Environmental Science & Technology Letters

pubs.acs.org/journal/estlcu

Letter

Quaternary Ammonium Compounds in Paired Samples of Blood and Indoor Dust from the United States

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Cite This: *Environ. Sci. Technol. Lett.* 2024, 11, 1308−1313

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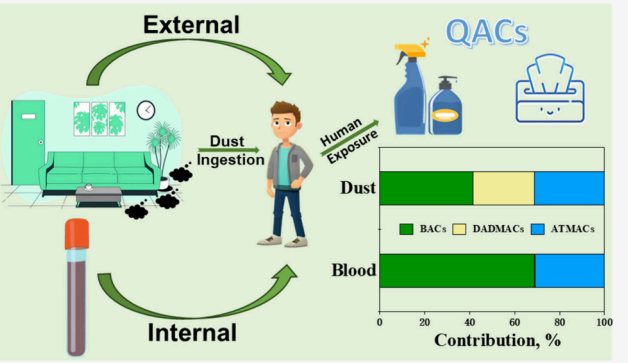
ABSTRACT: Previous studies of quaternary ammonium compounds (QACs) in the indoor environment have reported widespread presence of QAC in indoor dust. However, there are limited data on the contribution of dust ingestion to the QAC body burden. In this study, 18 QACs (6 benzylalkyldimethylammonium compounds [BACs], 6 dialkyldimethylammonium compounds [DADMACs], and 6 alkyltrimethylammonium compounds [ATMACs]) were analyzed in 81 paired samples of blood serum and dust collected in Indiana, United States. QACs were detected in 51−100% of the dust samples with the total QAC concentrations (∑QAC) ranging from 0.613 to 427 μg/g (median 56.9 μg/g). In contrast to dust samples, QACs were detected less frequently in blood serum with a median ∑QAC concentration of 3.66 ng/mL. The relative source contribution (RSC) of dust ingestion to serum levels was calculated using the PROTEX (PROduction-To-EXposure) model and was estimated as less than 1%, suggesting that hand-to-mouth contact, dietary intake, or inhalation could be more important exposure routes than dust ingestion. This is the first study to simultaneously measure QAC concentrations in indoor dust and blood, providing comprehensive assessment of the role of dust ingestion in QAC human exposure.



KEYWORDS: *quaternary ammonium compounds, disinfectants, indoor exposure, biomonitoring, exposure pathways, dust ingestion*

INTRODUCTION

Quaternary ammonium compounds (QACs) are synthetic chemicals used as antimicrobials, surfactants, preservatives, antistatic and softening agents, and dispersants in a variety of consumer products, including disinfectants, and personal care and pest control products. As a result of the common use of these products indoors, and especially due to the increased use of disinfectants during the COVID-19 pandemic, QACs are ubiquitous in the indoor environment,[1−3] posing widespread human exposure.[4,5] As such, QACs have been detected in indoor dust from homes in the United States, Europe, and China, with concentrations ranging from 13.1 to 58.9 μg/g.[1−3] In addition, QACs have been detected in human blood and feces and carboxylated and hydroxylated QAC metabolites have been found in urine.[4,6,7] However, biomonitoring of QACs is still in its infancy and the most suitable biomonitoring matrices that reflect the total body burden of the internal QAC exposure have not been identified. Moreover, it is unclear what are the most important exposure routes that contribute to the overall human exposure.

The relative source contribution (RSC) is a critical factor in establishing the importance of specific exposure routes/pathways of a chemical or agent of interest to ensure that total exposure does not exceed established health-protective reference doses (RfD) or threshold levels. The RSC can be estimated by directly evaluating all known human exposure routes, such as inhalation, ingestion, or dermal absorption; however, this approach may overlook potential contributions from less studied exposure pathways, such as mouthing-mediated ingestion (via hand-to-mouth contact).[8] Because the evaluation of all the possible exposure pathways can be a limiting step in certain cases, employing back-calculation from the internal dose using robust pharmacokinetic models is recommended to more accurately reflect aggregate exposure across multiple pathways.[8] For instance, a simple toxicokinetic model was utilized to estimate daily intake of per- and polyfluoroalkyl substance (PFAS) from drinking water based on serum measurements in the residents of Southeast Queensland, Australia, suggesting that the contribution to the overall PFAS body burden attributed to the consumption of drinking water was about 3%.[9] Using similar methods, the RSC of dust ingestion to the PFAS body burden of residents of Indiana, United States was estimated as 0.1−7%, which was

Received: September 11, 2024
Revised: October 19, 2024
Accepted: October 21, 2024
Published: November 6, 2024

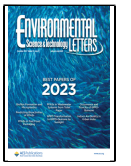


Table 1. Detection Frequencies (DF, %), Minimum (min), Maximum (max), and Median Concentrations of QACs in Dust (μg/g) and Serum (ng/mL) (n = 81 each) and Contribution (contr, %) of Each QAC to the ΣQAC Concentrations (based on median concentrations)[a]

	Dust					Serum				
	DF	Min	Max	Median	Contr	DF	Min	Max	Median	Contr
BACs										
C8-BAC	100	0.001	28.5	0.065	0.2	14	<MDL	0.04	<MDL	–
C10-BAC	99	<MDL	1.28	0.041	0.1	100	0.001	0.075	0.008	0.3
C12-BAC	100	0.056	91.6	6.97	17	100	0.058	6.92	0.857	29
C14-BAC	100	0.084	134	8.80	21	98	<MDL	9.70	0.951	32
C16-BAC	67	0.001	61.6	1.35	3.3	99	<MDL	4.32	0.243	8.1
C18-BAC	51	<MDL	33.8	0.030	0.1	19	<MDL	0.48	<MDL	–
∑BAC		**0.165**	**290**	**17.8**	**42**		**0.196**	**20.1**	**2.02**	**69**
DADMACs										
C8-DADMAC	99	<MDL	136	3.42	8.2	100	0.001	0.108	0.016	0.5
C10-DADMAC	100	0.076	61.8	7.86	19	10	<MDL	15.0	<MDL	–
C12-DADMAC	51	<MDL	0.893	0.003	0.01	25	<MDL	0.057	<MDL	–
C14-DADMAC	51	<MDL	0.099	0.001	0.01	28	<MDL	0.514	<MDL	–
C16-DADMAC	51	<MDL	7.47	0.006	0.01	14	<MDL	0.164	<MDL	–
C18-DADMAC	51	<MDL	82.3	0.009	0.02	6	<MDL	0.830	<MDL	–
∑DADMAC		**0.127**	**203**	**14.6**	**27**		**0.300**	**15.4**	**0.354**	**0.5**
ATMACs										
C8-ATMAC	96	<MDL	2.07	0.041	0.1	0	–	–	–	–
C10-ATMAC	100	0.021	181	6.13	15	38	<MDL	1.03	<MDL	–
C12-ATMAC	100	0.013	24.1	1.24	3.0	94	<MDL	2.04	0.047	1.6
C14-ATMAC	100	0.005	25.3	0.152	0.4	98	<MDL	2.89	0.609	20
C16-ATMAC	100	0.168	79.9	4.84	12	89	<MDL	4.53	0.250	8.4
C18-ATMAC	65	<MDL	31.8	0.548	1.3	75	<MDL	0.148	0.018	0.6
∑ATMAC		**0.250**	**204**	**16.6**	**31**		**0.136**	**5.89**	**0.998**	**31**
∑QAC		**0.613**	**427**	**56.9**			**0.817**	**30.2**	**3.66**	

[a]For all descriptive statistics, concentrations below the detection limits were substituted with method detection limit (MDL) values divided by 2.

generally lower than that from drinking water in that population (1.6−17.0%).[10]

PROTEX (PROduction-To-EXposure) is a comprehensive fate and exposure model that has been successfully applied to link exposure levels in the indoor environment with internal levels for polychlorinated biphenyls,[11,12] short-chain chlorinated paraffins,[13] as well as QACs.[14] This innovative model supports mechanistic simulations of human intake and uptake doses through multiple exposure pathways (e.g., mouthing-mediated ingestion [chemical-bound dust and chemical residuals], dermal absorption, inhalation, and dietary ingestion) and resulting concentrations in various bodily fluids (e.g., serum and urine).[14] The widespread presence of QACs in indoor dust underscores the importance of evaluating the contribution of dust ingestion as a potential exposure pathway to the overall exposure to these chemicals. Our previous research on QACs has shown the presence of of the three major QAC groups (BACs, DADMACs, and ATMACs) in indoor dust and in human serum, suggesting that dust ingestion may be a significant exposure pathway for QACs.[1,5] However, the lack of the paired samples of dust and serum in the latter studies has prevented us from estimating the contribution of dust ingestion to the body burden of QACs. In the current study, we collected matched samples of dust from households in Indiana, United States, and serum from the residents of these homes and analyzed these samples for a suite of 18 QACs that we have analyzed in our previous studies and that are commonly used in disinfectants and other consumer products (C8−C18-BACs, C8−C18-DADMACs, and C8−C18-ATMACs).[1,5,15] We used the PROTEX model to estimate the contribution of dust ingestion to the QAC internal body burden based on the concentration data from the matched dust-blood samples. This study combines environmental and biological monitoring with advanced modeling and provides a robust framework for understanding risks associated with exposure to QACs via dust ingestion.

METHODS AND MATERIALS

Sample Collection and Analysis. Paired dust and blood samples were collected in Indiana, United States from August-December 2020. A total of 81 participants were enrolled from the Person to Person (P2P) Health Interview Study cohort (https://precisionhealth.iu.edu/get-involved/person-to-person.html). The study was approved by the Indiana University Institutional Review Board and all participants provided their consent after being fully informed about the study. Dust and serum samples were obtained from each participant on the same day and kept in a cooler with ice packs before being delivered to the laboratory at the end of the day. Upon arrival to the laboratory at Indiana University, the serum was separated by centrifugation. All samples were stored at −20 °C until analysis. Demographic, behavioral, and product use information was collected from each participant using questionnaires. The dust and serum samples were processed and analyzed using methods previously established in our laboratory.[2,5] The complete analyte list, details of sample collection, treatment and analysis, quality control and assurance measures, population characteristics and exposure modeling using PROTEX are provided in the Supporting Information.

https://doi.org/10.1021/acs.estlett.4c00757
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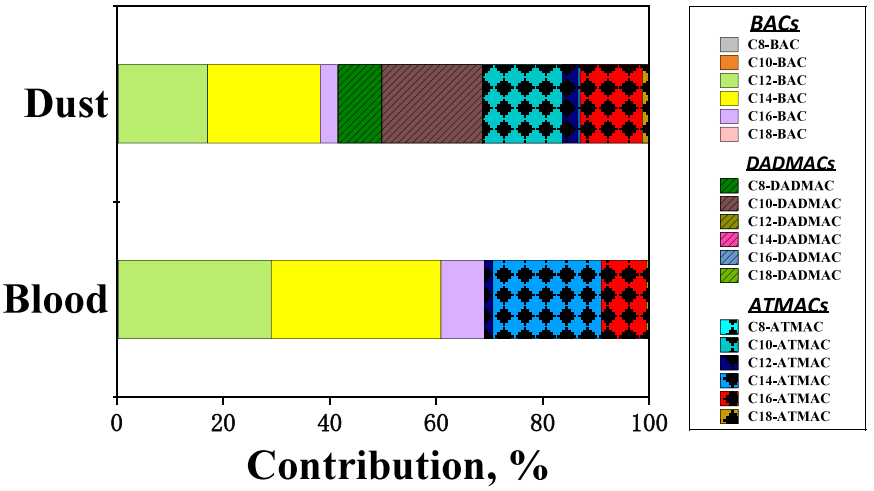

Figure 1. Percent contributions (calculated based on median concentrations) of the individual QACs to the ∑QAC concentrations in dust and blood serum.

Data Analysis. Serum concentration predictions ($C_{dust\ to\ serum}$) were estimated utilizing the PROTEX model as described in the Supporting Information. Descriptive statistics and regression analyses were performed in Minitab 19 and Microsoft Excel 2016. Plots were generated in Sigma Plot 13. A Mann−Whitney test was used for the comparison of the logarithmically transformed QAC concentrations in dust and blood. Spearman correlation analyses were applied to examine the relationships between the logarithmically transformed dust and serum concentrations. The nondetects were substituted with MDL/2 for all analyses. The significance level was set at $p < 0.05$.

RESULTS AND DISCUSSION

Dust Concentrations. QACs were detected in 51−100% of the dust samples at μg/g concentration levels (Table 1). The total QAC concentration (∑QAC, the sum of 18 QAC concentrations) varied from 0.613 to 427 μg/g (median 56.9 μg/g). The ∑QAC concentrations measured in these samples were comparable to those detected in dust samples collected from a different cohort in Indiana in June 2020 (median 58.9 μg/g).[1] However, QAC levels found in the present study were about 4 times higher than those in dust from homes in Belgium (median 14.7 μg/g),[3] which may be due to the differences in QAC use between the two countries. The European Union has banned the use of BACs in hand soap and body washes and is currently evaluating the safety of several QACs, including C12−C18 BACs and C12−C14 DADMACs in cleaning products and preservatives, while in the United States QACs are approved for use in personal care, disinfecting, and cleaning products as well as in other consumer products.[1,3] C12- and C14-BACs, C10-DADMAC, and C10- and C16-ATMACs were the most abundant QACs, and all together constituted more than 80% of the ∑QAC concentrations. Overall, BACs were the predominant QAC group detected in dust samples (median ∑BAC concentration [the sum of 6 BACs] 17.8 μg/g) and contributed 42% to the ∑QAC concentrations. DADMACs and ATMACs were found at slightly lower concentrations (median ∑DADMAC [the sum of 6 DADMACs] 14.6 μg/g and ∑ATMAC [the sum of 6 ATMACs] 16.6 μg/g) and constituted 27 and 31% of the ∑QAC concentrations, respectively. Overall, the contributions of the individual QAC groups to the ΣQAC concentrations in this study were similar to those found in our previous work (48, 30 and 22% for BACs, DADMACs, and ATMACs, respectively) and to that found in dust from Belgium (46, 27, 27% for BACs, DADMACs, and ATMACs, respectively).[3] These similar patterns found in different studies suggest that QAC contamination in the indoor environment may come from similar sources, such as the use of disinfecting products, as demonstrated in previous studies.[1−3]

Serum Concentrations. All QACs, except C8-ATMAC, were detected in serum samples and 9 QACs were found in more than 50% of the samples (Table 1). The serum ∑QAC concentrations ranged from 0.817 to 30.2 ng/mL with a median concentration of 3.66 ng/mL. These concentrations were comparable to those found in serum samples from two different cohorts in Indiana, United States (medians 3.41 and 6.04 ng/mL).[5] BACs were the most abundant QAC group measured in serum at a median ∑BAC concentration of 2.02 ng/mL (69% of the ∑QAC concentrations), followed by ATMACs (median ∑ATMAC concentration 0.998 ng/mL; 31% of the ∑QAC concentrations). DADMACS were found at low levels and constituted only 0.5% of the ∑QAC concentrations (median ∑DADMAC 0.354 ng/mL). The distribution of the three QAC groups in serum was different from that in dust (42, 27 and 31% vs 69, 0.50 and 31% for BACs, DADMACs and ATMACs, respectively; Figure 1). This distribution in serum was consistent with our previous findings, with DADMACs constituting a small portion of the serum ∑QAC concentrations.[5] Previous toxicokinetic animal studies have reported that DADMACs excrete unabsorbed in feces within 48 h after ingestion, providing a possible explanation for the low DADMAC levels in serum.[16] C12- and C14-BACs and C14-ATMAC constituted 20−32% of the serum ∑QAC concentrations. Our previous research demonstrated that C12- and C14-QACs tend to accumulate in blood due to their strong binding affinities to serum proteins and relatively slower metabolism compared to other QAC homologues.[5]

Dust Ingestion RSCs. The calculated RSCs of dust ingestion to the QAC body burden using the PROTEX model are shown in Table 2.

The median dust ingestion RSCs varied from 0.001 to 0.89% with the highest RSC estimated for C8-DADMAC (0.89%), followed by C12-ATMAC (0.15%) and C18-ATMAC

https://doi.org/10.1021/acs.estlett.4c00757
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Table 2. Calculated Median Relative Source Contributions (RSC, %) of Dust Ingestion to the QAC Body Burden[a]

QAC	RSC
C10-BAC	0.02
C12-BAC	0.03
C14-BAC	0.03
C16-BAC	0.02
C8-DADMAC	0.89
C12-ATMAC	0.15
C14-ATMAC	0.001
C16-ATMAC	0.07
C18-ATMAC	0.10

[a]Only QACs with detection frequencies of more than 50% in both dust and blood are included.

(0.10%). BACs generally had lower RSCs with the highest values found for C12 and C14-BACs (0.03%). Overall, more than 99% of the QAC body burden could not be explained through these RSC estimations, indicating that other exposure pathways contribute more significantly to the overall QAC body burden compared to dust ingestion. One possible reason is that QAC-containing products (e.g., disinfecting sprays and wipes) are directly applied to indoor surfaces and left to dry. Over time, water and other volatile components evaporate, leaving behind a layer of QACs as surface residue. Since this layer consists of a high concentration of pure-phase QACs, its contribution to human exposure through surface-to-hand and hand-to-mouth contact may be orders of magnitude higher than that of dust-bound QACs.[17] In addition, QACs are widely used as disinfectants in food preservation and processing, and they have been detected in milk,[18] fruits, and cheese[19] with concentrations up to 17.9 mg/kg suggesting food consumption could be an important exposure pathway for QACs. Moreover, our previous study found that indoor air QAC concentrations ranged from 0.10 to 4360 pg/m^3 with ATMACs found as the most abundant QAC group in air comprising 78% of the ∑QAC concentrations, indicating that inhalation could be an important exposure route for more volatile QACs.[5] A recent study also reported hand to mouth contact as the dominant exposure pathway (>90% of the total exposure) postapplication of the QAC-based products, and dermal absorption was suggested as a significant exposure pathway for BACs.[14]

Concentration Correlations. No significant associations were found between the individual or the total QAC concentrations in paired dust and blood samples. As described above, the estimated RSCs for dust ingestion account for less than 1% of the QAC body burden, which may explain the lack of significant associations between the blood and dust concentrations. Moreover, these results may also be due to the low bioavailability of QACs. Recent findings show that QACs are mainly excreted via feces.[20] Although a fraction of QACs are absorbed as a result of ingestion, they preferentially excrete into bile and undergo a rapid clearance from the body.[15] Intravenous administration of QACs to bile-cannulated rats shows that QACs with a molecular weight (MW) of over 200 are mainly excreted from the liver to bile.[21,22] Since most of the commercially used QACs have MWs above 300, it is possible that these QACs are predominantly excreted to bile and then are eliminated in feces.[16] In a recent study, QACs, notably in their unmetabolized form, were detected in human feces, indicating that biliary excretion is the primary pathway for the elimination of these chemicals.[4] Moreover, previous studies found that QACs undergo fast hepatic metabolism and form carboxylated and hydroxylated metabolites that can be detected in urine.[6,7,23] There are very limited data on the toxicokinetics and biomonitoring of QACs, which warrants more research directed at determining the most suitable biomonitoring matrix reflecting the total QAC exposure in humans. In the meantime, analyses of serum, urine, and feces could complement each other in providing information on bioaccumulation of QACs and their excretion pathways.

Correlations with Demographic and Behavioral Characteristics. More than half of the participants in this study indicated that they regularly used QAC-containing disinfecting products in their homes (Table S1). Forty-one percent of these reported disinfecting more than once a week, among which 78% used disinfecting sprays, while the rest used wipes. Overall, the median ∑QAC concentration in dust from the households that used QAC-containing disinfectants was significantly higher than that in homes that used disinfectants without QACs or did not disinfect at all ($p < 0.05$ [Mann−Whitney test]; medians 65.5 vs 48.3 ng/mL, respectively; Figure S1A). Homes that were more frequently disinfected (more than once per week) had significantly higher ∑QAC dust concentrations than those that were disinfected less often (less than once per week) ($p < 0.05$ [Mann−Whitney test]; medians 89.1 vs 62.1 μg/g, respectively; Figure S1B). Moreover, the median ∑QAC concentration in dust from homes that used disinfecting sprays was higher compared to those that used wipes, although this difference was not statistically significant (Mann−Whitney test; 70.0 vs 51.6 μg/g, respectively; Figure S1C). No significant relationship was found between the serum QAC concentrations and demographic and behavioral characteristics.

Strengths and Limitations. This study has several limitations. First, the study has a limited sample size collected from a limited geographic area, which may not be representative of the general population of the United States. Second, the study primarily focuses on dust ingestion, whereas other significant postapplication exposure pathways like dietary intake and dermal contact, as well as in-application exposure pathways like, inhalation during spraying cleaning products, have been shown as potential pathways of human exposure to QACs. Thus, exposure to QACs may be underestimated in this study. Other potential confounding factors (e.g., ventilation and house size) that might influence dust concentrations of QACs were not considered.[2] Only blood samples were collected and urine and feces samples that could be more suitable biomonitoring matrices for QAC exposure were not available.[4] Finally, there are uncertainties associated with algorithms and parametrization of the PROTEX model. While the physicochemical properties of neutral hydrophobic organic chemicals are well characterized, this knowledge is limited for the less studied ionizable and polar organic chemicals, such as QACs, that are highly hydrophilic and permanently charged. The differences in the behavior of these chemicals in terms of their interactions with polar reservoirs in indoor environments and with charged proteins and phospholipids in the human body remain unclear. In addition, our current modeling efforts relied on physiological and behavioral parameters representative of central tendency values for the general American population, which may not fully reflect the specific characteristics of the sampled population in our study. Nonetheless, this is the first study to examine the relationships among multiple QACs in paired dust and blood serum samples. Our findings

https://doi.org/10.1021/acs.estlett.4c00757
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indicate that QACs are ubiquitous in the indoor environment and the levels in indoor dust are dependent on product use. Yet the lack of correlation between the concentrations of QACs in dust and product use with blood levels suggests that factors and pathways other than dust ingestion may influence the body burden of these compounds. This study warrants further research on exposure pathways, toxicokinetics and biomonitoring of QACs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.4c00757.

Details of target analytes, sample collection, treatment, and analysis, quality assurance and control measures, demographic and behavioral characteristics, PROTEX model input, data analysis, and effect of disinfectant use on QAC concentrations in dust (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Indiana University, the Indiana Clinical and Translational Sciences Institute, and the National Natural Science Foundation of China (22206071) for funding this project. We also thank Indiana University Center for Survey Research and the Person to Person Health Interview Study for their support in recruitment and sample collection. We are grateful to the study participants for donating their time and samples.

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https://doi.org/10.1021/acs.estlett.4c00757
Environ. Sci. Technol. Lett. 2024, 11, 1308−1313