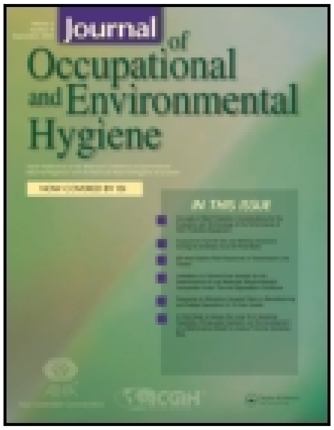

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Pharmaceutical Dust Exposure at Pharmacies Using Automatic Dispensing Machines: A Preliminary Study

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Automatic dispensing machines (ADMs) used in pharmacies concentrate and dispense large volumes of pharmaceuticals, including uncoated tablets that can shed dust. We evaluated 43 employees' exposures to pharmaceutical dust at three pharmacies where ADMs were used. We used an optical particle counter to identify tasks that generated pharmaceutical dust. We collected 72 inhalable dust air samples in or near the employees' breathing zones. In addition to gravimetric analysis, our contract laboratory used internal methods involving liquid chromatography to analyze these samples for active pharmaceutical ingredients (APIs) and/or lactose, an inactive filler in tablets. We had to choose samples for these additional analyses because many methods used different extraction solvents. We selected 57 samples for analysis of lactose. We used real-time particle monitoring results, observations, and information from employees on the dustiness of pharmaceuticals to select 28 samples (including 13 samples that were analyzed for lactose) for analysis of specific APIs. Pharmaceutical dust was generated during a variety of tasks like emptying and refilling of ADM canisters. Using compressed air to clean canisters and manual count machines produced the overall highest peak number concentrations (19,000–580,000 particles/L) of smallest particles (count median aerodynamic diameter ≤ 2 μm). Employees who refilled, cleaned, or repaired ADM canisters, or hand filled prescriptions were exposed to higher median air concentrations of lactose (5.0–12 μg/m^3) than employees who did other jobs (0.04–1.3 μg/m^3), such as administrative/office work, labeling/packaging, and verifying prescriptions. We detected 10 APIs in air, including lisinopril, a drug prescribed for high blood pressure, levothyroxine, a drug prescribed for hypothyroidism, and methotrexate, a hazardous drug prescribed for cancer and other disorders. Three air concentrations of lisinopril (1.8–2.7 μg/m^3) exceeded the lower bound of the manufacturer's hazard control band (1–10 μg/m^3). All other API air concentrations were below applicable occupational exposure limits. Our findings indicate that some pharmacy employees are exposed to multiple APIs and that measures are needed to control those exposures.

Keywords pharmaceutical dust, active pharmaceutical ingredients, APIs, mail order pharmacy, outpatient pharmacy, lactose, automatic dispensing machines, robotic pill dispensers

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INTRODUCTION

Of the 4.6 billion prescriptions filled in the United States in 2012, 3.5 billion were filled in retail pharmacies, 790 million were filled in mail order pharmacies, and 330 million were filled in medical pharmacies.[(1)] Of the approximately 282,000 pharmacists and 353,000 pharmacy technicians employed in the United States in 2012, 44% and 53%, respectively, worked in retail pharmacies; 22% and 16%, respectively, worked in medical pharmacies; and 2.7% of both worked in mail order or wholesale pharmacies.[(2,3)] Most mail order and some retail and medical pharmacies use automatic dispensing machines (ADMs) to fill prescriptions. While these machines reduce the number of prescriptions that require hand filling, they concentrate and dispense large volumes of pharmaceuticals. Some of these pharmaceuticals (i.e., uncoated tablets) can shed dust, and depending on the task or process, could become airborne and expose pharmacy employees.

Pharmaceutical tablets are typically homogenous mixtures containing active pharmaceutical ingredients (APIs) and excipients (inactive ingredients).[(4)] According to a compositional analysis of 200 commonly prescribed pharmaceutical tablets, magnesium stearate and lactose were the most common excipients used in 108 and 77 of the tablets, respectively.[(5)] Generally, a greater percentage of excipients are required for smaller dosages.[(5)] Tablets without film coating may be more friable than those with film coating. The dust produced from these friable tablets will often contain some APIs, which are designed to produce biological effects at low dosages.

While therapeutic for patients taking the drugs, APIs could produce undesirable effects in exposed workers. Several studies have found associations between pharmaceutical exposures (primarily in the pharmaceutical manufacturing industry) and adverse health effects, including hormonal changes, teratogenicity, cytotoxicity, respiratory sensitization, dermatitis, and allergic reactions.[6–9] A limited number of exposure assessments have been reported in the literature for this pharmaceutical manufacturing industry.[10–14] The most recent of these studies explored the use of inhalable dust measurements as a first approach to assessing occupational exposures.[14] Recent laboratory studies characterized the dustiness of pharmaceutical powders—an important determinant of occupational exposures in this industry.[15,16]

Few studies have explored pharmaceutical dust exposures in pharmacies where ADMs are used. Studies commissioned by an ADM manufacturer found that pressure-driven ADMs produced higher levels of pharmaceutical dust than gravity-fed ADMs. In particular, investigators in these studies measured higher PM2.5 number and mass concentrations near pressure-driven ADMs than gravity fed ADMs. They also detected active pharmaceutical ingredients (APIs) in the breathing zones of employees who worked near the pressure-driven ADMs.[17,18]

Under the National Institute for Occupational Safety and Health (NIOSH) Health Hazard Evaluation Program, we conducted evaluations at three pharmacies.[19–21] Employees at these pharmacies used gravity-fed ADMs for commonly prescribed pharmaceuticals and hand filled less commonly prescribed or special handling pharmaceuticals. Special handling pharmaceuticals included controlled substances, warfarin, and pharmaceuticals on the NIOSH list of hazardous drugs.

Findings from our first evaluation were previously reported in a case study.[22] We reported that dust originating from uncoated tablets could be released into employees' breathing zones during specific tasks, such as cleaning or refilling ADM canisters, and that this dust contained lactose (a common excipient) and one or more of 22 APIs. We also reported that personal air concentrations of warfarin (in total particulate) and lisinopril (in inhalable particulate) were below applicable occupational exposure limits (OELs). Warfarin is one of the few APIs that has OELs set by U.S. government or national organizations.[23,24] However, many APIs have OELs or hazard control bands set by pharmaceutical manufacturers; these include lisinopril.[25] In the two subsequent evaluations, we quantified several more APIs in air as inhalable particulate.

For this article, we combined the inhalable dust, lactose, and API exposure data from our evaluations of the three pharmacies for further analysis. We focused our analysis on inhalable particulate because most pharmaceuticals are water-soluble and capable of being absorbed anywhere in the respiratory system. Our primary objectives were to identify the job tasks with greatest potential for exposing employees to pharmaceutical dust and to characterize the API air concentrations and compare them to OELs or hazard control bands set by pharmaceutical manufacturers.

METHODS

Study Population

We evaluated pharmaceutical dust exposures at three pharmacies. Pharmacy A was a mail order pharmacy with two ADMs and 350 employees who filled ∼12,000 prescriptions per day (over two shifts). Pharmacy B was an outpatient pharmacy with two ADMs and 25 employees who filled ∼2,000 prescriptions per day (over one shift). Pharmacy C was a mail order pharmacy with one ADM and 175 employees who filled ∼14,000 prescriptions per day (over two shifts). These numbers do not include unit-of-issue prescriptions that are filled as originally packaged without counting. More than half of the pharmaceuticals dispensed were available as tablets. The pharmacies stocked between 19 (Pharmacy B) and 61 (Pharmacy A) pharmaceuticals on the NIOSH list of hazardous drugs; more than half were available as tablets.

Pharmacy A and C employees were required to wear either vinyl examination gloves or nitrile gloves when handling pharmaceuticals. Pharmacy B employees were required to wear nitrile gloves when handling pharmaceuticals. However, we observed inconsistent use of gloves at all pharmacies. None of the pharmacies required protective clothing. Pharmacies A and B did not have any local exhaust ventilation systems. Pharmacy C had a recirculation exhaust hood equipped with high-efficiency particulate air filtration in the area where ADM canisters were cleaned or repaired. However, we observed its use only once during a canister cleaning; the emptying and refilling of the canister was performed outside the hood. The hood did not appear large enough to accommodate those tasks. All pharmacies had voluntary respiratory protection programs. However, we observed only a few employees wearing NIOSH-approved N95 filtering facepiece respirators, and in many of these cases, they did not fit properly around the employee's nose and mouth.

Sampling and Analytical Methods

Table I summarizes the air sampling performed at each pharmacy. We conducted personal air monitoring over 3 consecutive days at each pharmacy. If an employee did not want to wear a sampling pump, we collected area air samples in the employee's workstation at breathing zone height. The only area air samples included in this article are those collected at breathing-zone height near employees who generally remained stationary ($n = 6$) or those collected in administrative offices mainly for an estimate of background dust concentrations ($n = 5$). We used high-flow sampling pumps (XR5000, SKC, Eighty Four, Pa.) to draw 2 L/min through IOM samplers loaded with tared 25-mm polytetrafluoroethylene filters. The samples were analyzed gravimetrically using NIOSH Method 0600.[26] All samples were time-weighted averaged over the collection period. Fifty-five samples were collected over an entire work shift (401–499 min), 11 samples were collected over 300–399 min, and six samples were collected over < 300 min (132–290 min). Generally, the reasons for the shorter duration samples (< 400 min) were that employees switched jobs or

TABLE I. Summary of Inhalable Particulate Air Sampling

Pharmacy	No. of employees sampled	No. of personal air samples	No. of area air samples	Total no. of air samples	No. of air samples analyzed for lactose	Air samples analyzed for specific APIs (no.)
A	11	25	4	29	29	Lisinopril (6)
B	3	5	0	5	4	Lisinopril (3), HCTZ (3), levothyroxine (1), loratadine (1)
C	29	31	7	38	24	Lisinopril (2), HCTZ (2), levothyroxine (1), warfarin (3), methotrexate (2), buspirone (1), captopril (1), furosemide (1), gabapentin (1), hydrocodone (5), methocarbamol (1), naproxen (1)
Totals	43	61	11	72	57	

finished early or we were delayed in deploying the sampling trains. Therefore, we assumed that these samples measured exposures representative of a typical work shift. The eight jobs that we sampled included:

1. *Cleaning/repairing canisters* - Employees removed and emptied the ADM canisters, disassembled the canisters if necessary, and then used alcohol wipes to clean the inside of the canisters before reassembly. Occasionally, employees used compressed air to blow out the canisters. We sampled employees who did this job at all the pharmacies. This was one of two jobs done intermittently throughout the day.
2. *Hand filling prescriptions* - Employees either used counting trays or manual counting machines to fill prescription bottles with less commonly prescribed or special handling pharmaceuticals, including hazardous drugs. Occasionally, employees used compressed air to blow out these machines. We sampled employees who did this job at all the pharmacies.
3. *Refilling canisters* - Employees opened the original manufacturers' pharmaceutical bottles and emptied them into canisters. This was either done at the ADM or in a separate area of the pharmacy. We sampled employees who did this job at all the pharmacies.
4. *Labeling/packaging* - Employees printed and pasted labels onto outgoing delivery orders. We sampled employees who did this job at Pharmacies A and C.
5. *Rinsing canisters* - Employees used water-based cleaning solutions to wash canisters that were especially dusty or slated for new pharmaceuticals. We sampled employees who did this job at Pharmacy A. This was one of two jobs done intermittently throughout the day.
6. *Verifying prescriptions* -Pharmacists inspected prescription bottles to verify their accuracy and ensure that all the pharmaceuticals were intact. We sampled employees who did this job at Pharmacy C.
7. *Housekeeping* - Employees swept and vacuumed floors and other surfaces, emptied trash, and cleaned other areas of the pharmacy. We sampled employees who did this job at Pharmacy C.
8. *Administration/office work* - Employees performed administrative work in offices that were separated from the pharmacy. We sampled employees who did this job at Pharmacies A and C.

We followed some of the employees who wore air samples throughout their workday and held real-time optical particle counters (MetOne HHPC-6, Hach, Loveland, Colo.) near their breathing zones to identify dusty tasks as indicated by peaks in particle number concentrations. These particle counters contained six channels from 0.3 to >10 μm and were set to sample 1 L of air over about 25 sec repeatedly throughout the day. We also recorded the types of tablets handled so that we could later identify air samples (previously analyzed gravimetrically) to be further analyzed for lactose and/or specific APIs (Table I).

TABLE II. Summary of the Liquid Chromatography Analytical Methods

Analyte	Extraction solvent	Column	Isocratic mobile phase	Detector	Detection limit (μg)
Lactose	Deionized water	Dionex CarboPac PA1, 4 mm × 250 mm	200 mM sodium hydroxide in deionized water	EC	0.002– 0.003
Lisinopril	Deionized water	Waters Spherisorb C8, 150 mm × 4.6 mm, 5 μm particle size	85% (Dipotassium phosphate, 0.1% phosphoric acid)/15% methanol	UV/Vis, 215 nm	0.1–0.2
HCTZ	Deionized water	Waters Spherisorb C8, 150 mm × 4.6 mm, 5 μm particle size	85% (Dipotassium phosphate, 0.1% phosphoric acid)/15% methanol	UV/Vis, 215 nm	0.02–0.1
Hydrocodone	50% (15 mM sodium lauryl sulfate, 15 mM dipotassium phosphate, 0.1% phosphoric acid)/5% acetonitrile/45% methanol	MacMod Halo C18, 4.6 mm × 75 mm, 2.7 μm particle size	50% 15 mM sodium lauryl sulfate, 15 mM dipotassium phosphate, 0.1% phosphoric acid, 5% acetonitrile	UV/Vis, 210 nm	0.01
Levothyroxine	30% deionized water (0.1% formic acid)/70% acetonitrile	Atlantis Hilic Silica, 50 mm × 2.1 mm, 3 μm pore size	30% deionized water (0.1% formic acid)/70% acetonitrile (0.1% formic acid)	MS/MS, 777.8/ 731.8 amu	0.0002– 0.0003
Methotrexate	25% 10 mM ammonium acetate (0.1% formic acid)/75% acetonitrile (0.1% formic acid)	Atlantis Hilic Silica, 4.6 mm × 100 mm, 3 um particle size	25% 10 mM ammonium acetate (0.1% formic acid), 75% acetonitrile (0.1% formic acid)	MS, 455.2/ 308.2 amu	0.0001
Loratadine	40% (1% triethylamine, 0.75% phosphoric acid)/60% acetonitrile	Dionex CarboPac PA1, 250 mm by 4 mm	40% (1% triethylamine, 0.75% phosphoric acid)/60% acetonitrile	UV/Vis, 215 nm	0.1
Buspirone	70% 10 mM monopotassium phosphate in deionized water/30% acetonitrile	Waters Xterra RP18, 4.6 mm × 150 mm, 3.5 μm particle size	70% 10 mM monopotassium phosphate in deionized water, 30% acetonitrile	UV/Vis, 238 nm	5
Captopril	5% methanol/45% deionized water/0.05% phosphoric acid	Zorbax XDB C18, 4.6 mm × 250 mm, 5 μm particle size	55% methanol/45% deionized water/0.05% phosphoric acid	UV/Vis, 220 nm	0.08

Continued on next page

TABLE II. Summary of the Liquid Chromatography Analytical Methods *(Continued)*

Analyte	Extraction solvent	Column	Isocratic mobile phase	Detector	Detection limit (μg)
Furosemide	60% (2% acetic acid in deionized water)/40% acetonitrile	Waters Xterra RP18, 4.6 mm × 150 mm, 3.5 μm particle size	60% (2% acetic acid in deionized water), 40% acetonitrile	UV/Vis	0.05
Gabapentin	10 mM sodium borate decahydrate	Zorbax SB C18, 4.6 mm × 250 mm, 5 μm particle size	70% (1% triethylamine, 0.75% phosphoric acid in deionized water), 30% acetonitrile	FL, 245 excitation, 480 emission	0.05
Methocarbamol	60% 20 mM monopotassium phosphate (pH = 3 with phosphoric acid) in deionized water/40% methanol	Waters Symmetry C18, 4.6 mm × 150 mm, 5 μm particle size	60% 20 mM monopotassium phosphate (pH = 3 with phosphoric acid) in deionized water, 40% methanol	UV/Vis, 275 nm	0.05
Naproxen	54% deionized water/5% acetonitrile/1% glacial acetic acid	MacMod Halo C18, 4.6 mm × 75 mm, 2.7 μm particle size	54% deionized water/45% acetonitrile/1% glacial acetic acid	UV/Vis 238 nm	0.0001

Note: EC = electrochemical, FL = fluorescence, MS = mass spectrometry, UV/Vis = ultraviolet/visible.

Information provided by employees on the dustiness of pharmaceuticals was also used to select APIs for analysis. We had a few employees wear more than one air sample during their workday. This allowed us to quantify an employee's air concentrations to more than one API and/or lactose because analyses of these compounds usually require different extraction solvents. The results were combined and are presented as one air sample for this article. Lactose, lisinopril, and hydrochlorothiazide (HCTZ) required the same extraction solvent (i.e., deionized water) and therefore could be analyzed from one air sample. Of the 28 air samples analyzed for specific APIs, 13 were also analyzed for lactose. We generally focused on APIs that had OELs or hazard control bands set by pharmaceutical manufacturers. Additionally, we made sure that our contract lab had analytical methods for the APIs we selected. Warfarin was analyzed using NIOSH Method 5002.[26] The other analytical methods developed by our contract lab, all of which utilized liquid chromatography, are summarized in Table II with additional details provided in the NIOSH reports.[19–21]

Data Analysis

We used SAS 9.3 statistical software (SAS Institute, Cary, N.C.) for most data and statistical analysis. We did not measure detectable concentrations of inhalable dust on 14 of the 72 air samples. For these samples we imputed with values created by dividing the minimum detectable concentrations by the square root of 2. Five of these samples were collected in administrative/office areas. All the lactose concentrations were detectable. Box and whisker plots were generated for describing inhalable dust and lactose concentrations by job. Pearson correlation was used to explore the relationship between log-transformed air concentrations of inhalable dust and lactose. A two-sample t-test was used to compare log-transformed lactose air concentrations measured during administration/office work to all other log-transformed lactose air concentrations. We reported ranges for the API air concentrations for comparison with applicable OELs.

We used Microsoft Excel (Microsoft, Redmond, Wash.) to analyze the real-time particle count data. We measured peak particle number concentrations during a variety of tasks. We calculated the count median aerodynamic diameter (CMAD) attributable to pharmaceutical dust during these peaks by first subtracting the background count levels and then by plotting the cumulative count distributions (using the mid-point of each channel). We also calculated the total particle number concentrations attributable to pharmaceutical dust during these peaks by subtracting background levels. We explored the relationships of these two variables stratified by three tasks:

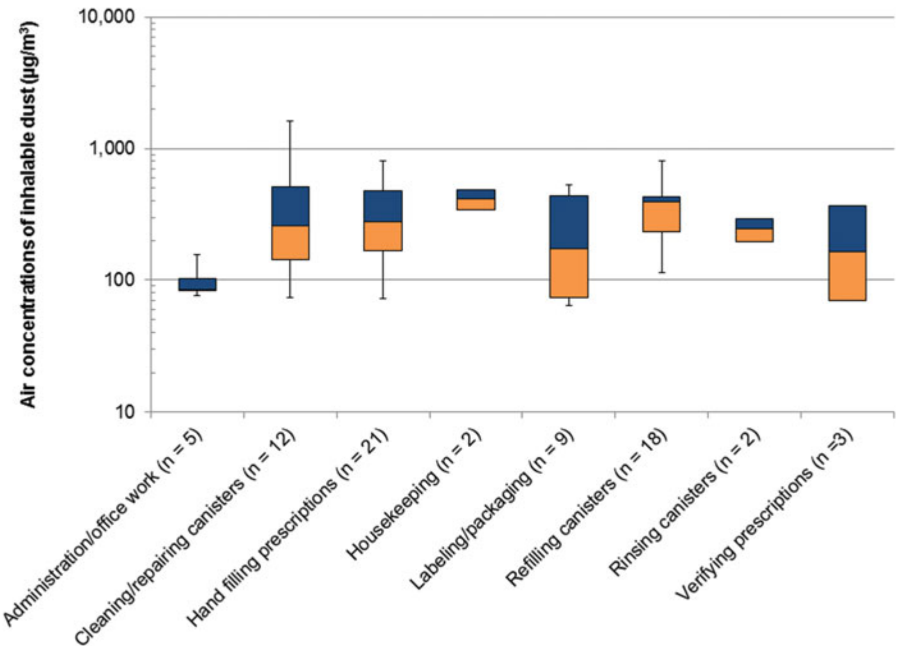

FIGURE 1. Inhalable dust air concentrations (minimum, maximum, and 25th, 50th, and 75th percentiles) by job. (Color figure available online).

1. cleaning canisters or manual count machines with compressed air,
2. cleaning canisters without compressed air, and
3. refilling canisters.

RESULTS

Air Concentrations of Inhalable Dust and Lactose

Figure 1 summarizes the inhalable dust air concentrations by job. The jobs resulting in the highest median inhalable dust

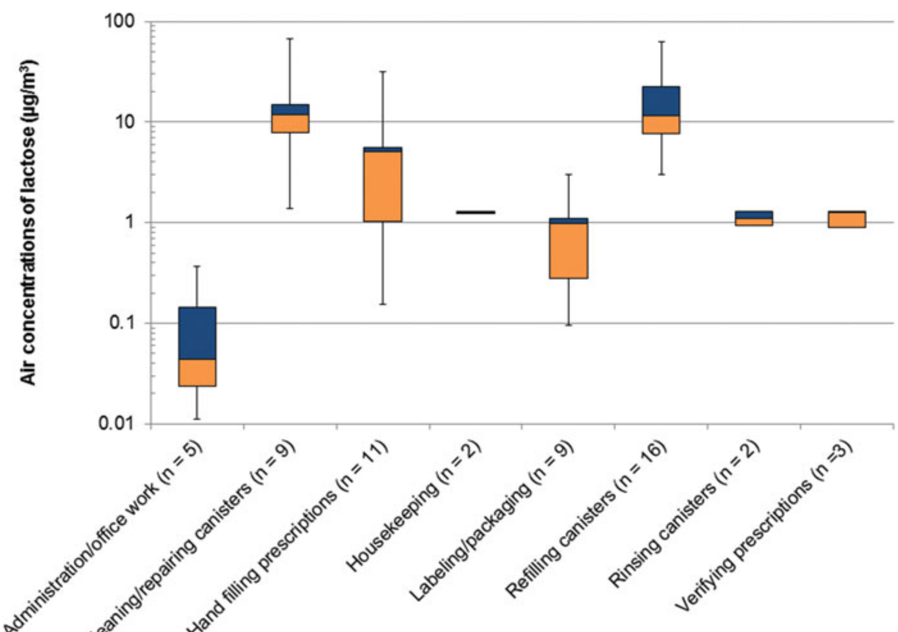

FIGURE 2. Lactose air concentrations (minimum, maximum, and 25th, 50th, and 75th percentiles) by job. (Color figure available online).

concentrations were housekeeping, refilling canisters, hand-filling prescriptions, and cleaning/repairing canisters. Figure 2 summarizes the lactose air concentrations by job. Employees who cleaned/repaired canisters, refilled canisters, and hand filled prescriptions were exposed to higher median air concentrations of lactose (5.0–12 $\mu g/m^3$) than employees who did other jobs (0.04–1.3 $\mu g/m^3$). The highest maximum air concentrations of lactose (31–67 $\mu g/m^3$) were also measured during these three jobs.

We found a statistically significant positive correlation between log-transformed air concentrations of inhalable dust and lactose ($r = 0.52$, $P < 0.01$, $n = 57$). This indicates that increasing inhalable dust concentrations were associated with increasing lactose concentrations. However, inhalable dust is non-specific and could include dust from sources other than the pharmaceuticals. Lactose, on the other hand, is specific to pharmaceutical tablets. Pharmaceuticals were not handled in administrative offices, which were located away from the rest of the pharmacy. This would explain why the mean area air concentrations of lactose measured in administrative offices ($n = 5$) were significantly less ($P < 0.01$) than all other mean air concentrations of lactose ($n = 52$). Other area air samples included in this article were collected in the hand filling ($n = 4$) and labelling/packaging areas ($n = 2$). Because employees in these areas were generally stationary, we believe the area air samples collected near them at breathing-zone height were able to provide reasonable estimates of their personal exposures.

Air Concentrations of Specific APIs

Table III summarizes the air concentrations of 13 APIs. Of these 13 APIs, 10 were detected in air. Of these 10 APIs, lisinopril, HCTZ, captopril, and furosemide are prescribed for high blood pressure; hydrocodone, methocarbamol, and naproxen for pain relief; levothyroxine for hypothyroidism; loratadine for allergies; and methotrexate for cancer, arthritis, or psoriasis.[27] Methotrexate was the only API we detected in air that is on the NIOSH list of hazardous drugs.[28] APIs were detected during cleaning/repairing canisters, refilling canisters, and hand filling prescriptions. However, we primarily targeted these three jobs because we suspected they had the highest potential for exposure. Three air concentrations of lisinopril (1.8–2.7 $\mu g/m^3$) exceeded the lower bound of the manufacturer's hazard control band.[25] We chose to compare to the lower bound of a hazard control band because it is more protective than comparing to the upper bound. The

TABLE III. Air Concentrations of 13 APIs

API	No. of samples	No. of non-detects	Range ($\mu g/m^3$)	OEL or hazard control band ($\mu g/m^3$)^A	Job(s) where detected
Lisinopril	11	7	< 0.10 – 2.7	1 – 10	Cleaning/repairing canisters, refilling canisters
HCTZ	5	1	< 0.23 – 35	100	Cleaning/repairing canisters, refilling canisters
Hydrocodone	5	1	< 0.01 – 0.07	5	Hand filling prescriptions
Warfarin	3	3	< 0.61 – < 0.64	100	
Levothyroxine	2	0	0.008 – 0.03	< 1	Cleaning/repairing canisters
Methotrexate	2	0	0.0002 – 0.007	0.3	Hand filling prescriptions
Loratadine	1	0	8.5	125	Cleaning/repairing canisters
Buspirone	1	1	< 5.8	10	
Captopril	1	0	0.89	100	Hand filling prescriptions
Furosemide	1	0	0.1	None	Refilling canisters
Gabapentin	1	1	< 0.06	1,200	
Methocarbamol	1	0	2.8	None	Refilling canisters
Naproxen	1	0	8.7	1,000	Cleaning/repairing canisters

^{A}As published in safety data sheets for lisinopril,[25] HCTZ,[30] hydrocodone,[31] levothyroxine,[29] methotrexate,[32] loratadine,[33] buspirone,[34] captopril,[35] gabapentin,[36] and naproxen.[37] As set by NIOSH, OSHA, and ACGIH® for warfarin.[23,24]

manufacturer's hazard control band for levothyroxine does not provide a lower bound, but the air concentrations we measured were more than an order of magnitude below the upper bound.[29] We could not find published manufacturer's OELs for furosemide or methocarbamol. All other air concentrations were below the applicable OELs.[23,24,30–37]

Two employees who refilled canisters and two employees who cleaned/repaired canisters were exposed to detectable levels of two APIs. However, quantitation of more than one API was not possible for most of the air samples we collected. This was because we only collected one air sample from most employees and most APIs require different extraction solutions.

Particle Count Distribution of Pharmaceutical Dust Releases

Figure 3 shows the relationship between the peak particle number concentration and CMAD for the pharmaceutical dust released into air during specific tasks. Varying peak number concentrations (3,000–69,000 particles/L) of a broad size-range of particles (i.e., CMAD < 1 μm to 10 μm) were released when canisters were refilled or cleaned without compressed air. In comparison, overall higher peak number concentrations (19,000–580,000 particles/L) of smaller particles (i.e., CMAD ≤ 2 μm) were released when compressed air was used to clean canisters or manual count machines. Particles ≤ 2 μm in aerodynamic diameter will remain suspended in still air for several hours, while larger particles (i.e., 10 μm) will settle out within minutes. In some cases, it took more than 1 hour for particle number concentrations to return to background after compressed air was used to clean canisters or manual count machines. Note that Figure 3 does not reflect the actual frequency of each task being completed. Generally, employees refilled canisters with tablets more frequently (10–50 times per day) than they cleaned canisters or manual count machines ($<$10 times per day). When canisters were cleaned without compressed air, the biggest releases of dust typically occurred when canisters were emptied of tablets and refilled.

DISCUSSION

Although we did air sampling at only three pharmacies, our findings indicate that pharmacy employees can be exposed to pharmaceutical dust during certain tasks. Our air sampling results may directly reflect inhalation exposures because most employees did not wear respiratory protection. The air samples we collected measured inhalable particulates, ranging from $<$1 μm to $>$100 μm in aerodynamic diameter.[24] Measuring inhalable particulate is the preferred method for pharmaceutical exposure assessments because many pharmaceuticals are water-soluble and can be absorbed anywhere in the respiratory system, including nasal passages.

The median inhalable dust concentrations we measured by job ranged from 84–420 μg/m^3. In comparison, investigators in a recent study of inhalable dust exposures in the pharmaceutical manufacturing industry measured substantially higher median exposures during jobs involving the handling of pharmaceutical powders (600–7,100 μg/m^3) and comparable

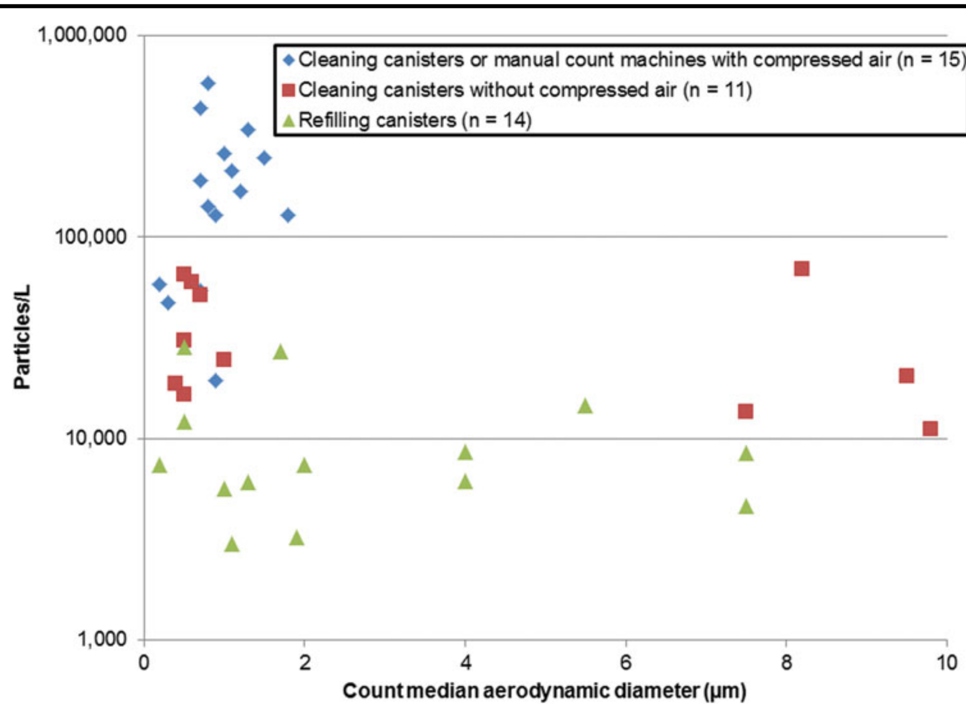

FIGURE 3. Peak particle number concentration versus count median aerodynamic diameter for pharmaceutical dust released during three categories of tasks. (Color figure available online).

median exposures during other jobs, such as blister packaging and film coating (100–400 μg/m^3).[14] Thus, the pharmacies we evaluated appear to produce less dust than some pharmaceutical manufacturing sites. Whereas pharmaceutical manufacturers are usually focused on producing one drug at a time, pharmacies dispense multiple drugs and so the airborne dust could contain a mixture of pharmaceuticals. Strong correlations (r > 0.98) between inhalable dust and specific API air concentrations for tasks involving pharmaceutical powders have been found in the pharmaceutical manufacturing industry.[14] In comparison, we found a weaker but statistically significant correlation between log-transformed air concentrations of inhalable dust and lactose ($r = 0.52$).

Although lactose is not used in all tablet formulations, and, when it is used, the proportions will vary,[5] our data suggest that lactose may be a better marker for pharmaceutical dust exposure than inhalable dust. We measured significantly lower mean air concentrations of lactose in the non-production areas (administrative offices) compared to the production areas, and we measured the highest median and maximum concentrations in or near the breathing zones of employees who directly handled pharmaceuticals or contaminated equipment, including those who cleaned/repaired canisters, refilled canisters, and hand filled prescriptions. Not surprisingly, employees who did these jobs were also exposed to a variety of APIs.

Most APIs do not have OELs set by federal agencies or national organizations; warfarin is one exception. Thus, when available, we used manufacturers' OELs or hazard control bands for comparing our results. Pharmaceutical manufacturers establish OELs or hazard control bands using a control banding process that considers the drugs' potency, severity of acute effects, lethal dose, irritation, and sensitization.[38–40] All air concentrations of APIs were below manufacturers' OELs or hazard control bands (lower bound), except for three personal air concentrations of lisinopril measured in pharmacies B and C. Possible acute health effects from exposures to lisinopril include dizziness, headache, and allergic reactions.[25] Other APIs may also elicit allergic reactions in sensitive individuals.[6–9,41] Because lisinopril acts on the renin-angiotensin system, fetal and neonatal injury are possible if substantial exposure occurs in the second or third trimester of pregnancy.[25]

Levothyroxine has one of the lowest hazard control bands of pharmaceuticals that are not classified as hazardous drugs. The manufacturer's hazard control band for levothyroxine has no lower bound (i.e., < 1 μg/m^3).[29] Although air concentrations of levothyroxine measured in pharmacies B and C were well below the upper bound of the manufacturer's hazard control band, maintaining exposures as low as feasible may be prudent to prevent effects on the thyroid. The safety data sheet for levothyroxine specifically recommends that, "All operations should be fully enclosed [with] no air recirculation permitted."[29] However, levothyroxine was handled without enclosures in pharmacies B and C.

Although each pharmacy stocked several hazardous drugs, methotrexate was the only hazardous drug we observed being dispensed (at pharmacy C), and hence, the only hazardous drug we sampled in air. The health risk from hazardous drugs depends on how much exposure an employee has to these drugs and how toxic they are.[42] Several studies have shown biological uptake of methotrexate in exposed workers.[43–45] The safety data sheet for methotrexate lists a number of potential acute health effects from occupational exposures including eye and mucous membrane irritation.[32] More serious acute and chronic effects are possible with therapeutic use, including gastrointestinal disturbances, effects on blood and blood-forming organs, and damage to a developing fetus if taken when pregnant.[32,46,47] We found quantifiable levels of methotrexate in two air samples collected near employees who hand filled hazardous drugs without engineering controls. The air concentrations were well below the manufacturer's OEL.[19] Nevertheless, the safety data sheet for methotrexate recommends that employees "Use a laboratory fume hood, vented enclosure, glove box, or other effective containment."[32]

Our exposure assessments, while limited, provide the most complete picture of pharmaceutical dust exposures in pharmacies published to date. The air sampling results were collected over a 3-day period at each pharmacy and thus may not be representative of exposures throughout the year. Also, we were not able to quantify all possible API exposures primarily because of laboratory analytical limitations, and not all the quantified APIs had published OELs for comparison. For these reasons, simply comparing measured API air concentrations to OELs may not give a clear indication of an employee's risk from inhalation exposure. Our sampling results confirm that four employees were exposed to detectable levels of two APIs. Other employees were also likely exposed to multiple APIs, but we could not confirm this due to the limitations of our sampling and analytical methods. Health effects from exposure to multiple APIs are not well understood, but additive or synergist effects may be possible. Whereas severe health effects are possible from inhalation exposures to hazardous drugs like those containing steroid hormones or antineoplastic ingredients,[6,8 42] eye and upper respiratory irritation are probably the most likely health effects that would manifest from inhalation exposures to many of the commonly prescribed pharmaceuticals.[9]

The real-time particle measurements we collected indicate that the size of pharmaceutical particles produced will depend on the task being performed. Using compressed air to clean canisters and manual count machines produced overall higher peak number concentrations (19,000–580,000 particles/L) of smaller particles (CMAD ≤ 2 μm) than other means of cleaning canisters. That particles ≤ 2 μm in aerodynamic diameter remain airborne longer than larger particles implies that use of compressed air could increase employees' exposures by increasing the exposure time and spread of airborne dust throughout the workplace. When inhaled, these small particles can also penetrate deeply into the lungs. This could increase the probability of effects to the lower respiratory system. However, small particles carry less mass than large particles, and for highly soluble pharmaceuticals, the deposition site in the lungs may not be a critical factor for toxicity. Nevertheless, using compressed air to clean equipment containing biologically active residues should be avoided.

We measured the lowest peak particle number concentrations (3,000–28,000 particles/L) during the refilling of canisters. However, this task was done with much greater frequency than the cleaning of canisters or manual count machines. This could explain why air concentrations of lactose measured during refilling of canisters and cleaning/repairing of canisters were comparable. Further study exploring the relationship between pharmaceutical dust exposures and the frequency of dust-producing tasks (e.g., number of tablet refills) is warranted.

In addition to inhalation exposures, the potential for skin or clothing contamination also exists. Airborne pharmaceutical dust will eventually deposit onto surfaces. We observed white dust on a variety of surfaces, including personal clothing. At pharmacies B and C, we measured higher quantities of lactose on work surfaces in production areas than non-work surfaces (i.e., undisturbed areas) or work surfaces in non-production areas.[20,21] Most pharmacy employees wore either vinyl or nitrile gloves when handling pharmaceuticals, but no pharmacy employees wore protective clothing. Therefore, take-home exposure is possible. Children may be especially susceptible to adverse health effects from API exposures.[48]

CONCLUSION

Pharmacies that use automation still require employees to directly handle pharmaceuticals or contaminated equipment. Sampling air for lactose allowed us to estimate employees' exposure to pharmaceutical dust at three of these pharmacies. The highest air concentrations of lactose were measured on employees who cleaned or repaired canisters, refilled canisters, and hand filled prescriptions. In addition to lactose, many of these same employees were exposed to one or more APIs. Therefore, comprehensive occupational health and safety programs should be developed at these pharmacies. As is the case with job hazard analysis, managers of these programs should first collect information on the potential for workplace exposures to APIs and health risk of those exposures; this information is essential for establishing standard operating procedures and identifying the need for control measures such as replacing friable tablets with film-coated tablets, using local exhaust ventilation, or using personal protective equipment and clothing. Further study is warranted to characterize and identify the main determinants of pharmaceutical dust exposures at mail order, medical, and retail pharmacies, particularly those that use pressure-driven ADMs or dispense hazardous drugs.

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