004 and 2024 from the two databases yielded 1,170 results (Table A1 and A2), before deduplication.

Table A1. PubMed Search Strategy (August 9, 2024)

Search number	Query	Filters	Results
#5	#1 AND (#2 OR #3 OR #4)	from 2004/1/1 - 2024	533
#4	"Vaginal Absorption"[Mesh:NoExp] OR "Absorption, Physiological"[Mesh:NoExp] OR "Environmental Exposure"[Mesh:NoExp] OR "Clinical Laboratory Techniques"[Mesh] OR "Biomarkers"[Mesh] OR concentration*[Text Word] OR expos*[Text Word] OR absorb*[Text Word] OR absorp*[Text Word] OR accumulat*[Text Word] OR bioaccumulat*[Text Word] OR "Laboratory Technique*"[Text Word] OR "Laboratory Diagnos*"[Text Word] OR "Laboratory Exam*"[Text Word] OR "Laboratory Test*"[Text Word] OR Biomarker*[Text Word] OR "Biological Marker*"[Text Word] OR "Biologic Marker*"[Text Word] OR "Clinical Marker*"[Text Word] OR "Surrogate Marker*"[Text Word] OR "Surrogate Endpoint*"[Text Word] OR "Surrogate End Point*"[Text Word] OR "Immune Marker*"[Text Word] OR "Immunologic Marker*"[Text Word] OR "Laboratory Marker*"[Text Word] OR "Serum Marker*"[Text Word] OR "Biochemical Marker*"[Text Word]	from 2004/1/1 - 2024	4,932,649

Search number	Query	Filters	Results
#3	"Hazardous Substances"[Mesh:NoExp] OR "Poisons"[Mesh:NoExp] OR "Hazardous Substance*"[Text Word] OR "Hazardous Material*"[Text Word] OR "Toxic Substance*"[Text Word] OR "Toxic Environmental Substance*"[Text Word] OR Biohazard*[Text Word] OR chemical*[Text Word] OR aluminosilicate[Text Word] OR amosite[Text Word] OR amphibole[Text Word] OR apatite[Text Word] OR aroclor[Text Word] OR asbestos[Text Word] OR asphalt[Text Word] OR "biodegradable plastic*"[Text Word] OR "black carbon"[Text Word] OR cellulose[Text Word] OR chrysotile[Text Word] OR clinoptilolite[Text Word] OR "coal tar"[Text Word] OR concrete[Text Word] OR crocidolite[Text Word] OR "ethylene oxide"[Text Word] OR explosive[Text Word] OR "flame retardant"[Text Word] OR additive[Text Word] OR dye[Text Word] OR dyes[Text Word] OR dyed[Text Word] OR formaldehyde[Text Word] OR freon[Text Word] OR fuel[Text Word] OR "fuller earth"[Text Word] OR glass[Text Word] OR "gutta percha"[Text Word] OR hexachlorobiphenyl[Text Word] OR "hydrochloric acid"[Text Word] OR ink[Text Word] OR "industrial effluent"[Text Word] OR "industrial enzyme"[Text Word] OR "toxic substance*"[Text Word] OR "infusorial earth"[Text Word] OR latex[Text Word] OR "lubricating agent*"[Text Word] OR "methylcyclopentadienylmanganese tricarbonyl"[Text Word] OR "mineral fiber*"[Text Word] OR montmorillonite[Text Word] OR nutraceutical[Text Word] OR oil[Text Word] OR oils[Text Word] OR oily[Text Word] OR paint*[Text Word] OR paraffin[Text Word] OR "perfluorodecanoic acid"[Text Word] OR petrochemical[Text Word] OR "petroleum derivative"[Text Word] OR plastic*[Text Word] OR plasticizer*[Text Word] OR polyvinylchloride[Text Word] OR "propylene oxide"[Text Word] OR pumice[Text Word] OR resin[Text Word] OR rubber[Text Word] OR silastic[Text Word] OR solvent*[Text Word] OR steel[Text Word] OR "sucrose acetate isobutyrate"[Text Word] OR tar[Text Word] OR tetrachlorobiphenyl[Text Word] OR "toluene diisocyanate"[Text Word] OR tremolite[Text Word] OR vermiculite[Text Word] OR vinegar[Text Word] OR vinyl[Text Word] OR vinylidene[Text Word] OR zeolite[Text Word] OR "banned ingredient*"[Text Word] OR capsaicin[Text Word] OR carcinogen*[Text Word] OR "cigarette smoke"[Text Word] OR "dimethyl sulfate"[Text Word] OR "electronic cigarette vapor"[Text Word] OR hemolysin[Text Word] OR "toxic substance"[Text Word] OR "irritant agent"[Text Word] OR "mutagenic agent"[Text Word] OR poison*[Text Word] OR pyrogen[Text Word] OR "teratogenic agent"[Text Word] OR "tobacco smoke"[Text Word] OR "toxic gas"[Text Word] OR toxin*[Text Word] OR pesticide*[Text Word] OR environmental[Text Word] OR systemic[Text Word] OR physiological[Text Word] OR mutagen[Text Word] OR contamina*[Text Word] OR "volatile organic compound*"[Text Word] OR phthalate*[Text Word] OR paraben*[Text Word] OR bisphenol*[Text Word] OR triclocarban*[Text Word]	from 2004/1/1 - 2024	4,256,866

Search number	Query	Filters	Results
#2	"Metals"[Mesh] OR "Metalloids"[Mesh] OR metal*[Text Word] OR Actinium[Text Word] OR Americium[Text Word] OR Berkelium[Text Word] OR Californium[Text Word] OR Curium[Text Word] OR Einsteinium[Text Word] OR Fermium[Text Word] OR Lawrencium[Text Word] OR Mendelevium[Text Word] OR Neptunium[Text Word] OR Nobelium[Text Word] OR Plutonium[Text Word] OR Protactinium[Text Word] OR Thorium[Text Word] OR Uranium[Text Word] OR Cesium[Text Word] OR Francium[Text Word] OR Lithium[Text Word] OR Potassium[Text Word] OR Rubidium[Text Word] OR Sodium[Text Word] OR Barium[Text Word] OR Calcium[Text Word] OR Radium[Text Word] OR Strontium[Text Word] OR Antimony[Text Word] OR Bismuth[Text Word] OR Cadmium[Text Word] OR Chromium[Text Word] OR Cobalt[Text Word] OR Copper[Text Word] OR Gallium[Text Word] OR Germanium[Text Word] OR Gold[Text Word] OR Hafnium[Text Word] OR Indium[Text Word] OR Iridium[Text Word] OR Iron[Text Word] OR Lead[Text Word] OR Manganese[Text Word] OR Mercury[Text Word] OR Molybdenum[Text Word] OR Nickel[Text Word] OR Niobium[Text Word] OR Osmium[Text Word] OR Palladium[Text Word] OR Platinum[Text Word] OR Rhenium[Text Word] OR Rhodium[Text Word] OR Ruthenium[Text Word] OR Silver[Text Word] OR Tantalum[Text Word] OR Technetium[Text Word] OR Thallium[Text Word] OR Tin[Text Word] OR Tungsten[Text Word] OR Vanadium[Text Word] OR Zinc[Text Word] OR Zirconium[Text Word] OR Aluminum[Text Word] OR Beryllium[Text Word] OR Magnesium[Text Word] OR Titanium[Text Word] OR Scandium[Text Word] OR Yttrium[Text Word] OR Metalloid*[Text Word] OR "Semi-Metal*"[Text Word] OR "Semi Metal*"[Text Word] OR Arsenic[Text Word] OR Boron[Text Word] OR Polonium[Text Word] OR Silicon[Text Word] OR Tellurium[Text Word]	from 2004/1/1 - 2024	2,807,802
#1	"Menstrual Hygiene Products"[Mesh:NoExp] OR tampon[Text Word] OR tampons[Text Word]	from 2004/1/1 - 2024	1,197

Figure 2. Screenshot of the PubMed search strategy and filter applied (August 9, 2024)

#5	Search: **#1 AND (#2 OR #3 OR #4)** Filters: **from 2004/1/1 - 2024** Sort by: **Publication Date**	533
#4	Search: **"Vaginal Absorption"[Mesh:NoExp] OR "Absorption, Physiological"[Mesh:NoExp] OR "Environmental Exposure" [Mesh:NoExp] OR "Clinical Laboratory Techniques"[Mesh] OR "Biomarkers"[Mesh] OR concentration*[Text Word] OR expos*[Text Word] OR absorb*[Text Word] OR absorp*[Text Word] OR accumulat* [Text Word] OR bioaccumulat*[Text Word] OR "Laboratory Technique*"[Text Word] OR "Laboratory Diagnos*"[Text Word] OR "Laboratory Exam*"[Text Word] OR "Laboratory Test*"[Text Word] OR Biomarker*[Text Word] OR "Biological Marker*"[Text Word] OR "Biologic Marker*"[Text Word] OR "Clinical Marker*"[Text Word] OR "Surrogate Marker*"[Text Word] OR "Surrogate Endpoint*"[Text Word] OR "Surrogate End Point*"[Text Word] OR "Immune Marker*" [Text Word] OR "Immunologic Marker*"[Text Word] OR "Laboratory Marker*"[Text Word] OR "Serum Marker*"[Text Word] OR "Biochemical Marker*"[Text Word]** Filters: **from 2004/1/1 - 2024** Sort by: **Publication Date**	4,932,649
#3	Search: **"Hazardous Substances"[Mesh:NoExp] OR "Poisons" [Mesh:NoExp] OR "Hazardous Substance*"[Text Word] OR "Hazardous Material*"[Text Word] OR "Toxic Substance*"[Text Word] OR "Toxic Environmental Substance*"[Text Word] OR Biohazard*[Text Word] OR chemical*[Text Word] OR aluminosilicate[Text Word] OR amosite[Text Word] OR amphibole[Text Word] OR apatite[Text Word] OR aroclor[Text Word] OR asbestos[Text Word] OR asphalt[Text Word] OR "biodegradable plastic*"[Text Word] OR "black carbon" [Text Word] OR cellulose[Text Word] OR chrysotile[Text Word] OR clinoptilolite[Text Word] OR "coal tar"[Text Word] OR concrete[Text Word] OR crocidolite[Text Word] OR "ethylene oxide"[Text Word] OR explosive[Text Word] OR "flame retardant"[Text Word] OR additive[Text Word] OR dye[Text Word] OR dyes[Text Word] OR dyed[Text Word] OR formaldehyde[Text Word] OR freon[Text Word] OR fuel[Text Word] OR "fuller earth"[Text Word] OR glass[Text Word] OR "gutta percha"[Text Word] OR hexachlorobiphenyl[Text Word] OR "hydrochloric acid"[Text Word] OR ink[Text Word] OR "industrial effluent"[Text Word] OR "industrial enzyme"[Text Word] OR "toxic substance*"[Text Word] OR "infusorial earth"[Text Word] OR latex[Text Word] OR "lubricating agent*"[Text Word] OR "methylcyclopentadienylmanganese tricarbonyl"[Text Word] OR "mineral fiber*"[Text Word] OR montmorillonite[Text Word] OR nutraceutical[Text Word] OR oil[Text Word] OR oils[Text Word] OR oily[Text Word] OR paint*[Text Word] OR paraffin[Text Word] OR "perfluorodecanoic acid"[Text Word] OR petrochemical[Text Word] OR "petroleum derivative"[Text Word] OR plastic*[Text Word] OR plasticizer*[Text Word] OR polyvinylchloride[Text Word] OR "propylene oxide"[Text Word] OR pumice[Text Word] OR resin[Text Word] OR rubber[Text Word] OR silastic[Text Word] OR solvent*[Text Word] OR steel[Text Word] OR "sucrose acetate isobutyrate"[Text Word] OR tar[Text Word] OR tetrachlorobiphenyl[Text Word] OR "toluene diisocyanate"[Text Word] OR tremolite[Text Word] OR vermiculite[Text Word] OR vinegar[Text Word] OR vinyl[Text Word] OR vinylidene[Text Word] OR zeolite[Text Word] OR "banned ingredient*"[Text Word] OR capsaicin[Text Word] OR carcinogen* [Text Word] OR "cigarette smoke"[Text Word] OR "dimethyl sulfate" [Text Word] OR "electronic cigarette vapor"[Text Word] OR hemolysin[Text Word] OR "toxic substance"[Text Word] OR "irritant agent"[Text Word] OR "mutagenic agent"[Text Word] OR poison* [Text Word] OR pyrogen[Text Word] OR "teratogenic agent"[Text Word] OR "tobacco smoke"[Text Word] OR "toxic gas"[Text Word] OR toxin*[Text Word] OR pesticide*[Text Word] OR environmental[Text Word] OR systemic[Text Word] OR physiological[Text Word] OR mutagen[Text Word] OR contamina* [Text Word] OR "volatile organic compound*"[Text Word] OR phthalate*[Text Word] OR paraben*[Text Word] OR bisphenol*[Text Word] OR triclocarban*[Text Word]** Filters: **from 2004/1/1 - 2024** Sort by: **Publication Date**	4,256,866
#2	Search: **"Metals"[Mesh] OR "Metalloids"[Mesh] OR metal*[Text Word] OR Actinium[Text Word] OR Americium[Text Word] OR Berkelium[Text Word] OR Californium[Text Word] OR Curium[Text Word] OR Einsteinium[Text Word] OR Fermium[Text Word] OR Lawrencium[Text Word] OR Mendelevium[Text Word] OR Neptunium[Text Word] OR Nobelium[Text Word] OR Plutonium[Text Word] OR Protactinium[Text Word] OR Thorium[Text Word] OR Uranium[Text Word] OR Cesium[Text Word] OR Francium[Text Word] OR Lithium[Text Word] OR Potassium[Text Word] OR Rubidium[Text Word] OR Sodium[Text Word] OR Barium[Text Word] OR Calcium[Text Word] OR Radium[Text Word] OR Strontium[Text Word] OR Antimony[Text Word] OR Bismuth[Text Word] OR Cadmium[Text Word] OR Chromium[Text Word] OR Cobalt[Text Word] OR Copper[Text Word] OR Gallium[Text Word] OR Germanium[Text Word] OR Gold[Text Word] OR Hafnium[Text Word] OR Indium[Text Word] OR Iridium[Text Word] OR Iron[Text Word] OR Lead[Text Word] OR Manganese[Text Word] OR Mercury[Text Word] OR Molybdenum[Text Word] OR Nickel[Text Word] OR Niobium[Text Word] OR Osmium[Text Word] OR Palladium[Text Word] OR Platinum[Text Word] OR Rhenium[Text Word] OR Rhodium[Text Word] OR Ruthenium[Text Word] OR Silver[Text Word] OR Tantalum[Text Word] OR Technetium[Text Word] OR Thallium[Text Word] OR Tin[Text Word] OR Tungsten[Text Word] OR Vanadium[Text Word] OR Zinc[Text Word] OR Zirconium[Text Word] OR Aluminum[Text Word] OR Beryllium[Text Word] OR Magnesium[Text Word] OR Titanium[Text Word] OR Scandium[Text Word] OR Yttrium[Text Word] OR Metalloid*[Text Word] OR "Semi-Metal*"[Text Word] OR "Semi Metal*"[Text Word] OR Arsenic[Text Word] OR Boron[Text Word] OR Polonium[Text Word] OR Silicon[Text Word] OR Tellurium[Text Word]** Filters: **from 2004/1/1 - 2024** Sort by: **Publication Date**	2,807,802
#1	Search: **"Menstrual Hygiene Products"[Mesh:NoExp] OR tampon[Text Word] OR tampons[Text Word]** Filters: **from 2004/1/1 - 2024** Sort by: **Publication Date**	1,197

Filters applied: From 2004/1/1 to 2024. Clear all

Table A2. Embase Search Strategy (August 9, 2024)

No.	Query	Results
#5	#1 AND (#2 OR #3 OR #4) AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [preprint]/lim) AND [humans]/lim AND [english]/lim AND [2004-2024]/py	637
#4	'absorption'/de OR 'environmental exposure'/de OR 'bioaccumulation'/de OR 'laboratory diagnosis'/exp OR 'biological marker'/de OR concentration* OR expos* OR absorb* OR absorp* OR accumulat* OR bioaccumulat* OR 'laboratory technique*' OR 'laboratory diagnos*' OR 'laboratory exam*' OR 'laboratory test*' OR biomarker* OR 'biological marker*' OR 'biologic marker*' OR 'clinical marker*' OR 'surrogate marker*' OR 'surrogate endpoint*' OR 'surrogate end point*' OR 'immune marker*' OR 'immunologic marker*' OR 'laboratory marker*' OR 'serum marker*' OR 'biochemical marker*'	7334687
#3	'environmental, industrial and domestic chemicals'/exp OR 'industrial chemical'/exp OR 'toxic substance'/exp OR 'hazardous substance*' OR 'hazardous material*' OR 'toxic environmental substance*' OR biohazard* OR chemical* OR aluminosilicate OR amosite OR amphibole OR apatite OR aroclor OR asbestos OR asphalt OR 'biodegradable plastic*' OR 'black carbon' OR cellulose OR chrysotile OR clinoptilolite OR 'coal tar' OR concrete OR crocidolite OR 'ethylene oxide' OR explosive OR 'flame retardant' OR additive OR dye OR dyes OR dyed OR formaldehyde OR freon OR fuel OR 'fuller earth' OR glass OR 'gutta percha' OR hexachlorobiphenyl OR 'hydrochloric acid' OR ink OR 'industrial effluent' OR 'industrial enzyme' OR 'toxic substance*' OR 'infusorial earth' OR latex OR 'lubricating agent*' OR 'methylcyclopentadienylmanganese tricarbonyl' OR 'mineral fiber*' OR montmorillonite OR nutraceutical OR oil OR oils OR oily OR paint* OR paraffin OR 'perfluorodecanoic acid' OR petrochemical OR 'petroleum derivative' OR plastic* OR plasticizer* OR polyvinylchloride OR 'propylene oxide' OR pumice OR resin OR rubber OR silastic OR solvent* OR steel OR 'sucrose acetate isobutyrate' OR tar OR tetrachlorobiphenyl OR 'toluene diisocyanate' OR tremolite OR vermiculite OR vinegar OR vinyl OR vinylidene OR zeolite OR 'banned ingredient*' OR capsaicin OR carcinogen* OR 'cigarette smoke' OR 'dimethyl sulfate' OR 'electronic cigarette vapor' OR hemolysin OR 'toxic substance' OR 'irritant agent' OR 'mutagenic agent' OR poison* OR pyrogen OR 'teratogenic agent' OR 'tobacco smoke' OR 'toxic gas' OR toxin* OR pesticide* OR environmental OR systemic OR physiological OR mutagen OR contamina* OR 'volatile organic compound*' OR phthalate* OR paraben* OR bisphenol* OR triclocarban*	10606373

No.	Query	Results
#2	'metal'/exp OR 'metalloid'/exp OR metal* OR actinium OR americium OR berkelium OR californium OR curium OR einsteinium OR fermium OR lawrencium OR mendelevium OR neptunium OR nobelium OR plutonium OR protactinium OR thorium OR uranium OR cesium OR francium OR lithium OR potassium OR rubidium OR sodium OR barium OR calcium OR radium OR strontium OR antimony OR bismuth OR cadmium OR chromium OR cobalt OR copper OR gallium OR germanium OR gold OR hafnium OR indium OR iridium OR iron OR lead OR manganese OR mercury OR molybdenum OR nickel OR niobium OR osmium OR palladium OR platinum OR rhenium OR rhodium OR ruthenium OR silver OR tantalum OR technetium OR thallium OR tin OR tungsten OR vanadium OR zinc OR zirconium OR aluminum OR beryllium OR magnesium OR titanium OR scandium OR yttrium OR metalloid* OR 'semi-metal*' OR 'semi metal*' OR arsenic OR boron OR polonium OR silicon OR tellurium	6261114
#1	'feminine hygiene product'/exp OR tampon OR tampons	4161

Figure 3. Screenshot of the Embase Search Strategy (August 9, 2024)

#5	#1 AND (#2 OR #3 OR #4) AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [preprint]/lim) AND [humans]/lim AND [english]/lim AND [2004-2024]/py	637
#4	'absorption'/de OR 'environmental exposure'/de OR 'bioaccumulation'/de OR 'laboratory diagnosis'/exp OR 'biological marker'/de OR concentration* OR expos* OR absorb* OR absorp* OR accumulat* OR bioaccumulat* OR 'laboratory technique*' OR 'laboratory diagnos*' OR 'laboratory exam*' OR 'laboratory test*' OR biomarker* OR 'biological marker*' OR 'biologic marker*' OR 'clinical marker*' OR 'surrogate marker*' OR 'surrogate endpoint*' OR 'surrogate end point*' OR 'immune marker*' OR 'immunologic marker*' OR 'laboratory marker*' OR 'serum marker*' OR 'biochemical marker*'	7,334,687
#3	'environmental, industrial and domestic chemicals'/exp OR 'industrial chemical'/exp OR 'toxic substance'/exp OR 'hazardous substance*' OR 'hazardous material*' OR 'toxic environmental substance*' OR biohazard* OR chemical* OR aluminosilicate OR amosite OR amphibole OR apatite OR aroclor OR asbestos OR asphalt OR 'biodegradable plastic*' OR 'black carbon' OR cellulose OR chrysotile OR clinoptilolite OR 'coal tar' OR concrete OR crocidolite OR 'ethylene oxide' OR explosive OR 'flame retardant' OR additive OR dye OR dyes OR dyed OR formaldehyde OR freon OR fuel OR 'fuller earth' OR glass OR 'gutta percha' OR hexachlorobiphenyl OR 'hydrochloric acid' OR ink OR 'industrial effluent' OR 'industrial enzyme' OR 'toxic substance*' OR 'infusorial earth' OR latex OR 'lubricating agent*' OR 'methylcyclopentadienylmanganese tricarbonyl' OR 'mineral fiber*' OR montmorillonite OR nutraceutical OR oil OR oils OR oily OR paint* OR paraffin OR 'perfluorodecanoic acid' OR petrochemical OR 'petroleum derivative' OR plastic* OR plasticizer* OR polyvinylchloride OR 'propylene oxide' OR pumice OR resin OR rubber OR silastic OR solvent* OR steel OR 'sucrose acetate isobutyrate' OR tar OR tetrachlorobiphenyl OR 'toluene diisocyanate' OR tremolite OR vermiculite OR vinegar OR vinyl OR vinylidene OR zeolite OR 'banned ingredient*' OR capsaicin OR carcinogen* OR 'cigarette smoke' OR 'dimethyl sulfate' OR 'electronic cigarette vapor' OR hemolysin OR 'toxic substance' OR 'irritant agent' OR 'mutagenic agent' OR poison* OR pyrogen OR 'teratogenic agent' OR 'tobacco smoke' OR 'toxic gas' OR toxin* OR pesticide* OR environmental OR systemic OR physiological OR mutagen OR contamina* OR 'volatile organic compound*' OR phthalate* OR paraben* OR bisphenol* OR triclocarban*	10,606,373
#2	'metal'/exp OR 'metalloid'/exp OR metal* OR actinium OR americium OR berkelium OR californium OR curium OR einsteinium OR fermium OR lawrencium OR mendelevium OR neptunium OR nobelium OR plutonium OR protactinium OR thorium OR uranium OR cesium OR francium OR lithium OR potassium OR rubidium OR sodium OR barium OR calcium OR radium OR strontium OR antimony OR bismuth OR cadmium OR chromium OR cobalt OR copper OR gallium OR germanium OR gold OR hafnium OR indium OR iridium OR iron OR lead OR manganese OR mercury OR molybdenum OR nickel OR niobium OR osmium OR palladium OR platinum OR rhenium OR rhodium OR ruthenium OR silver OR tantalum OR technetium OR thallium OR tin OR tungsten OR vanadium OR zinc OR zirconium OR aluminum OR beryllium OR magnesium OR titanium OR scandium OR yttrium OR metalloid* OR 'semi-metal*' OR 'semi metal*' OR arsenic OR boron OR polonium OR silicon OR tellurium	6,261,114
#1	'feminine hygiene product'/exp OR tampon OR tampons	4,161

Appendix B. Evidence Tables

Table B1. Characteristics and Outcomes of Included Studies

Study details	Participants	Study Characteristics	Results
Reference: Shearston et al. 2024[7] **Study design:** Laboratory analysis of tampon samples **Type of study:** Bench **Purpose:** To evaluate the concentrations of 16 metal(loid)s in 30 tampons from 14 tampon brands and 18 product lines and compare the concentrations by tampon characteristics. **Funding:** NIEHS of the NIH (P30 ES009089, F 31 ES033098, T32 ES007322); NHLBI of the NIH (F31 HL172608), the National Institute of Nursing Research of the NIH (R00 NR017191) **Conflict of interest:** None	**Sample size:** n = 60 tampon samples (representing 30 unique tampons and 24 unique brand-product line-absorbency combinations) **Mean age (range):** NA **Race/ethnicity N (%):** NA **Comorbidities N (%):** NA **Inclusion criteria:** a variety of tampon products, representing multiple manufacturers, brands, product lines, and absorbencies. Selected products were generally listed as top sellers on a major online retailer, as we as "store-brand" products (products with the brand name of the store where purchased or made specifically for that store) from several large chain retailers in the US. Products were generally selected if described as having greater absorbencies to ensure that there was enough material for multiple tests.	**Device type/brand:** 14 brands analyzed; names NR **Device material:** 16 non-organic (Rayon or mixture of cotton, rayon and viscose); 15 organic (100% cotton); 1 NR **Exposure details (number of tampons/cycle):** NA **Comparator:** NA **Method of analysis:** Non-mercury metals in the tampon digest was assessed using a perkinElmer NexION 350S Inductively Coupled Plasma Mass Spectrometry with dynamic reaction cell (ICP-DRC-MS). For Hg, Agilent 8900 ICP-MS equipped with an Agilent SPS 4 autosampler system. **Mean follow-up period, years:** NA **Endpoints assessed:** Laboratory outcomes found in the device	**Safety outcomes:** NR **Biomarkers identified in human samples:** NR **Biomarkers/laboratory outcomes found in the device:** Metal concentrations (ng/g) in tampon samples, reported as GM (GSD) [As]: 2.56 (2.02) [Ba]: 1,100 (4.60) [Ca]: 39,000 (2.17) [Cd]: 6.74 (2.67) [Co]: 19.8 (2.17) [Cr]: < MDL (NA) [Cu]: 78.9 (2.00) [Fe]: 3,099 (2.68) [Hg]: < MDL (NA) [Mn]: 296 (2.38) [Ni]: 80.1 (1.44) [Pb]: 120 (2.24) [Se]: 28.5 (6.04) [Sr]: 190 (2.74) [V]: 6.37 (2.71) [Zn]: 52,000 (1.93) Effect estimates and 95% CIs from metal-specific mixed median quantile regression models evaluating the relationship between select tampon characteristics and metal concentrations (ng/g): <u>Organic (n = 14) vs non-organic* (n = 44)</u> [As]: 4.53 (2.32, 6.75) [Ba]: -1,346.22 (-2,028.06, -664.37) [Ca]: 78,980.41 (55,0.16.32, 102,944.5) [Cd]: -9.93 (-13.62, -6.23) [Co]: -22.53 (-27.24, -17.82) [Cr]: 18.98 (1.59, 36.36) [Cu]: -15.02 (-57.07, 27.03)

Study details	Participants	Study Characteristics	Results
	Exclusion criteria: NR		[Fe]: 14,152.14 (10,017.3, 18,286.98) [Hg]: 0.01 (-0.47, 0.48) [Mn]: 213.91 (43.97, 383.84) [Ni]: -4.51 (-28.33, 19.31) [Pb]: -155.46 (-191.38, -119.55) [Se]: 0.71 (-146.2, 147.61) [Sr]: 612.72 (2.88, 1,222.55) [V]: 26.03 (9.92, 42.15) [Zn]: -48,605.46 (-63.500.14, -33.710.77) Purchased in EU/UK (n = 8) vs US* (n = 52) [As]: 0.82 (-2.97, 4.62) [Ba]: 1,621.01 (-3,669.28, 6,911.31) [Ca]: 22,983.52 (-60,802.61, 106,769.6) [Cd]: -8.17 (-12.78, -3.56) [Co]: -17.22 (-25.76, -8.68) [Cr]: -0.65 (-11.86, 10.55) [Cu]: 50.22 (-423.06, 523.5) [Fe]: 2,104.58 (-7,308.49, 11,517.65) [Hg]: -0.4 (-1.3, 0.5) [Mn]: -62.7 (-513.32, 387.91) [Ni]: 25.48 (-24.73, 75.7) [Pb]: -133.14 (-177.35, -88.94) [Se]: 81.67 (-281.53, 444.87) [Sr]: 89.73 (-114.27, 293.72) [V]: 4.00 (-8.8, 16.8) [Zn]: -45,440.21 (-60.499.03, -30.381.39) Plastic (n = 46) vs no or cardboard applicator* (n = 14) [As]: 0.12 (-2.21, 2.44) [Ba]: 276.28 (-2,598, 3,150.56) [Ca]: -13,715.6 (-59.954.51, 32,523.31) [Cd]: 2.81 (-4.48, 10.1) [Co]: 2.45 (-28.84, 33.74) [Cr]: 5.81 (-2.76, 14.39) [Cu]: -17.12 (-182.72, 148.49) [Fe]: -1,589 (-6,614.45, 3,435.75)

Study details	Participants	Study Characteristics	Results
			[Hg]: -0.02 (-1.42, 1.39) [Mn]: -55.35 (-268.46, 157.76) [Ni]: -10.16 (-44.43, 24.12) [Pb]: 71.23 (-20.06, 162.51) [Se]: -320.29 (-697.01, 56.43) [Sr]: -49.34 (-210.52, 111.84) [V]: -4.11 (-14.62, 6.4) [Zn]: 24,738.98 (-381.54, 49,859.51) <u>Store-brand (n = 11) vs name brand* (n = 49)</u> [As]: -0.86 (-3.04, 1.31) [Ba]: 2,503.34 (-945.84, 5,952.51) [Ca]: -27,120.2 (-56.811.56, 2,571.15) [Cd]: -4.86 (-12.01, 2.29) [Co]: -0.93 (-56.55, 54.7) [Cr]: 2.15 (-14.13, 18.44) [Cu]: 81.26 (15.68, 146.85) [Fe]: -608.85 (-6,306.63, 5,088.93) [Hg]: -0.26 (-1.11, 0.6) [Mn]: -206.76 (-438.46, 24.94) [Ni]: 50.1 (21.97, 78.23) [Pb]: -23.45 (-148.22, 11.32) [Se]: 454.39 (23.54, 885.23) [Sr]: 40.62 (-134.46, 215.71) [V]: 0.92 (-11.59, 13.44) [Zn]:-21,721.58 (-42,772.55, -670.61) *Reference groups **Study limitations:** No sufficient power to assess statistical differences by absorbency, lot number, brand, or manufacturer; it is not possible to consider the three non-US tampons included in the analysis to be representative or most tampons available in the EU/UK; multiple statistical tests were conducted, increasing the possibility of type I error (false positives); this study does not provide information about the

Study details	Participants	Study Characteristics	Results
			potential bio-accessibility of tampon metals and this cannot estimate health risks (if any) from tampon use.
Reference: Ding et al. 2022[11] **Study design:** Non-randomized, repeated measures, experimental study; measurements in urine samples **Type of study (bench/clinical):** Clinical **Purpose:** To examine the variations of VOC concentrations during menstrual cycles; to evaluate the relationships between the use of menstrual products and urinary VOC concentrations; and link urinary VOC concentrations to those measured in menstrual products. **Funding:** NIEHS-NIH (P30ES017885, R01-ES026964), CDC/NIOSH (T42-OH008455) **Conflict of interest:** None	**Sample size:** 25 reproductive-aged women with 100 repeated measures collected **Median age (IQR):** 23 (22-25) years **Race/ethnicity N (%):** White: 11 (44.0) Black: 6 (24.0) Asian: 8 (32.0) **Comorbidities N (%):** Smoking status Never smoke: 23 (95.8) Former smoker: 1 (4.2) Current smoker: 0 (0) Missing: 1 **Inclusion criteria:** Age between 20 and 49 years, have at least one menstrual period in the past 3 months, variations of menstrual cycle lengths within 7 days, the average menstrual cycle length	**Device type/brand:** NR; participants were given menstrual products they preferred to use **Device material:** NR **Exposure details:** Use of tampons, pads, or panty liners No: 0 (0) Yes: 24 (100) Missing: 1 Use of tampons or pads during period Pad or liner only: 13 (59.1) Tampon only: 5 (22.7) Both tampon and pad: 4 (18.2) Missing: 2 Duration of menstrual bleeding (median, IQR): 5 (5 - 7) days Duration of heavy bleeding (median, IQR): 2 (2-3) days **Comparator:** NA **Method of analysis:** Urinary VOC concentrations were measured using gas chromatography-mass	**Safety outcomes:** NR **Biomarkers identified in human samples:** Effect estimates of associations between the use of menstrual products and specific gravity-adjusted VOC concentrations for tampons only reported as (β, 95% CI and p-value) with pads or liners only as the reference group: Hexane: 0.56 (-0.84, 2.00) log ng/g, p = 0.43 n-Nonane: -1.52 (-7.03, 3.98) log ng/g, p = 0.59 Hexanal: 1.28 (-0.71, 3.27) log ng/g, p = 0.21 Nonanal: -0.16 (-0.78, 0.46) log ng/g, p = 0.61 Benzene: -0.23 (-1.58, 1.12) log ng/g, p = 0.74 Toluene: -0.52 (-2.18, 1.14) log ng/g, p = 0.54 p-Isopropyltoluene: -0.06 (-1.32, 1.23) log ng/g, p = 0.93 2-Butanone: 1.58 (0.16, 3.00) log ng/g, p = 0.03 Methyl isobutyl ketone: 0.63 (0.03, 1.22) log ng/g, p = 0.04 *analyses controlled for race, study visits, background VOC exposure, and use of other FHPs. Women who used both tampons and pads/liners were not included in the analysis Median (IQR), [Max] VOC concentrations Hexane: 1.3 (0.5, 4.3) [491.9] ng/mL n-Nonane: 0.01 (<LOD, 0.05) [1.2] ng/mL Hexanal: 0.2 (0.1, 0.3) [0.9] ng/mL

Study details	Participants	Study Characteristics	Results
	of 21-40 days, and self-identified with one of the designated racial/ethnic groups (White, Black, Asian) **Exclusion criteria:** Currently pregnant, breastfeeding, or diagnosed by physicians with a vaginal infection, uterine fibroids, polycystic ovarian syndrome, or endometriosis in the past 12 months	spectroscopy. 98 target VOCs were measured. **Mean follow-up period, years:** The first-morning urine samples were collected four times across two menstrual cycles, including 7 days before the start of menstruation (visit 1), 3 days after the onset of period or the end of the heavy bleeding (visit 2), 7 days after the onset of period or the end of menstruation (visit 3), and 7 days after the end of the period (visit 4) **Endpoints assessed:** biomarkers identified in human samples	Nonanal: 0.1 (0.04, 0.2) [1.3] ng/mL Benzene:0.02 (<LOD, 0.04) [3.0] ng/mL Toluene: 0.07 (0.03, 0.2) [3.4], ng/mL p-Isopropyltoluene: 0.02 (<LOD, 0.06) [0.2] 2-Butanone: 2.0 (0.9, 4.2) [37.2] ng/mL Methyl isobutyl ketone: 0.1 (0.07, 0.3) [1.8] ng/mL **Biomarkers/laboratory outcomes found in the device:** NR **Study limitations:** Small cohort of women from the University of Michigan, and thus results may not be generalizable to the general population; the study excluded women with irregular menstrual cycles; the study did not recruit or engage women who did not use tampons or pads;the study failed to collect information on many other covariates, such as body weight; thus the findings need to be interpreted with caution; urine concentrations may not be the optimal biomarker.
Reference: Ding et al. 2020[12] **Study design:** Cross-sectional analysis of NHANES data **Type of study (bench/clinical):** Clinical **Purpose:** To evaluate whether the use of FHPs was associated with VOC exposures among reproductive-aged women in the US **Funding:** NIEHS-NIH (P30-ES017885), CDC (T42-OH008455) **Conflict of interest:** None	**Sample size:** 2,432; 851 (35%) reported tampon use **Mean age (SE):** 34.9 (0.3) **Race/ethnicity N (%):** White: 1,166 (48.0) Black: 511 (21.0) Mexican American: 547 (22.5) Other Hispanic: 107 (4.4) Other race/ethnicity: 101 (4.2) **Comorbidities:** BMI, kg/m^2 (mean, SD): White: 27.3 (0.3) Black: 31.2 (0.4) Mexican American: 29.2 (0.4) Other Hispanic: 29.1 (0.5)	**Device type/brand:** NR; participants answered a questionnaire about the use of FHP and douching practices. **Device material:** NR **Exposure details (use of tampon in the past month), %:** White: 53% Black: 36% Mexican American: 25% Other Hispanic: 29% Other race/ethnicity: 33% **Comparator:** Other FHPs were assessed (sanitary napkin, vaginal douche, feminine spray, feminine powder, wipes/towelettes, other products) **Method of analysis:** whole blood concentrations of VOCs	**Safety outcomes:** NR **Biomarkers identified in human samples:** Adjusted % change (95% CI) in VOC concentrations in tampons in the past month compared to never users: Bromodichloromethane, (n = 756): -6.8 (-26.0, 17.5) Chloroform, (n = 704): -9.5 (-28.5, 14.7) Dibromochloromethane, (n = 763): -6.0 (-25.8, 19.0) 1,4-Dichlorobenzene, (n = 758): -16.9 (-333, 3.5) Ethylbenzene, (n = 784): 5.7 (-7.2, 20.4) Toluene, (n = 822): 5.4 (-13.8, 29.0) m-/p-xylene, (n = 827): 9.8 (-2.4, 23.6) *models were adjusted for age at interview, race/ethnicity, educational attainment, income-to-poverty ratio, BMI, pregnancy status, and menopausal status **Biomarkers/laboratory outcomes found in the device:** NR **Study limitations:** The cross-sectional nature of the NHANES data, which cannot rule out the possibility of reverse causality; VOCs with detection rates <50% were excluded in

Study details	Participants	Study Characteristics	Results
	Other race/ethnicity: 25.8 (0.5) **Inclusion criteria:** Women aged 20-49 years with self-reported data on FHPs use **Exclusion criteria:** NR	measured by headspace solid-phase microextraction/gas chromatography/isotope dilution mass spectrometry **Mean follow-up period, years:** NA **Endpoints assessed:** biomarkers identified in human samples	the analyses, which limited the ability to evaluate some relationships; the FHP data were collected in 2001-2004, which may not reflect current feminine hygiene practices, and it is possible that the industry has changed the manufacturing processes and formulations since then; FHP data were collected through questionnaires, which are subject to recall bias and misclassification; the timing of feminine hygiene practices can also be influenced by sexual activity, vaginal symptoms, and the menstrual cycle; NHANES did not collect data on FHP use among Asian American or Indigenous women.
Reference: Gao et al. 2020[8] **Study design:** Assessment of EDCs in FHPs **Type of study (bench/clinical):** Bench **Purpose:** To elucidate the occurrence and profiles of phthalates, parabens, bisphenols, and TCC in FHP; determine the dermal exposure doses of the chemicals from the use of products, and evaluate the significance of FHPs as a source of EDC exposure in women **Funding:** NR **Conflict of interest:** None	**Sample size:** Tampons (n = 12) **Mean age (range):** NA **Race/ethnicity N (%):** NA **Comorbidities N (%):** NA **Inclusion criteria:** FHPs were purchased in several supermarkets in and around albany, New York, USA. Products were from 47 popular brands of varying prices that were widely marketed throughout the US and used by American women **Exclusion criteria:** NR	**Device type/brand:** NR **Device material:** Cotton: n = 4 Cotton, rayon, polyester, polypropylene, polyethylene: n = 3 Rayon, cotton fiber, polyester, polyethylene: n = 2 Rayon, polyester, polyethylene, polyester: n = 1 Avec fiber (plastic tampon): n = 2 **Exposure details (number of tampons/cycle):** NA **Comparator:** Pads, wipes, bacterial creams and solutions, deodorant sprays **Method of analysis:** Solvents used for extraction and instrumental analysis included methanol, hexane, methyl-*tert*-butyl-ether, dichloromethane, acetone, and water. Pthalates were determined using an Agilent Technologies 7890A gas	**Safety outcomes:** NR **Biomarkers identified in human samples:** NR **Biomarkers/laboratory outcomes found in the device:** Concentrations of phthalates (ng/g), reported as mean, median and range DMP: 412, 214, 141-1650 DEP: 192, 190, 127-262 DIBP: 128, 99.2, 57.9 - 326 DBP: 378, 125, 72.0 – 2,240 BBzP: < LOD DEHP: 744, 267, 64.1 – 4,680 DCHP: not detected DNHP: not detected DOP: not detected $\sum_9$ Phtalate: 1850, 1130, 621 – 6160 Concentrations of parabens (ng/g), reported as mean, median and range MeP: 18.2, 15.3, 0.01 – 5.85 EtP: 27.6, 25.2, 0.02 – 89.9 PrP: 2.01, 0.46, < LOD – 12.8 BuP: 0.06, < LOD – 0.48 BzP: < LOD HeP: < LOD $\sum_6$ Paraben: 47.9, 42.7, 0.04 – 162 Concentrations of bisphenols and TCC (ng/g), reported as mean, median and range

Study details	Participants	Study Characteristics	Results
		chromatography system coupled with an Agilent Technologies 5975C mass spectrometer. Parabens, bisphenols, and TCC were determined using a Shimadzu Prominence modular high-performance liquid chromatography system (Shimadzu Corporation, Kyoto, Japan) coupled with an API 3200 electrospray triple quadrupole mass spectrometer (ESI-MS/MS; Applied Biosystems, Foster City, CA). The daily exposure doses via dermal absorption were calculated using the equation: DED = C_1 x M_1 x N x A/BW Where DED is the daily exposure dose (µg/kg-bw/day), C_1: is the measured concentration of phthalates, parabens, bisphenols, and TCC; M_1 is the weight (g) of the the tampons; N is the number of tampons used per day; A is the transdermal absorption rate, and BW is the average body weight of women. **Mean follow-up period, years:** NA **Endpoints assessed:** Biomarkers/laboratory outcomes found in the device	BPF: 5.60, 4.82, < LOD – 15.4 BPA: 0.87, 0.70, < LOD – 2.46 BPP: < LOD BPS: 0.02, < LOD, < LOD – 0.22 BPZ: < LOD $\sum_6$Bisphenol: 6.49, 5.56, < LOD – 15.6 TCC: 0.05, < LOD, < LOD – 0.44 BPAP: not detected BPAF: not detected BPB: not detected Dermal absorption doses (ng/kg-bw/day) of phthalates, reported as median and maximum DMP: 4.940, 38.03 DEP: 4.384, 6.051 DIBP: 2.288, 7.518 DBP: 2.885, 51.67 BBzP: < 0.001, < 0.001 DEHP: 0.308, 5.400 Total: 1.309, 7.105 Dermal absorption doses (ng/kg-bw/day) of parabens, reported as median and maximum MeP: 0.176, 0.676 EtP: 0.291, 1.037 PrP: 0.005, 0.148 BuP: < 0.001, 0.006 BzP: < 0.001, < 0.001 HeP: < 0.001, < 0.001 Total: 0.493, 1.866 Dermal absorption doses (ng/kg-bw/day) of bisphenols and TCC, reported as median and maximum BPF: 0.056, 0.177 BPA: 0.008, 0.028 BPB: < 0.001, < 0.001 BPS: < 0.001, 0.003 BPZ: < 0.001, < 0.001 Total: 0.064, 0.180 TCC: < 0.001, < 0.001

Study details	Participants	Study Characteristics	Results
			Study limitations: The samples are limited to one geographic location and therefore representativeness of the samples for the entire country as well as for all feminine hygiene products may have been tempered; the calculated exposure doses involve uncertainties. Considering the high transdermal absorption properties of the vulvar skin and vaginal mucosa, values of 20% and 100% were used to estimate high exposure scenarios in this study, which may be an overestimate of the actual exposure doses. Furthermore, the transfer rates of phthalates, parabens, bisphenols and TCC from FHPs are not known; the types of feminine hygiene products analyzed in this study are not exhaustive; other potential EDCs that may be present in FHPs were not analyzed.
Reference: Lin et al. 2020[9] **Study design:** Analysis of VOCs present in FHPs **Type of study (bench/clinical):** Bench **Purpose:** To analyze the VOC composition in FHPs in the US market and to estimate the potential for health risks associated with their use **Funding:** NIEHS-NIH (grant P30ES017885) **Conflict of interest:** None	**Sample size:** n = 22 **Mean age (range):** NA **Race/ethnicity N (%):** NA **Comorbidities N (%):** NA **Inclusion criteria:** a broad range of FHPs that included popular brands and products from Statista.com and Amazon.com. Tampons selection was based on the " best sellers" list from Amazon.com. Bestselling products from several store brands and included at least one " organic" or "natural" labeled product of each type of FHP were also included. All products were purchased locally (Michigan) or online.	**Device type/brand:** n = 17 brands (NR); n = 5 store brands (NR); regular-sized **Device material:** Organic: n = 2 Non-organic: n =20 **Exposure details (number of tampons/cycle):** NA **Comparator:** feminine wash, pads, feminine wipe, feminine spray and powder, feminine moisturizer **Method of analysis:** analyses used a short-path automated thermal desorption system (ATD, Scientific Instrument Services, Inc., Ringoes, New Jersey, USA) coupled to a gas chromatography-mass spectrometer (GC-MS, Model 6890/5973, Agilent Technologies, Santa Clara, California, USA) equipped with	**Safety outcomes:** NR **Biomarkers identified in human samples:** NR **Biomarkers/laboratory outcomes found in the device:** Reported as median, mean (SD), range in ng/g Aldehydes: 52, 56 (31), 13 - 138 Alkanes: 28, 138 (506), 6.9 - 2402 Aromatics: 3.7, 5.0 (4.9), 0.9 - 23 Halohydrocarbons: 1.9, 2.4 (2.1), 0.1 – 7.2 Terpenes: 3.5, 67 (292), 0.5 - 1374 Ketones: 1.4, 3.5 (4.9), < MDL - 23 Esters: 0.4, 0.8 (1.0), < MDL – 3.1 Mean and median concentrations (ng/g) of VOC compared between store brand (no, n = 17/yes, n = 5) tampons Halohydrocarbon: NS (values NR) Terpenes: no = 5.3 (86), yes = 1.4 (1.5), p = 0.03 Butanal: no = 1.0 (0.9), yes = 2.8 (3.3), p = 0.03 Octanal: no = 3.4 (8.7), yes = 1.5 (2.0), p = 0.03 *p*-isopropyl toluene: no = 0.3 (1.5), yes = 0.1 (0.1), p = 0.03 Limonene: no = 5.0 (85), yes = 1.1 (1.5), p = 0.05 n-Decane: NS (values NR) Chloroform: no = 1.0 (1.6), yes = 1.8 (3.5), p = 0.08 Ethylbenzene: no = 0.1 (0.2), yes = 0.4 (0.4), p = 0.08

Study details	Participants	Study Characteristics	Results
	Exclusion criteria: NR	a cryotrap/focuser (-140C to focus, 250C to inject) **Mean follow-up period, years:** NA **Endpoints assessed:** biomarkers/laboratory outcomes found in the device	Mean and median concentrations (ng/g) of VOC compared between "organic" (no, n = 20/yes, n = 2) tampons Halohydrocarbon: no = 1.9 (2.6), yes = 0.3 (0.3), p = 0.05 Terpenes: NS (values NR) Butanal: NS (values NR) Octanal: NS (values NR) *p*-isopropyl toluene: NS (values NR) Limonene: NS (values NR) n-Decane: no = 2.3 (101), yes = 0.2 (0.2), p = 0.009 Chloroform: no = 1.4 (2.2), yes = < MDL, p = 0.08 Ethylbenzene: NS (values NR) **Study limitations:** The sample size was relatively small for some types of FHP; the assumed scenario, while conservative, may not accurately reflect all or typical situations; risks were estimated only for target VOCs (no quantification of non-target compounds, inorganic, semi-volatile, or microbiological constituents).
Reference: Singh et al. 2019[13] **Study design:** Prospective cohort (BioCycle study) **Type of study (bench/clinical):** Clinical **Purpose:** To examine the potential associations between tampon use and metal concentrations, and biomarkers of inflammation and oxidative stress among healthy women **Funding:** Intramural Research Program of the Eunice Kennedy Shiver National Institute of Child Health and Human Development, NIH (Contract number: HHSN2752000403394C,	**Sample size:** tampon users (n = 158), non-tampon users (n = 97), total (n = 259) **Mean age (SD):** Users: 27.87 (8.66) Non-users: 27.16 (7.73) **Race/ethnicity (%):** White: users 79.0, non-users 26.88 Black: users 8.55, non-users 39.78 Other: users 11.84, non-users 33.33 **Comorbidities (%):** Smokers: users 5.26, non-users 1.08 BMI (mean, SD)	**Device type/brand:** NR **Device material:** NR **Exposure details (number of tampons/cycle):** median 4 tampons/cycle (IQR: 3-5) **Comparator:** Non-tampon users **Method of analysis:** Oxidative stress and inflammation biomarker concentrations in blood samples **Mean follow-up period:** two menstrual cycles **Endpoints assessed:** Biomarkers identified in human samples	**Safety outcomes:** NR **Biomarkers identified in human samples:** Metal concentrations [µg/L], as GM (GSD) Cadmium: users: 0.26 (1.90), non-users: 0.33 (1.90) Mercury: users: 1.08 (2.75), non-users: 1.01 (2.47) Metal concentrations [µg/dL], as GM (GSD) Lead: users: 0.85 (1.53), non-users: 1.01 (1.62) Biomarker concentrations, as GM (GSD) TBARS [nmol/mL]: users: 0.85 (1.27), non-users: 0.85 (1.25) PON1A [µmol/min/L]: users: 113.12 (1.24), non-users: 111.39 (1.22) PON1P [µmol/min/L]: users: 179.35 (1.84), non-users: 212.90 (1.83) Isoprostane [pg/ml]: users: 47.80 (1.37), non-users: 46.11 (1.45) CRP [mg/L]: users: 1.32 (6.48), non-users: 3.17 (13.60)

Study details	Participants	Study Characteristics	Results
HHSN275201100002I, Task 1 HHSN27500001), and NIEHS (P30 ES000002, P30 ES009089, and R01 ES028805) **Conflict of interest:** None	Users: 23.91 (3.63), non-users: 24.43 (4.27) **Inclusion criteria:** Healthy, regularly menstruating women (who self-reported menstrual cycle lengths between 21 and 35 days for the past 6 months), aged 18 – 44 years, followed for 2 menstrual cycles **Exclusion criteria:** women who planned to or were actively trying to conceive, a self-reported BMI < 18 or > 35 kg/m^2 at baseline, not between the ages of 18-44 years, and histories of gynecologic or other chronic diseases.		Linear regression models to estimate the association between tampon use and metal exposure, oxidative stress and inflammation biomarkers, expressed as (exp(β) of the ratio of the expected GM for those who used tampons over those who did not, 95% CI Cadmium (µg/L): 0.94 (0.78, 1.14) Lead (µg/dL): 0.91 (0.80, 1.05) Mercury (µg/L): 1.24 (0.92, 1.67) TBARS (nmol/mL) Menses: 0.99 (0.94, 1.05) Early-follicular phase: 1.01 (0.95, 1.06) Menstruating week: 1.00 (0.95, 1.05) Cycle: 1.00 (0.95, 1.05) Cycle except menstruating week: 1.04 (0.99, 1.08) PON1A (µmol/min/L) Menses: 1.03 (0.99, 1.08) Early-follicular phase: 1.00 (0.96, 1.04) Menstruating week: 1.00 (0.96, 1.04) Cycle: 1.00 (0.97, 1.03) Cycle except menstruating week: 1.00 (0.97, 1.03) PON1P (µmol/min/L) Menses: 1.02 (0.91, 1.15) Early-follicular phase: 1.02 (0.91, 1.14) Menstruating week: 1.01 (0.91, 1.12) Cycle: 0.95 (0.89, 1.02) Cycle except menstruating week: 0.96 (0.90, 1.03) Isoprostane (pg/ml) Menses: 1.04 (0.95, 1.14) Early-follicular phase: 1.05 (0.96, 1.15) Menstruating week: 1.05 (0.96, 1.14) Cycle: 1.03 (0.96, 1.11) Cycle except menstruating week: 1.02 (0.95, 1.09)

Study details	Participants	Study Characteristics	Results
			CRP (mg/L) Menses: 1.06 (0.85, 1.32) Early-follicular phase: 0.93 (0.75, 1.16) Menstruating week: 0.98 (0.80, 1.20) Cycle: 0.94 (0.76, 1.15) Cycle except menstruating week: 0.90 (0.73, 1.11) *models were adjusted for age, BMI, smoking, education, race, parity, physical activity, birth control use and marital status. For mercury, the model was additionally adjusted for fish consumption **Biomarkers/laboratory outcomes found in the device:** NR **Study limitations:** The BioCycle study was designed to study oxidative stress and inflammation, metal exposure was not measured in the same way as the mechanistic biomarkers. The metals were measured from a single whole-blood sample collected approximately 16 days before the beginning of the first menstrual cycle during the study and no additional collection was obtained before the second menstrual cycle. This may not have accurately represented the levels of these metals when the women were using tampons in cycles one and two; no other tampon-relevant chemicals were measured (e.g., pesticides), so exposure measurement error can be an important source of bias in the study; tampon use was self-reported, therefore exposure measurement error is also likely; the sample size is small, limiting the power to detect statistically significant associations; results may not be generalizable because most of the participants were highly educated; possibility of residual confounding.
Reference: Branch et al. 2015[14] **Study design:** Cross-sectional **Type of study (bench/clinical):** Clinical **Purpose:** To evaluate whether vaginal douching and other	**Sample size:** Total sample: n = 739 White: n = 396 Black: n = 163 Mexican American: n = 180 **Age, n (%):**	**Device type/brand:** NR **Device material:** NR **Exposure details (tampon use in the past month, %):** White: 55 Black: 31 Mexican American: 22	**Safety outcomes:** NR **Biomarkers identified in human samples:** Associations of tampon use and phthalate metabolite concentrations (ng/ml), expressed as % change (95% CI) MEP Unadjusted (n = 739): -6.4 (-24.9, 16.6) Adjusted (n = 731): 6.1 (-16.0, 35.5)

Study details	Participants	Study Characteristics	Results
feminine hygiene products increase exposure to phthalates among US reproductive-aged women **Funding:** Pew Charitable Trusts, Passport Foundation, Forsythia Foundation, the Fred Gellert Family Foundation. And NIEHS-NIH (R00ES019881) **Conflict of interest:** None	20-29 White: 29 Black: 34 Mexican American: 42 30-39 White: 33 Black: 32 Mexican American: 32 40-49: White: 38 Black: 34 Mexican American: 26 **Race/ethnicity, N (%):** White: 396 (53.6) Black: 163 (22.0) Mexican American: 180 (24.4) **Comorbidities, (%):** BMI < 25 White: 44 Black: 24 Mexican American: 26 BMI 25 – 30 White: 27 Black: 25 Mexican American: 33 BMI ≥ 30 White: 29 Black: 52 Mexican American: 41 **Inclusion criteria:** Female participants aged 20 – 49 who had self-reported data on FHP use from NHANES surveys 2001-2002 and 2003-2004. Participants	**Comparator:** Other FHPs assessed included sanitary napkins, vaginal douche, feminine spray, feminine powder, wipes/towelettes **Method of analysis:** Spot urine samples; concentrations of phthalate metabolites were quantified using solid phase extraction-high performance liquid chromatography-isotope dilution-tandem mass spectrometry. **Mean follow-up period:** NA **Endpoints assessed:** Biomarkers identified in human samples	 MnBP Unadjusted (n = 739): 2.4 (-11.8, 18.9) Adjusted (n = 731): 4.1 (-11.0, 21.9) *the reference group is non-users of tampons. *MEP and MnBP were natural log-transformed *both models adjusted for urinary creatinine. Adjusted models additionally controlled for age, race/ethnicity, BMI, and educational attainment **Biomarkers/laboratory outcomes found in the device:** NR **Study limitations:** cross-sectional design precludes the ability to make any causal inferences about the direction of the associations; there may be residual confounding from unaccounted phthalate sources; no information on the chemical ingredients of the douches used by study participants; likely exposure misclassification since the study had only one single spot urine measurement and phthalates have a short-life in the human body.

Study details	Participants	Study Characteristics	Results
	with urinary measurements of MEP and MnBP **Exclusion criteria:** Participants who did not self-identify as non-Hispanic White, non-Hispanic Black, or Mexican American		
Reference: Gaudiani et al. 2011[15] **Study design:** Case series **Type of study (bench/clinical):** clinical **Purpose:** To report two cases of young women with severe anorexia nervosa reporting vaginal bleeding that persisted for months despite trials of topic and systemic conjugated estrogen therapy **Funding:** NR **Conflict of interest:** NR	**Sample size:** n = 2 **Age (years):** Case 1 & 2: 32 **Race/ethnicity:** Case 1 & 2: Caucasian **Comorbidities:** Case 1: history of anorexia nervosa since the age of 15 BMI: 10.7, representing 50% of ideal body weight Case 2: history of anorexia nervosa since 16 years, Crohn's disease, BMI of 14, representing 73% of ideal body weight **Inclusion criteria:** Patients with severe anorexia nervosa, both weighing less than 70% of ideal body weight and hospitalized in an acute medical center for complications of malnutrition and monitored refeeding, incidentally complained	**Device type/brand:** NR **Device material:** NR **Exposure details:** daily tampon use **Comparator:** NA **Method of analysis:** Pelvic ultrasound; pelvic exam **Mean follow-up period, years:** NA **Endpoints assessed:** Safety outcomes	**Safety outcomes:** Vaginal ulcerations: 2 In both cases, outpatient providers had presumed that months of daily vaginal bleeding were due to endometrial atrophy, but bleeding persisted despite varying doses of systemic hormonal therapies. Ultimately, the history of daily tampon use was elicited during both patient's inpatient hospitalizations, and a speculum and pelvic examination revealed traumatic vaginal ulcerations in the setting of atrophic vaginal mucosa. Cessation of tampon use and initiation of conjugated estrogen vaginal cream resolved the vaginal bleeding. **Biomarkers identified in human samples:** NR **Biomarkers/laboratory outcomes found in the device:** NR **Study limitations:** NR

Study details	Participants	Study Characteristics	Results
	of persistent vaginal bleeding. **Exclusion criteria:** NA		
Reference: Archer et al. 2005[10] **Study design:** Experimental; detection of dioxins **Type of study (bench/clinical):** Bench **Purpose:** To assess the level of dioxins in tampons, thus quantifying maximum dioxin exposure **Funding:** FDA Office of Women's Health **Conflict of interest:** NR	**Sample size:** NR **Mean age (range):** NA **Race/ethnicity N (%):** NA **Comorbidities N (%):** NA **Inclusion criteria:** Tampons of regular absorbency (2 lots) and of highest absorbency (2 lots), defined as 6-9g absorbency for regular and 12-15g absorbency for Superplus absorbency. **Exclusion criteria:** NR	**Device type/brand:** Seven brands (NR) **Device material:** Varying % in the composition of rayon-cotton (quantification NR) to 100% cotton (number of samples NR) **Exposure details (number of tampons/cycle):** NA **Comparator:** NA **Method of analysis:** Gas Chromatography/High Resolution Mass Spectrometry using a Micromass Autospec ultima high resolution mass spectrometer at 10,000 mass resolution **Mean follow-up period, years:** NA **Endpoints assessed:** Biomarkers/laboratory outcomes found in the device	**Safety outcomes:** NR **Biomarkers identified in human samples:** NR **Biomarkers/laboratory outcomes found in the device:** Most detected quantities were at or near detection limit values. (results presented in Figures) **Study limitations:** NR

Abbreviations: As: arsenic; Ba: barium; BBzP: butyl benzyl phthalate; BMI: body mass index; BPA: bisphenol A; BPB: bisphenol BBPAF: bisphenol AF; BPAP: bisphenol AP; BPF: bisphenol F; BPP: bisphenol P; BPS: bisphenol S; BPZ: bisphenol Z; BuP: butyl-paraben; BzP: benzyl-paraben; Ca: calcium; Cd: cadmium; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CMC: caboxymethyl cellulose; Co: cobalt; Cr: chromium; CRP: c-reactive protein; Cu: copper; DBP: dibutyl phthalate; DCHP: dicyclohexyl phthalate; DEP: diethyl phthalate; DEHP: di(2-ethylhexyl) phthalate; DIBP: di-iso-butyl phthalate; DMP: dimethyl phthalate; DNHP: di-n-hexyl phthalate; DOP: di-n-octyl phthalate; EDCs: endocrine-disrupting chemicals; EtP: ethyl-paraben; EU: Europe; Fe: iron; FHP: female hygiene product; GM: geometric mean; GSD: geometric standard deviation; HeP: heptyl-paraben; HIV: human immunodeficiency virus; Hg: mercury; HPV: human papilloma virus; IQR: interquartile range; LOD: limit of detection; MDL: method detection limit; MeP: methyl-paraben;MEP: mono-ethyl phthalate; Mn: manganese; MnBP: mono-n-butyl phthalate; NA: not applicable; NHANES: National Health and Nutrition Examination Survey; NHLBI: National Health, Lung and Blood Institute; Ni: nickel; NIEHS: National Institute of Environmental Health Sciences; NIH: National Institutes of Health; NIOSH: National Institute for Occupational Safety and Health; Pb: lead; PON1A: human serum paraoxonase 1 arylestarase; PON1P: human serum paraoxonase 1 paraoxonase; PrP: propyl- paraben; SD: standard deviation; Se: selenium; SE: standard error; Sr: strontium; TBARS: thiobarbituric acid reactive substances; TCC: triclocarban; UK: United Kingdom; US: United States; V: vanadium; VOC: volatile organic compounds; Zn: zinc;

Appendix C. Excluded Studies

Table C1. Excluded Studies

Reference	Reason for Exclusion
Albani et al. 2018[17]	OUS
Briancesco et al. 2018[18]	OUS
Brzezinski et al. 2004[19]	OUS
Burger et al. 2011[20]	OUS
Chase et al. 2010[21]	OUS
Chase et al. 2007[22]	OUS
Chiaruzzi et al. 2020[23]	OUS
Desmedt et al. 2020[24]	OUS
Farage et al. 2011[25]	Study design not of interest (book chapter)
Glick et al. 2016[26]	Clearly off topic or doesn't address any KQs
Harley et al. 2016[27]	Intervention not of interest (personal hygiene products did not include tampons)
Harlow et al. 2009[28]	Study design not of interest (validation of a self-reported questionnaire)
Heffernan et al. 2007[29]	Study design not of interest (not tampon)
Hochwalt et al. 2023[30]	Study design not of interest (Narrative review)
Jacquemond et al. 2018[31]	OUS
Jiménez-Díaz et al. 2016[32]	OUS
Kullberg et al. 2020[33]	Intervention not of interest (not a tampon; sanitary pad)
Marcelis et al. 2022[34]	OUS
Marroquin et al. 2024[4]	Other - SLR used as a source to identify primary studies
Mortensen et al. 2019[35]	Not English language
Nalini et al. 2024[36]	Intervention not of interest (not a tampon; foreign object)
Nicole et al. 2014[37]	Study design not of interest (narrative review)
North et al. 2011[38]	Intervention not of interest (not a tampon; vaginal cup)
Parsonnet et al. 2009[39]	Study design not of interest (editorial commentary)
Schlievert et al. 2007[40]	Intervention not of interest (the sample combined tampons and diaphragms)
Şedivý et al. 2008[41]	OUS
Tessandier et al. 2021[42]	OUS
Tessandier et al. 2023[43]	OUS
Upson et al. 2022[5]	Other - SLR used as a source to identify primary studies
Verhoeven et al. 2004[44]	OUS
Zhou et al. 2023[45]	OUS
Hochwalt et al. 2010[46]	Toxic shock syndrome
Strandberg et al., 2009[47]	Toxic shock syndrome
Hill et al., 2010[48]	Toxic shock syndrome
Hill et al., 2005[49]	Toxic shock syndrome

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