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# Mutagenic and Carcinogenic Hazards of Settled House Dust II: Salmonella Mutagenicity

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Settled house dust (SHD) is a complex mixture that contains numerous chemical contaminants. Very little is known about the hazards of SHD as compared to other complex matrices such as air and soil. In this study, the mutagenic hazards associated with the extracts of sieved dust from 52 homes were examined using the Salmonella Mutagenicity Test. All of the SHD samples displayed mutagenic activity and the mean mutagenic potencies ranged from 2300 to 23 600 revertants per gram. Testing with various *Salmonella* strains revealed a predominance of frameshift mutagens in the dust samples. Analyses showed that polycyclic aromatic hydrocarbons (PAHs) were likely responsible for a quarter of the mutagenic activity of the SHD samples. In an effort to identify factors that influenced dust mutagenicity, the relationships between SHD mutagenicity and household activities were investigated. Mutagenicity was positively correlated with parameters such as the time since last vacuuming ($r^2 = 0.11$, $p < 0.05$) and the number of people living in the home ($r^2 = 0.11$–$0.43$, $p < 0.05$). However, the causative factors responsible for these relationships remain unclear.

## Introduction

Settled house dust (SHD) is a heterogeneous and complex mixture made up of biological derivatives, fibers, minerals, and deposited aerosols. In addition, numerous chemical contaminants are known to adhere to SHD particles (*1*–*6*). Although it is generally acknowledged that many chemical pollutants can be associated with SHD, the hazards (i.e., toxicity) associated with dust−contaminant mixtures are not well understood, and few researchers have attempted to characterize the hazards posed by contaminants in SHD as compared to other matrices such as air, water, or food.

Understanding the hazards posed by the complex matrix of SHD is important for the protection of human health and, in particular, the health of those vulnerable individuals who are the most exposed. Preschool children can be exposed to SHD and its associated contaminant load by their close proximity to the floor, frequent hand-to-mouth behavior, and the accidental ingestion of dust particles that have adhered to food, toys, or skin (*7*). It is estimated that young children ingest between 10 and 100 mg of dust per day (*8*–*10*), in comparison with adults who ingest an estimated 0.56 mg per day (*8*). A small percentage of children are also known to exhibit pica behavior, which involves the intentional eating of nonfood items. These children may ingest up to 10 g of soil and dust per day (*11*). In addition, children may also be more vulnerable to the adverse effects of exposure to dust−contaminant mixtures because of the immature state of their organs, nervous system, and immune system (*12*).

One of the end points that can be used to assess and track the hazards posed by SHD is mutagenic activity. Preliminary data indicates that SHD is mutagenic (*13*); however, the extent of the mutagenicity and the nature of the mutagens in SHD are poorly understood and largely unknown. Identifying the hazardous components in SHD that can pose a risk to children is of significant value because contaminant control or containment and risk reduction requires knowledge of the identity of the putative toxicants.

It is possible that polycyclic aromatic hydrocarbons (PAHs) and related polycyclic aromatic compounds (PACs) (i.e., nitroarenes and aromatic amines) may be responsible for a portion of the mutagenic activity of SHD. As products of combustion, PAHs are ubiquitous in the environment and regularly occur in a variety of complex environmental matrices (e.g., soil, airborne particulates) (*14*). Many PAHs are potent mutagens (*15*), and a variety of PAHs have been detected in SHD samples (see Maertens et al. (*16*) for a review).

This work, which is the second in a pair of publications that examine the mutagenic activity and carcinogenic hazards of SHD, employs the Salmonella Mutagenicity Test to evaluate the mutagenic activity of SHD samples collected from homes in Ottawa, Canada. The concentrations of PAHs in the SHD samples were assessed (*17*), and the extent to which these PAHs contributed to mutagenic activity of the SHD samples was evaluated. In addition, relationships between household characteristics (e.g., smoking, cooking activities, cleaning habits) and dust mutagenicity were examined in an attempt to identify factors that influence dust mutagenicity.

## Experimental Section

**Study Design and Dust Sample Collection.** Dust samples were collected between November 2002 and March 2003 from homes located in Ottawa, Canada. A two-stage stratified random sampling process was used to select homes that were representative of both urban and suburban locations within the city. A description of the sampling design is provided elsewhere (*18*). Vacuum cleaner bags were collected from 75 participating homes. The bags were removed from the vacuum cleaner, placed in zip-seal plastic bags (Fisher Scientific, Ottawa, Canada), and transported to the laboratory where they were stored at −20 °C. Of the 75 samples collected, 52 samples contained sufficient dust for mutagenicity testing.

**Sample Preparation, Extraction, and Chemical Analyses.** A description of the preparation, extraction, and chemical analyses of the dust samples is provided in our companion manuscript (*17*). Briefly, 3 g of sieved dust sample (<150$\mu$m) was extracted with dichloromethane/hexane (1:1) via accelerated solvent extraction. High molecular weight compounds were then removed from the extracts using gel permeation chromatography. Eluted samples were reduced under nitrogen to 0.5 mL and then brought up to 2 mL in dimethylsulfoxide (DMSO).

**Mutagenicity Testing.** The Salmonella Mutagenicity Test was carried out according to the plate incorporation test methods described in Maron and Ames (*19*) and Mortelmans and Zeiger (*20*). Briefly, the dust extracts were combined with the *Salmonella* tester strain, a metabolic activation mixture (when required), and molten agar in a test tube. The contents were vortexed briefly, poured onto a glucose

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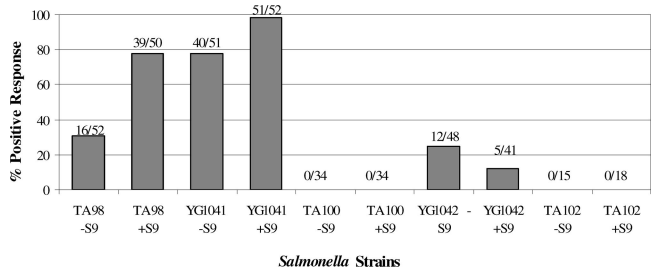


**FIGURE 1. Frequency distribution of the mutagenic responses to SHD extracts. The values above the bars indicate the number of positive responses as a fraction of the total tested.**

minimal agar plate, and allowed to solidify. The plates were inverted and incubated at 37 °C for 72 h. Following incubation, the number of revertant colonies on each plate was scored using a Protocol RGB Colony Counter (Synbiosis, Frederick, MD). Minor modifications to the published methods included the addition of histidine and biotin to the bottom agar, as opposed to the top agar, and using nutrient agar for the master plates.

Five strains of *Salmonella typhimurium* were used to test the dust samples. TA98 was used to detect frameshift mutations, whereas TA100 was used to detect base pair mutations. TA102, a *Salmonella* strain that is particularly sensitive to oxidative damage, is primarily reverted by small in-frame deletions and base-substitutions at an AT-rich site (*21–24*). In addition to these standard tester strains, mutagenicity assessments included newer metabolically enhanced strains based on TA98 and TA100. These strains, denoted YG1041 and YG1042, respectively, overexpress the *Salmonella* classical nitroreductase and *O*-acetyl transferase and show enhanced sensitivity to nitroarenes and aromatic amines (*25*). TA98, TA100, and TA102 were either purchased from Moltox Inc. (Boone, NC) or donated by Dr. Iain Lambert (Carleton University, Ottawa, Canada). YG1041 and YG1042 were donated by Dr. Takehiko Nohmi (National Institute of Health Sciences, Tokyo, Japan).

Positive controls consisted of 2-aminoanthracene (CAS# 613-13-8), mitomycin C (CAS# 50-07-7), 2-nitrofluorene (CAS# 607-57-8), daunomycin (CAS# 20830-81-3), and methyl methanesulfonate (CAS# 66-27-3) (Moltox Inc., Boone, NC). Dimethyl sulfoxide (DMSO) was used as the negative (solvent) control. Five concentrations of each dust extract, ranging from 0.5 to 50 mg equivalent of dust per plate, were tested with each *Salmonella* strain. Each dose was tested in triplicate. All dust extract samples were tested with and without a metabolic activation mixture. The metabolic activation mixture consisted of 2% v/v microsomal salt solution, 50% v/v 0.2 M phosphate buffer (pH 7.4), and 5% v/v Aroclor 1254-induced Sprague–Dawley rat liver S9 (protein levels 35.7−43.5 mg $mL^{-1}$, Moltox Inc.). Experiments were replicated only for those samples demonstrating equivocal responses.

Test results were considered to be positive if a dose-related increase in the number of revertants was observed, and the number of revertants was at least double the background for at least two consecutive test concentrations. The mutagenic potency of each sample was calculated from the initial slope of the linear portion of the dose–response curve using least-squares linear regression analyses.

**Statistical Analyses.** All analyses were performed using the SAS System software, version 8.2, for Windows (*26*). Data analyses were conducted using three sets of data: the mutagenic potency data, the PAH concentration data (*17*), and the homeowner survey data. Descriptive statistics (e.g., sample size, minimum, maximum, mean) were calculated for each of these data sets individually. Ordinary least-squares linear regression, Pearson correlations, and one-way analysis of variance (ANOVA) were employed to investigate empirical relationships between mutagenic activity and variables related to dust contamination and home characteristics.

To equalize the variance across the range of observations, all mutagenic potency and PAH concentration data were log transformed prior to the data analyses. Similarly, the data for two variables contained in the homeowner survey (vacuum frequency and the number of people living in the house) were log transformed. The Shapiro−Wilk statistic and inspection of normal probability plots were used to assess normality and, by extension, the constant variance of the residuals. Significant outliers were identified by calculation of the studentized deleted residual for each residual error value (*27*). For data analysis purposes, half of the method detection limit was substituted for observations where PAH concentrations were below detection (*28, 29*).

## Results and Discussion

**Mutagenicity Testing of the Whole Dust Extracts.** All of the SHD extracts tested in this study elicited a significant mutagenic response on at least one of the *Salmonella* strains. The number of extracts that tested positive with each strain is shown in Figure 1 as a percentage of the total number of extracts tested. Positive responses were more frequently observed with the frameshift mutation strains (i.e., TA98 and YG1041), as opposed to the base pair mutation strains (i.e., TA100 and YG1042). The highest number of positive responses was observed using YG1041, with all but one extract testing positive when metabolic activation was added. No positive responses were obtained with TA102, suggesting that the samples do not contain oxidative mutagens that induce mutations at the AT-rich *hisG428* allele. Consequently, TA102 testing was discontinued after completing the assessments of approximately one-third of the samples. Similarly, none of the dust elicited a positive response with the base pair substitution detecting strain TA100. Although no significant positives were obtained with TA100, a number of dust extracts did show some evidence of a weak dose–response at higher concentrations. However, at higher concentrations many of the samples also displayed evidence of toxic effects (thinning of background lawn and pinpoint nonrevertant colonies). These results may indicate that base pair mutagens were present in the samples but only at low concentrations.

The number of positive results observed with TA98 can be compared to that observed in a study by Roberts et al. that examined the TA98 mutagenicity of SHD extracts in DMSO (*13*). Thirty-four percent of the samples in that study tested positive on TA98 without S9, and 19% tested positive with S9. In comparison, the results obtained in current study shows a similar percentage of samples (i.e., 31%) that tested positive without S9, whereas a much larger percentage (78%) tested positive with S9. The higher response in the present study may have resulted from an additional clean up step that removed high molecular weight compounds that can interfere with the efficacy of the test system (*30, 31*).

A summary of the mutagenic potencies of each dust sample that elicited a positive is shown in Table 1. The TA98 mutagenic potency of the dust samples ranged from 1620

**TABLE 1. Minimum, Maximum, and Mean *Salmonella* Mutagenic Potencies (Revertants $g^{-1}$) of SHD Extracts**

| strain | metabolic activation | percent positive[a] | minimum | maximum | arithmetic mean | SEM[b] | geometric mean |
|---|---|---|---|---|---|---|---|
| TA98 | +S9 | 78 | 1620 | 14 452 | 4319 | 427 | 3768 |
| | −S9 | 31 | 780 | 43 283 | 5099 | 2657 | 2293 |
| YG1041 | +S9 | 98 | 2622 | 37 965 | 15 408 | 1203 | 13 268 |
| | −S9 | 78 | 1287 | 188 429 | 11 430 | 4803 | 5132 |
| YG1042 | +S9 | 12 | 10 390 | 55 624 | 27 264 | 7587 | 23 593 |
| | −S9 | 25 | 1922 | 16 300 | 8429 | 1333 | 7156 |

[a] Percentage of samples tested that were considered to be mutagenic. [b] Standard error of the arithmetic mean.

to14 452 revertants $g^{-1}$ with S9 and 780 to 43 283 revertants $g^{-1}$ without S9. In comparison, although minimum potencies were similar, much lower maximum potencies were obtained in the Roberts et al. study. Their values ranged from 1340 to 4 180 revertants $g^{-1}$ with S9 and 1090 to 6570 revertants $g^{-1}$ without S9. This could indicate a higher concentration of mutagens or more potent mutagens in the extracts evaluated in the present study. Alternatively, the difference in mutagenicity may have resulted from the different extraction techniques used. Roberts et al. extracted their samples by sonication using a technique that was "designed to allow consistent comparisons between samples rather than exhaustive extraction of mutagens". It is possible that the ASE extraction used in the present study was a more effective technique for extracting mutagens and resulted in higher potency levels.

In addition to the standard tester strains such as TA98 and TA100, this study employed the metabolically enhanced YG strains. These strains tended to show a more frequent positive response, and for YG1041, a response that is approximately 4–5-fold more potent than that obtained for TA98. These results suggest the presence of aromatic amines, nitroarenes, or both in the samples. Both nitroarenes and aromatic amines are ubiquitous environmental contaminants that are known to yield strong positive responses in the Salmonella Mutagenicity Test (*32, 33*). Moreover, nitroarenes elicit extremely strong responses on the metabolically enhanced YG strains without S9, and aromatic amines elicit strong responses in the presence of S9 activation (*25*). Although nitroarenes and aromatic amines can act as either frameshift or base pair mutagens (*34, 35*), in this study, the highest number of positive responses was seen with the frameshift detecting strain YG1041. This frameshift activity suggests the presence of heterocyclic amines which tend to show a stronger response on frameshift strains in comparison with base pair strains (*36, 37*). Heterocyclic amines, such as those that have been associated with high-temperature cooking of meat (e.g., PhIP, IQ, etc.), are known to be potent S9-activated frameshift mutagens (*38*).

Although the highest frequency of positive mutagenic responses was seen with YG1041 +S9, some of the most potent responses were observed in the few SHD extracts that tested positive with YG1042 +S9. This suggests the presence of hitherto unknown compounds that elicit base pair mutations (*39, 40*). However, the literature on the base pair mutagenicity of aromatic amines is sparse, and it is a reasonable assumption that the observed response may be elicited by a different class of S9-activated mutagens whose activity is enhanced by the YG strain enzymes nitroreductase and *O*-acetyl transferase. Although there is a paucity of information on the mutagenic activity of other polycyclic aromatic compounds, several researchers have demonstrated that some *O*-heterocyclics (e.g., *2H*-1-benzopyran-2-one) and *S*-heterocyclics (e.g., benzo[*b*]phenanthro[*2,3-d*]thiophene) are S9-activated base-pair mutagens (*41, 42*). Nevertheless, at the present time there is not enough information regarding the effect of nitroreductase and *O*-acetyl transferase on the activity of *O*- and *S*-heterocyclic compounds.

**TABLE 2. Published *Salmonella* Mutagenic Potency for Nine PAHs**

| PAH | TA98 +S9 mutagenic potency (revertants $\mu g^{-1}$) | ref |
|---|---|---|
| phenanthrene | 1.38 | *45* |
| pyrene | 8.32 | *46* |
| benz[*a*]anthracene | 56.0 | *47* |
| chrysene | 0.516 | *45* |
| benzo[*b*]fluoranthene | 61.0 | *48* |
| benzo[*k*]fluoranthene | 59.0 | *48* |
| benzo[*a*]pyrene | 488 | *45* |
| benzo[*g,h,i*]perylene | 7.52 | *45* |
| dibenz[*a,h*]anthracene | 39.0 | *48* |

**Empirical Analyses of Settled House Dust Mutagenic Activity, PAH Contamination, and Household Attributes.** *Empirical Relationships Between Dust Mutagenicity and PAH Content.* The companion paper in this issue summarizes the PAH contamination of the SHD samples (i.e., Table 2) (*17*). The sum of the 13 PAHs targeted for analyses, referred to hereafter as total PAHs, ranged between 1.5 and 325 $\mu g\ g^{-1}$ with a geometric mean of 12.9 $\mu g\ g^{-1}$.

Linear regression analyses revealed significantly positive relationships between PAH concentration and both the TA98 +S9 and YG1041 +S9 mutagenic responses (Figure 2). The coefficients of determination (i.e., $r^2$ values) indicate that the targeted PAHs account for a substantial portion (23−44%) of the variation in the mutagenic activity of the SHD samples. Since PAHs require metabolic activation for mutagenic activity, it is not surprising to see a lack of correlations between PAH concentration and mutagenic activity without S9 on any strain (data not shown). As expected, the TA98 relationship is stronger (i.e., higher $r^2$) than the YG1041 relationship. Since YG1041 responses are influenced by compounds other than PAHs.

Additional analyses used mutagenic potency data for individual PAHs to assess the extent to which the targeted PAHs could account for the mutagenic activity of SHD extracts. Nine of the 13 PAHs analyzed in this study are known *Salmonella* mutagens and their mutagenic potencies are summarized in Table 2. The published potency value for each PAH and its actual concentration in the SHD were used to establish a set of predicted mutagenicity values. Under an assumption of additivity, which is a reasonable assumption for mixtures of unsubstituted, homocyclic PAHs with a similar mode of action (*43, 44*), the predicted mutagenicity values for each PAH were then summed to obtain an expected mutagenic potency value for each SHD extract. These "expected" mutagenicity values, which are based on PAH

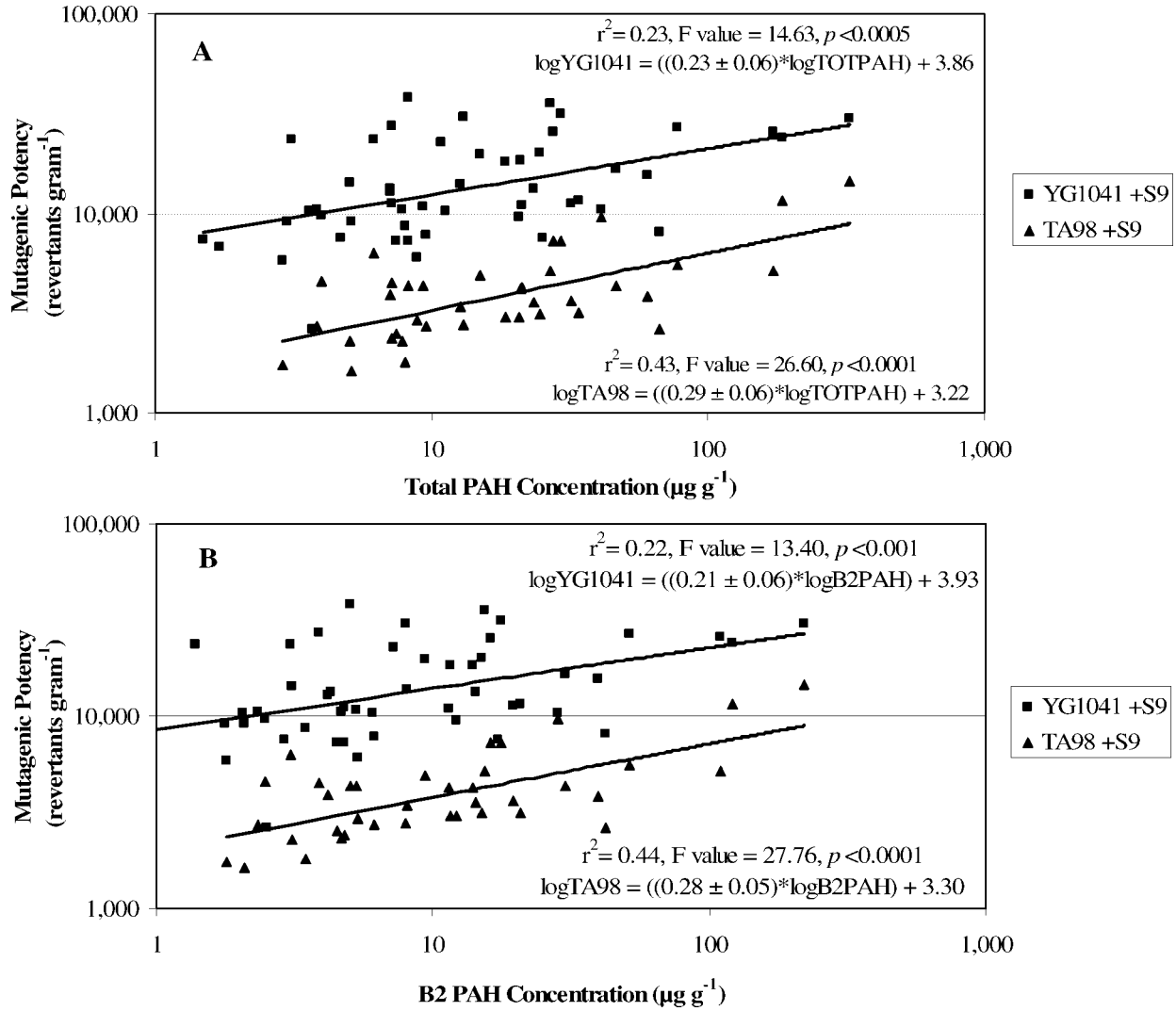


**FIGURE 2. Relationships between the PAH concentration and the S9-activated mutagenic potency of SHD samples collected from 51 homes in Ottawa. Both figures show the relationships for *Salmonella* TA98 and YG1041. (A) Total of 13 targeted PAHs. (B) total of seven PAHs classified as B2 carcinogens by the U.S. EPA.**

contamination alone, were then compared with the observed SHD mutagenic potency values. The analyses were restricted to TA98 data because there is very little published data on the mutagenicity of individual PAHs on YG1041 and YG1042.

The expected PAH-related mutagenic potencies of the SHD samples ranged from 160 to 26 000 revertants $g^{-1}$and accounted for between 4 and 244% of the observed mutagenic potencies (see Table 1, Supporting Information). Only 6 comparisons yielded values greater than 100% (i.e., expected greater than observed), and the majority of the values (i.e., 30 out of 38) were less than 50%. The median value was approximately 25% indicating that, in general, the nine targeted mutagenic PAHs account for approximately one-quarter of the mutagenic activity of the SHD samples. This value corresponds with that provided in our earlier study which reviewed the PAH contamination of over 130 SHD samples and found that less than 24% of TA98 +S9 mutagenic activity of SHD extracts could be accounted for by priority PAHs (*16*). Calculations for other particulate matrices have yielded comparable results with PAHs accounting for less than 24% of the TA98 +S9 mutagenic activity of outdoor air (*49*), and 17–25% of the TA98 +S9 mutagenic potency of contaminated soils (*50*). Nevertheless, it should also be noted that the lower-than-expected level of mutagenic activity may also be related to the S9 concentration employed in this study (~0.86% v/v in the top agar).

The results of the above calculations show that in most cases the prediction based on the content of priority PAHs dramatically under-estimates the observed mutagenic activity of the SHD extracts. Presumably, this indicates that the SHD extracts contain other unidentified mutagens, and the responses obtained on the YG strains with S9 indicate that these unknowns likely include aromatic amines. However, in six cases (i.e., SHD samples S011, E028, E029, E024, E018, and C001) where the PAH levels were notably elevated, the expected mutagenic activity based on PAH content was greater than that observed. In three of these cases, the difference was substantial (i.e., S011, E018, and E029). Several publications have noted that the mutagenic or tumorigenic activity of complex PAH mixtures can be less than that predicted from the mixture composition (*44, 51–54*). Moreover, the phenomenon was particularly apparent at elevated contaminant concentrations. It has been suggested that the reduced activity is a consequence of competitive inhibition or saturation of cytochrome P450 isozymes that are required for the metabolism and activation of mutagenic and carcinogenic PAHs (i.e., 1A1, 1A2, 1B1) (*43, 44, 53, 55*). Nevertheless, the results of studies that have investigated a less-than-additive effect have not been consistent or conclusive. For a review of these studies, see The U.S. Department of Health and Human Services (*56*), Shimada (*57*), and Table 5 in White (*43*).

*Empirical Relationships Between Dust Mutagenicity and Household Attributes.* Empirical relationships between SHD mutagenicity and the attributes of the homes were investigated. These attributes (see Table 2, Supporting Information) reflect activities and lifestyle factors that may contribute to SHD contamination and mutagenic activity.

Linear regression analyses revealed that the TA98 −S9, YG1041 +S9, YG1042 +S9, and YG1042 −S9 mutagenic potencies were significantly related to the number of inhabitants in the household. Each of these statistically significant relationships was positive, except for the YG1042 +S9 relationship, which was negative, likely because of the extremely small sample size ($N = 5$). The positive relationships suggest that households with more inhabitants contain dusts that are more contaminated with mutagenic substances. Linear regression also identified a weak, but significant positive relationship between the TA98 +S9 mutagenic potency and the time since the last vacuuming took place ($N = 38$, $r^2 = 0.11$, $F$ value $= 4.48$, $p < 0.05$).

The mutagenicity of the SHD samples was found to be negatively related to three household activities that involve combustion. YG1042 −S9, TA98 +S9, and YG1041 −S9 mutagenic potencies were significantly lower in houses where occupants burned incense ($N = 12$, $r = -0.61$, $F$value $= 6.04$, $p < 0.04$), burned candles ($N = 39$, $r = -0.52$, $F$value $= 13.96$, $p < 0.0007$), or a used secondary heating source ($N = 40$, $r = -0.31$, $F$value $= 4.17$, $p < 0.05$), respectively. These findings were contrary to what was expected because combustion events are known to generate PAHs and would be expected to increase the mutagenic activity of SHD (*59, 60*). However, other investigators have noted that combustion events leading to obvious indoor pollution (e.g., cigarette smoking, stir frying) can elicit compensatory responses such as increased ventilation (*61*), which could reduce ambient levels of contaminants and, consequently, the mutagenic activity of SHD.

The aforementioned study by Roberts et al. (*13*) also examined the relationships between SHD mutagenicity and household characteristics. They noted only one significant association between TA98 +S9 mutagenic potency and household income. Weak associations, though not statistically significant, were also noted between the TA98 +S9 mutagenic activity and the age of carpet, between TA98 −S9 activity and the level of nearby traffic, and TA98 −S9 activity and the presence of smoking in the home. Therefore, although there is some evidence to indicate that human activities, home location, cleaning habits, and household ventilation can affect the contamination and mutagenic hazards of SHD, a more focused study would be required to convincingly delineate the activities and household attributes that contribute to SHD contamination and mutagenic activity.

This study and its companion on PAH contamination and cancer risk clearly demonstrate that SHD contains carcinogenic combustion byproducts (i.e., PAHs) that can contribute to substantial levels of mutagenic activity. The mutagenic activity cannot be entirely explained by the observed concentrations of PAHs, and bioassay-directed investigations to isolate and identify the putative mutagens in SHD seem a promising area for future research. Identifying the hazardous components in SHD is of significant value because contaminant control requires knowledge of the putative substances. Such work, as well as quantifying exposure to components of SHD in human populations and designing household surveys that unmistakably identify activities that contribute to contamination and mutagenicity, will permit the implementation of remedial measures to reduce contamination, reduce exposure, and consequently, reduce or eliminate the risk of adverse effect.

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## Supporting Information Available

Table 1 contains the observed and expected *Salmonella* mutagenic potency values for extracts of SHD samples. Expected mutagenic potency values were based on PAH content only and were calculated by summing the predicted contributions from each PAH (i.e., product of mutagenic potency and PAH concentration). Table 2 contains details regarding the topics included in the Health Canada Indoor Air Study November 2002–March 2003. Survey questions were abbreviated and include only those relevant to settled house dust. This material is available free of charge via the Internet at http://pubs.acs.org.

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