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ORIGINAL RESEARCH

Plasticizers, antioxidants, and other contaminants found in air delivered by PVC tubing used in respiratory therapy

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ABSTRACT: Of the many compounds that leach from respiratory therapy tubing into air passing through it, we selected five compounds to analyze. The five compounds are known to be potentially carcinogenic, toxic or known to induce estrogenic activity. Parts-per-million and parts-per-billion concentrations of these species were found in the air passing through the tubing: the plasticizers di-(2-ethylhexyl) phthalate (DEHP) and di-ethyl phthalate (DEP), the antioxidants butylated hydroxy toluene (BHT) and *p*-nonylphenol (*p*-NP), and the contaminant (from commercial preparation of DEHP) 2-ethylhexanol (2-EH). These levels are high enough to cause some concern about exposure for patients who use oxygen on a long-term basis, those sensitive or allergic to these species, or those with asthma. A method was developed for analysis of solid tubing samples, showing great variability in concentrations of small, volatile molecules from sample to sample. A method was also developed for pre-concentration of small molecules onto Tenax adsorbants from air passing through the tubing. Both solid samples and adsorbant loaded with analyte were analyzed by direct dynamic thermal desorption gas chromatography mass spectrometry (GCMS). This study does not imply that adverse reactions by patients to chemical compounds leaching from respiratory medical tubing will occur but that further investigation is warranted. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: respiratory therapy; plasticizers; DEHP; *p*-nonylphenol; asthma; estrogenic activity

INTRODUCTION

Anecdotal stories of patient displeasure with the odor of 'oxygen' administered for medical purposes suggest that it may be important to identify and study the health effects of compounds coming through hospital tubing during administration of oxygen. In the present paper, we report the values obtained in a preliminary study of volatile compounds found in air passing through respiratory therapy tubing (Hill, 1997), and compare them with literature values for exposure levels and health effects. A literature review on research regarding exposure to plasticizers and other xenobiotics ('unnatural' substances) by respiratory and non-respiratory routes related to this paper has been published (Hill *et al.*, 2001). [Plasticizers are small organic molecules that are added to polyvinyl chloride (PVC) tubing to act as lubricants between the polymer chains and also improve flexibility and workability of materials (McMurry, 1988). They help prevent the PVC from becoming brittle at room temperature.] Studies reviewed include the exposure of individuals to these compounds from environmental (Group 1986; Jobling *et al.*, 1995; Klotz *et al.*, 1996; Lau *et al.*, 1996; Stancel *et al.*, 1995; Vitali *et al.*, 1993), occupational (Astill *et al.*, 1996a,b; Bardana and Andrach 1983; Vainiotalo and Pfaffli, 1990), household (Oie *et al.*, 1997) and medical (Doelman *et al.*, 1990a,b; Dohl *et al.*, 1997; Gibson *et al.*, 1976; Hall, 1997; Jaeger and Rubin, 1972; Khaliq *et al.*, 1992; Labow *et al.*, 1990; Nassberger *et al.*, 1987; Ono *et al.*, 1975; Rock *et al.*, 1986; Roth *et al.*, 1988; Snell, 1989) settings.

In this study, dry air was passed through polyvinyl chloride medical tubing. Volatile organic compounds released from the tubing into the air passing through it were pre-concentrated on a bed of powdered adsorbant. The compounds collected from the air over a period of hours were analyzed by gas chromatography/mass spectrometry (GC-MS). At least 30 compounds found in the PVC tubing leached into the tubing's airspace (Hill, 1997). The plasticizers, antioxidants, catalysts, and other contaminants that were detected included suspected carcinogens (Schulz, 1989; Hirzy, 1989; Kluwe, 1986), toxic substances (Astill *et al.*, 1996a,b), compounds with offensive odor (Vitali *et al.*, 1993) and those with unknown effects on lung tissue and the body. Five compounds with known health risks (see Table 1) were

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Abbreviations used: BHP, butylated hydroxytoluene; DDTD, direct dynamic thermal desorption; DEHP, di-(2-ethylhexyl)phthalate; DEP, di-ethyl phthalate; 2-EH, 2-ethylhexanol; *p*-NP, *p*-nonylphenol.

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Table 1. List of compounds found in medical tubing with their known and health suspected health effects

Compound (abbreviation)	Usage	Known health effects	Suspected health effects
2-Ethyl 1-hexanol (2-EH)	Preparation of DEHP	Hepatotoxicity in rodents	
Butylated hydroxy toluene (BHT)	Antioxidant		Weakly estrogenic
Diethyl phthalate (DEP)	Plasticizer		Carcinogen
p-Nonylphenol (*p*-NP)	Antioxidant	Birth defects and mortality in waterbirds	Estrogen-like properties
Di-(2-ethylhexyl) phthalate (DEHP)	Plasticizer	Negative respiratory reactions	Hepatotoxin, carcinogen, teratogen, mutagen

selected for quantification in this study. Analytical results were used to estimate the maximum does of these contaminants that a patient might be exposed to under conditions used for delivering oxygen through PVC tubing used with nasal canula. Results would probably be different with the moisturized oxygen-enriched air used in respiratory therapy, compared with this preliminary study using dry air.

The following substances were detected in samples of PVC tubing and from air that passed through the tubing: the plasticizers di-(2-ethylhexyl) phthalate (DEHP) and di-ethyl phthalate (DEP), the antioxidants, butylated hydroxytoluene (BHT), and *p*-nonylphenol (*p*-NP), and the contaminant (from commercial preparation of DEHP) 2-ethylhexanol (2-EH), and many other chemical compounds.

DEHP and DEP have potential for allergen-induced asthma (Doelman *et al.*, 1990a, b; Labow *et al.*, 1990; Oie *et al.*, 1997; Roth *et al.*, 1988; Vainiotalo and Pfaffli, 1990) and suspected carcinogenic properties (Schulz, 1989; Hirzy, 1989). Serum levels of phthalate esters, including DEHP and DEP, have recently been shown to correlate with the incidence of early breast development in girls, as early as one year of age (Colon *et al.*, 2000). The compounds, 2-EH and *p*-NP have potential for hepatoxicity (Kluwe, 1986) and estrogenic activity (Jobling *et al.*, 1995; Soto *et al.*, 1991) respectively. (Alkylphenols such as *p*-nonylphenol are used as antioxidants to strengthen and stabilize plastics.) BHT is a dominant species present in tubing used in medical applications and is weakly estrogenic. Genetic predisposition and subsequent environmental exposure to allergens can contribute to the development of asthma (Doelman *et al.*, 1990a,b; Hall, 1997). The results of this preliminary study suggest that further work is warranted to determine whether exposure of patients to components of plastic tubing used in medical treatment presents a health risk.

EXPERIMENTAL

Materials. Polyvinyl chloride tubing from Baxter Healthcare (no. 001301; lot numbers Y6K0025 and Y6H0127) with an internal diameter of 3.94 mm and length of 14.1 cm ($5\frac{9}{16}$ in) was used for this study. The tubing was stored in its original plastic package at room temperature before use, and cut to size using a razor blade previously rinsed with isopropyl alcohol, dried and heat cured by flame.

2-EH, BHT, DEP, *p*-NP and DEHP, purchased from Aldrich, were used as standards for calibration to determine the amount of each compound (plasticizer and antioxidant) in the medical tubing. Standard mixtures of these compounds in equal concentrations using methylene chloride as the solvent were sampled by direct injection and analyzed by GC-MS. To generate external standard-response calibration curves, injections of the standards were made using volumes of 1 μL (Hill, 1997). Concentrations were 2, 10, 50, 100 and 150 μg/mL (ppm).

Methods. Figure 1 shows a schematic for the manifold system used to hold the PVC tubing and collect the volatile compounds from the air onto Tenax adsorbant (Supelco, Bellafonte, PA, USA). Ultrapure air from Connecticut Airgas was passed through a hydrocarbon trap (carbon), then delivered via a four-valve manifold to PVC tubing or copper tubing as control. Tenax filters were placed between these valves and the PVC tubing samples or

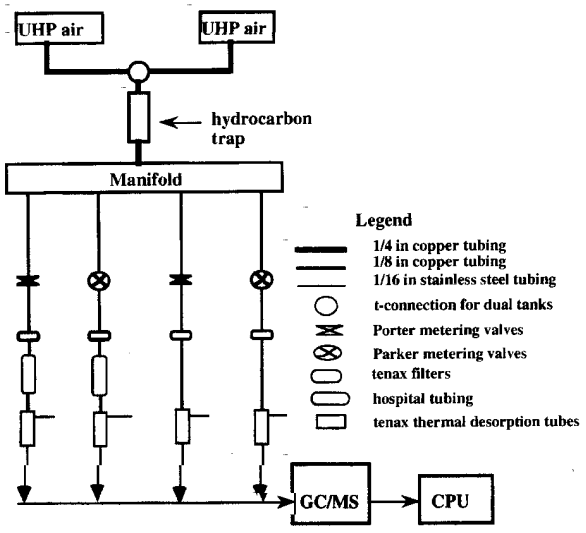

Figure 1. Diagram of experimental setup. Hospital tubing was placed on two lines each with a different metering valve. Controls (no tubing) for each hospital tube were continuous copper tubing with valves matched to respective PVC test lines.

copper tubing to minimize possible contamination contributed by valves. The Tenax (TenaxGR) used in the filters is a phenylene oxide polymer that is graphitized with carbon by the manufacturer (Supelco, Bellafonte, PA, USA). Downstream from the manifold were four additional valves used for finite flow control of the air. Two of the valves were Porter valves, and two were Parker valves (Hartford Valve Co, Hartford, CT, USA) as they were available at the time for these experiments. Data obtained using hospital tubing was always compared with a control gas line using the same type of valve at the manifold, but with no plastic tubing in the copper gas-line.

Medical-grade hospital tubing was attached to the manifold system via Swagelok and Luer lock fittings (Figure 1). Custom-made pre-concentration devices referred to as 'thermal desorption tubes' that contained non-graphitized Tenax in small quartz tubes were attached to the tubing via Luer lock fittings. A bubbler was attached to the distal end of the Tenax device so that the flow rate could be monitored at this site using a Gilmont flowmeter (Fisher Scientific, NJ, USA).

Analysis of the volatile species preconcentrated in the desorption tubes was performed using direct dynamic thermal desorption (DDTD) (Ezrin and Lavigne, 1991) with a gas chromatograph-mass spectrometer (Hewlett Packard gas chromatograph HP5890 series II and mass selective detector HP5971A, Palo Alto, CA, USA). The instrument was equipped with a split/splitless injector. GC analyses were performed using a Supelcowax 10 capillary column, (30 m × 0.25 mm internal diameter) a fused silica column coated with carbowax and cross-linked with polyethylene glycol, having a film thickness of 0.25 μm (Supelco, Bellafonte, PA, USA). The flowrate of the carrier gas, helium, was approximately 1.0 mL/min. The temperatures of the injection port and the interface were set to 250°C. The standards were injected directly into the GC-MS via a splitless mode of injection and otherwise treated similarly to the Tenax samples with the GC temperature program as described below.

Two sets of experiments were performed for these lots of medical tubing: (1) thermal desorption of volatile compounds directly from PVC tubing using a decreased injection port temperature on the GC (160°C); and (2) analysis by DDTD GC-MS for volatile compounds collected on Tenax from air flowing through tubing on the manifold. Milligram quantities of PVC sample tubing were placed in desorption tubes for analysis of volatile compounds. Likewise, desorption tubes used to collect volatile organics from air flowing through tubing were placed in the customized injection port of the GC (Ezrin and Lavigne, 1991).

Air was purged from the DDTD device by the carrier gas and then the volatiles contained on the PVC tubing or Tenax were thermally desorbed (250 and 160°C, respectively, for 2 min) onto the head of the GC column via a splitless injection method, while the front portion of the GC column was cryogenically cooled with liquid nitrogen. Due to the nature of the cryo-focusing method employed and the technique used to collect the samples, a splitless injection method was used (Hill, 1997; Ezrin and Lavigne, 1991). Conditions for separation by GC were as follows: the initial oven temperature was held at 35°C for 2 min (while the sample was collected at the head of the column), and the temperature was increased from the initial to the final temperature at a rate of 15°/min. The final temperature was 250°C.

In the mass spectrometer, ionization of the chemical species was made by electron impact at an ionization potential of 70 eV. The scan range was *m/z* 10–550. Sample peaks from the GC were identified with MS by plots of total ion counts using a mass spectral database library from John Wiley and Sons (Agilent Technologies Inc., Palo Alto, CA, USA), as well as standard samples for the five compounds shown in Table 1.

Direct injection GC-MS of standards for external calibration. Quantification of compounds found in the tubing and adsorbed on Tenax (preconcentration of air passing through PVC tubing) was based on direct injection of standard solutions. Collection and recovery efficiency studies for compounds adsorbed and thermally desorbed from the Tenax, respectively, were not performed. The tabulated data for hospital tubing analyzed directly or air samples examined by the pre-concentration method using DDTD GC-MS were calculated using standard curves generated from standards directly injected (DIR) into the GC-MS. The range of concentrations of standards was 2–150 μg/mL or ppm. All individual calibration curves used three concentrations (Hill, 1997). Peak areas representing each compound were integrated for each injection of standard at the different concentrations and plotted vs moles of standard. Linear regression equations were generated from the curves using CricketGraph© (Computer Associates International Inc., Islandia, NY, USA).

The five compounds, 2-EH, BHT, DEP, *p*-NP and DEHP, in hospital tubing, lot Y6K0025, were identified by retention time and mass spectral analysis (Hill, 1997). The amounts of BHT and DEHP were determined in both lots of tubing but the amounts of 2-EH, DEP and *p*-NP were not determined in hospital tubing, lot Y6H0127, as standards for these compounds were not obtained at the time of analysis for this preliminary study.

Additional validation of direct injection of standards for quantification of these compounds included *F* and *t*-tests. A modified *t*-test was used to determine if the mean responses obtained from both DDTD and direct injection of standards in methylene chloride were the same for each compound. An *F*-test was performed to compare the precision of the two methods (Miller and Miller, 1984).

RESULTS

Analysis of volatile components released by solid PVC tubing at 250°C

The objective for analyzing solid samples of hospital tubing directly using DDTD GC-MS was to determine the presence of the five compounds in the tubing. Chromatographic and mass spectral results for one lot of hospital tubing, Y6K0025, analyzed directly by the thermal desorption technique (DDTD GC-MS), are represented in Figs 2 and 3, respectively. Figure 2 shows the chromatogram for the analysis of PVC tubing (lot Y6K0025) by direct dynamic thermal desorption. A list of the majority of components found in each lot of hospital tubing appears in the first column of Table 2. The signal size for 2-EH, DEHP, DEP and *p*-NP is reported relative to BHT for comparison between experiments, with BHT being assigned a value of 100%. For lot

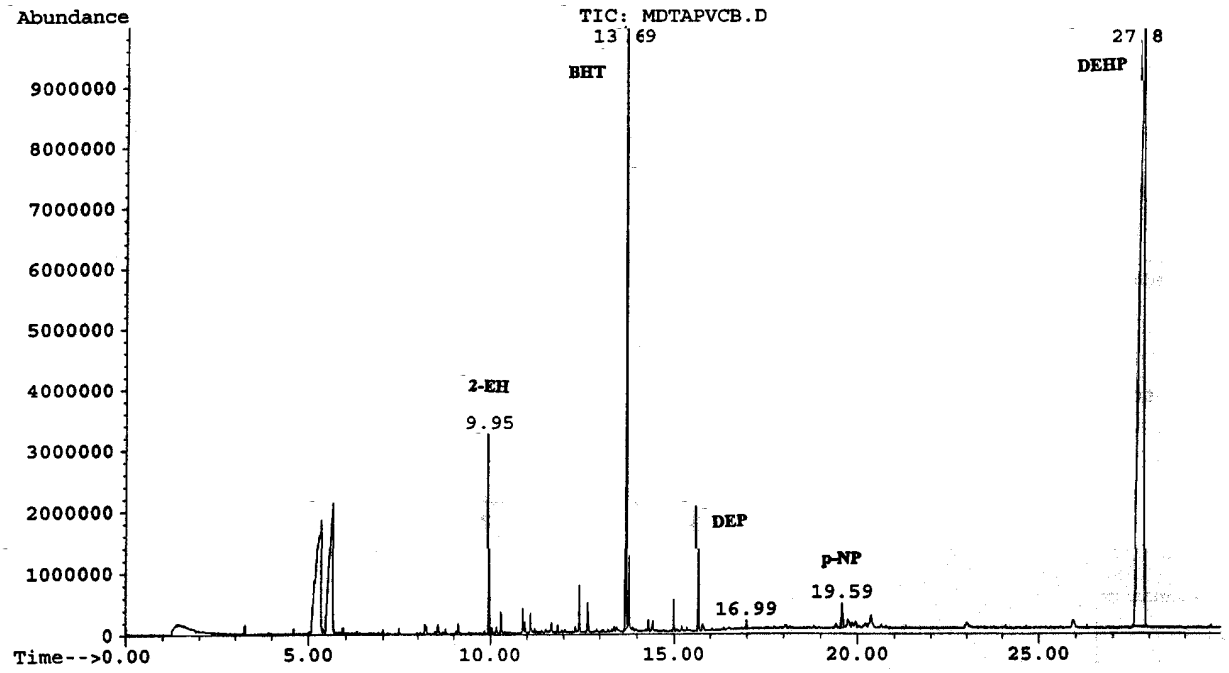

Figure 2. Direct dynamic thermal desorption GC-MS results for collection of volatile compounds from hospital tubing, lot no. Y6K0025. Sample size of tubing used in the desorption method was 11.46 mg.

Y6K0025, it was determined experimentally that the amounts of 2-EH, DEHP, DEP and *p*-NP relative to BHT were 33, 120, 1.2 and 7.5% respectively [1]. In lot Y6H0127, the amount of DEHP desorbed from the tubing was 31% relative to BHT. The amounts of these compounds were compared to BHT because this compound was found in both lots of tubing in consistent measurable amounts.

Analysis of volatile components and contaminants found in air passing through PVC tubing

The tubing used in the study was 14.1 cm long compared with the clinically used length of 243.8 cm from the individual package. The flow rate of 5 mL/min used in the study was much lower than the clinically used 3000 mL/min. A patient's maximum exposure to these compounds in a 24 h period can therefore be estimated as follows:

$$\text{exposure} = (\mu\text{g compound}) =$$
$$(\mu\text{g compound found}) \times (243.8/14.1 \text{ cm})$$
$$\times (24/17 \text{ h}) \times (3000/5 \text{ mL min})$$

(Hill, 1997). Table 3 gives estimates for maximum exposure to compounds via respiratory therapy in a 24 h period. In addition, a comparison to data from the literature on the amount of DEHP a patient is exposed to during treatment is given.

Figures 4 and 5 show the chromatograms for volatile components contained on Tenax from air passing through both lots of hospital tubing. The chromatogram b in Figs 4 and 5 represents the controls in which no tubing was present on the manifold line (Fig. 1). The last two columns in Table 2 show contaminants found in air flowing through the two lots of hospital tubing, along with control data for all-metal gas lines. As for the solid PVC samples, volatile components of PVC tubing and air passing through the tubing included aromatic, nonaromatic and aliphatic hydrocarbons, alcohols, ketones and breakdown products of dicumyl peroxide, a cross-linking agent. Note that DEHP tends to be ubiquitous in all experiments and may be caused by environmental levels (Oie *et al.*, 1997).

Quantitative results for the five components of interest are given in Table 4. The amounts of each compound per liter of air are reported. In some cases DEHP was observed but was less than the limit of detection (Table 5). With respect to the results listed in Table 4, similar amounts of BHT were observed in all air samples (four total) for two experiments using lot no. Y6H0127. In one experiment, similar amounts of DEHP were observed for two tubing samples. In the third experiment using the same lot of PVC tubing, the discrepancies in the observed amounts of DEHP between the two tubing samples was so great that the results are not included here. In these

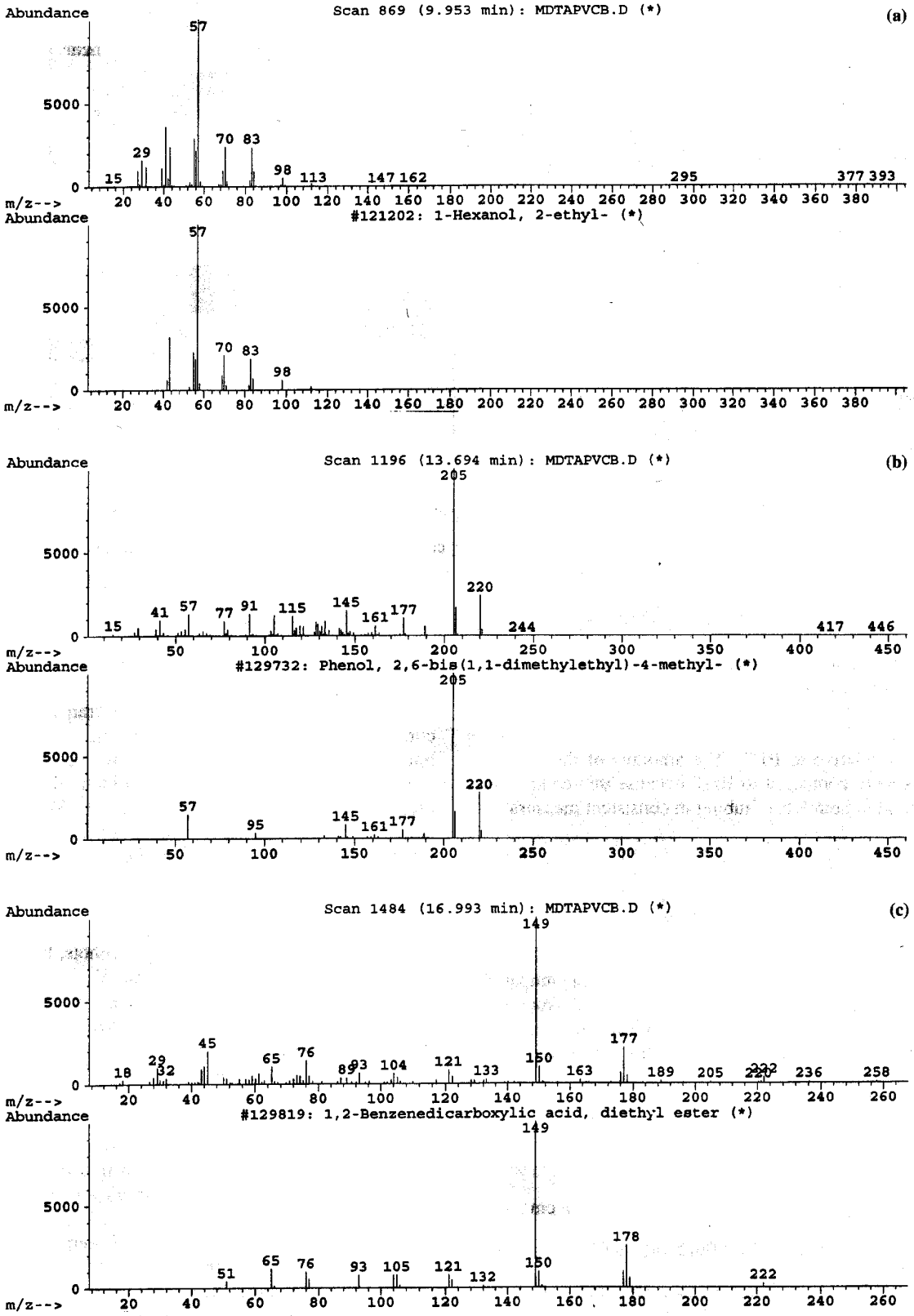

Figure 3. *Continued.*

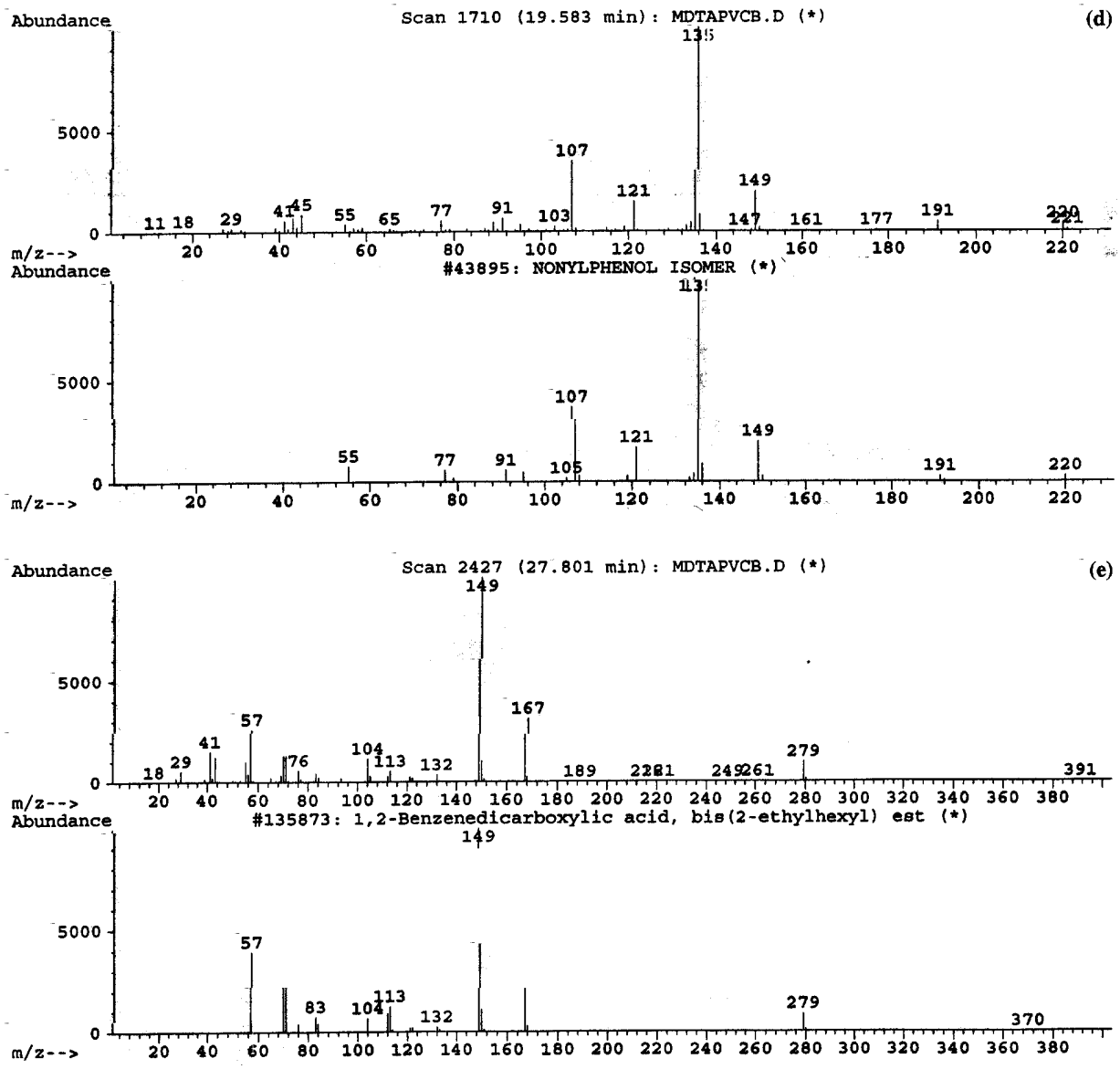

Figure 3. Mass spectra for compounds collected from air passing through the hospital tubing by preconcentration and DDTD GC-MS. The upper spectrum is from the sample; the lower spectrum is from the spectral library. (a) 2-EH; (b) BHT; (c) DEP; (d) *p*-NP; (e) DEHP.

experiments, 2-EH, DEP and *p*-NP were qualitatively identified by library match but not quantitated.

Table 4 also lists the results for analysis of air passing through hospital tubing, lot no. Y6K0025. Three experiments were performed in which two samples of hospital tubing were analyzed along with two controls when air was passed through the manifold system in the absence of hospital tubing. For this lot of medical tubing, a total of six hospital tubing samples were tested. In this series of experiments considerable amounts of 2-EH and BHT were observed. Small amounts of *p*-NP, DEHP and DEP were observed and in some cases library matches were not available, so that these compounds were not quantitated. The amount of DEHP observed in some of the samples and some of the controls was less than the limit of quantitation.

As can be observed from the table, DEHP was found in the Tenax used in the control, an indication of the ubiquity of this plasticizer in the environment. Also, when the Tenax was prepared for collection of volatile compounds by baking and testing (Hill, 1997), GC-MS results showed DEHP as it desorbed from the Tenax. The amount detected in blank runs was usually less than the limit of quantitation, 16.4 ng/L air.

The results as shown in Table 4 indicate that DEHP volatilizes onto Tenax for both lots Y6K0025 and

Table 2. Volatile compounds found in solid samples of hospital tubing

Compound	Volatilized from solid tubing lot Y6H0127, peak height relative to BHT	Volatilized from solid tubing tubing lot Y6K0025, peak height relative to BHT	Found in air passed through tubing lot Y6H0127 PVC	Control	Found in air passed through tubing lot Y6K0025 PVC	Control
BHT	1.000	1.000	√		√	
DEP	1.000	0.00792	√		√	
DEHP	0.93	0.458	√	√	√	√
2-EH	0.24	0.0958	√	√	√	√
p-Ponyl phenol	0.053	0.01417	√		√	
Benzoic acid	0.21					
Ionol	0.167	0.03625				
Cumyl alcohol	0.160	0.01167				
7-Methyl tridecane	0.10					
2,5-Dimethyl-3-hexanone	0.080					
1,1-Dimethylethyl-4-methoxy phenol	0.063	0.01708	√		√	
Ethyl tetramethyl heptane	0.052					
2-Pentyl furan	0.047		√			
Tetradecane	0.0427					
3-Methyl-5 propyl nonane	0.0387					
3-Ethyl-5-methyl hexanone	0.0347					
2,6-Dimethyl octane	0.0347					
Acetophenone	0.028	0.0408	√		√	√
2,2,5-Trimethyl hexane	0.0273					
Pentadecane	0.0247		√		√	
Hexadecane	0.0247		√		√	
1,2,3-Propanetriol	0.0247		√		√	
Heptadecane	0.020		√			
3-Methyl-3-hexanol	0.0167					
Hexanal	0.018	—	—			
Decanal	0.0147	0.00375	√		√	
2,2,9-Trimethyl decane	0.012					
2-Ethyl hexanal	0.0113					
Dimethyl nonane	0.0113					
α-Methyl styrene	0.010		√		√	
Styrene	0.0087	—	√			
3-Methyl nonane	0.0087	0.0154				
Propanal	0.0064					
Cyclohexanone	0.006					
2,2,6-Trimethyl octane	0.006					
5-Methyl undecane	0.0047	0.01875				
Acetone	0.0028	0.0025	√	√	√	√
Acetaldehyde	0.0028	—		—		

Compounds are listed in order of decreasing peak height for lot Y6H0127 after the five compounds focused on in this study.

Table 3. Results for compounds found in air in the present study and reported in the literature

Compound in hospital tubing	Range (mg)[a] (present study)	Source	DEHP exposure
2-EH	0.23–27	DEHP (present study) inhalation by preterm infants (Roth *et al.*, 1988)	0.071–0.092 mg 24 µg to 100 mg per 24 h
BHT	3.3–9.2	Blood transfusion (Jaeger and Rubin, 1972)	14–600 mg
DEP	0.00–0.035	Hemodialysis treatment	
p-NP	0.00–0.14	Gibson *et al.*, 1976	90–150 mg
		Ono, 1975 Airborne human exposure (home)	0.14–1.75 mg 0.4 µg/day

[a] Assumes linear extrapolation from conditions of study (14.1 cm length of PVC respiratory therapy tubing, 17 h, 5 mL/min) to estimated patient exposure in one day (243.8 cm length of PVC respiratory therapy tubing, 24 h, 3000 mL/min).

Table 4. Experimental results for volatile components released into air from hospital tubing using DDTD GC-MS

Compound	Lot no.	1 Tubing section 1 (ng/L air)	2 Tubing section 2 (ng/L air)	3 Control 1 (no tubing) (ng/L air)	4 Control 2 (no tubing) (ng/L air)
BHT	Y6H0127	104 ($n=2$)	92.7 ($n=2$)	nd	nd
DEHP		<16	<16	<16	nd
2-EH	Y6K0025	152 ($n=3$)	363; <6.9	<6.9	<6.9
BHT		87.1 ($n=3$)	60.7 ($n=2$)	nd	nd
DEP		<4.5	<4.53	nd	nd
p-NP		<7.3	nd	nd	nd
DEHP		<16	<16	<16	<16

Note: mass of Tenax for tubing no. Y6K0025, was 14.0–14.8 mg and the mass of Tenax varied by less than 5.5%. Mass of Tenax for tubing, no. Y6H0127, was 11.1–12.2 mg and varied by less than 8.7%. Collection efficiency of Tenax toward analytes was not measured. nd = not detected.

Y60H127. However, we found DEHP to volatilize into the airspace of the tubing less readily for lot Y6K0025 than Y60H127 (Hill, 1997), even though more DEHP was found in lot Y6K0025 from direct dynamic thermal desorption of this tubing, as observed in Fig. 2.

Direct dynamic thermal desorption and direct injection of standards

In the analysis of PVC tubing for plasticizers and additives, the collection efficiency of the Tenax and desorption of the compounds from the Tenax onto the column would be important for more accurate quantification of these compounds in the tubing. As mentioned previously, collection efficiency experiments on Tenax were not performed in this preliminary study. To validate the use of direct injection of standards for quantifying compounds thermally desorbed from PVC tubing and Tenax, the ratio of the integrated area to the number of moles for each compound at concentrations of 50 and 150 ppm were calculated. A graph of these numbers for DDTD and DIR was plotted for these concentrations (Fig. 6). This graph provides a conceptual view of the performance of DDTD as a sample introduction method compared with DIR. In addition, for a comparison of DDTD to DIR, a *t*-test showed that the mean response values were the same for both methods and an *F*-test determined that the DIR method is more precise than DDTD for quantification of these compounds and that the methods are significantly different.

Limit of detection and linear dynamic range

The linear dynamic range for this study was approximately 10–150 ppm as the calibration curves showed evidence of nonlinearity at higher concentrations (>150 ppm). Table 5 lists the linear regression data related to graphs reported elsewhere (Hill, 1997). The minimum detectable analytical signal, y, which is three times the standard deviation of the blank, s_b, was calculated. Estimated limits of detection for each compound were calculated and are reported in Table 5 (Miller and Miller, 1984).

DISCUSSION

A normal active adult inhales 14 m^3 of air in 24 h while infants per kilo weight have respirational volumes twice as large as adults (Oie *et al.*, 1997). As DEHP volatilizes slowly from plastic household products, airborne human exposure is estimated to be 0.4 μg/day (Oie *et al.*, 1997). Vapor phase exposure via respiratory therapy is estimated in the present study, which underestimates the real total exposure to DEHP and other listed compounds. A patient undergoing respiratory therapy will exceed the estimated airborne human exposure to DEHP 100-fold in a 24 h period. This could be harmful in the long-term care of patients on respiratory therapy, especially for allergy-sensitive or asthmatic individuals. Short-term care effects may not be significant with respect to toxicity.

Table 5. Linear regression results for standards from direct injection GC-MS

Compound	Equation	*r*-Value	Standard error (y/x)	Limit of detection (nmols)
2-EH	$y = 1.20 \times 10^{17}x + 5.03 \times 10^{5}$		2.63×10^{15}	0.27
BHT	$y = 5.60 \times 10^{17}x + 5.25 \times 10^{5}$		9.39×10^{15}	0.13
DEP	$y = 4.59 \times 10^{17}x - 2.95 \times 10^{6}$		5.4×10^{15}	0.10
p-NP	$y = 1.18 \times 10^{17}x - 1.37 \times 10^{6}$		2.76×10^{15}	0.17
DEHP	$y = 7.56 \times 10^{17}x + 5.63 \times 10^{6}$		2.65×10^{16}	0.21

Note: concentration range is 2–150 μg/mL. In the standard curves, the x-axis represents moles of 2-EH, BHT, DEP, *p*-NP, DEHP and the y-axis represents integrated peak area from the gas chromatogram.

The deviation of DEHP from linearity in the curve shown in Fig. 6 may be explained by two factors. One factor is the affinity of DEHP for Tenax. DEHP may bind strongly to the Tenax and not be desorbed efficiently from the Tenax during thermal desorption. In addition, the low volatility (Group, 1986; Staples *et al.*, 1997) of the DEHP may affect its vaporization from Tenax. Table 6 shows the amounts (moles) of 2-EH, BHT, BHT, DEP, *p*-NP and DEHP recovered from 11 mg of PVC tubing and from air preconcentrated on Tenax, under the same conditions. The amount of compound released by DDTD from solid samples of PVC did not predict the amount of the same compound recovered from air samples passing through hospital tubing. This observation may be

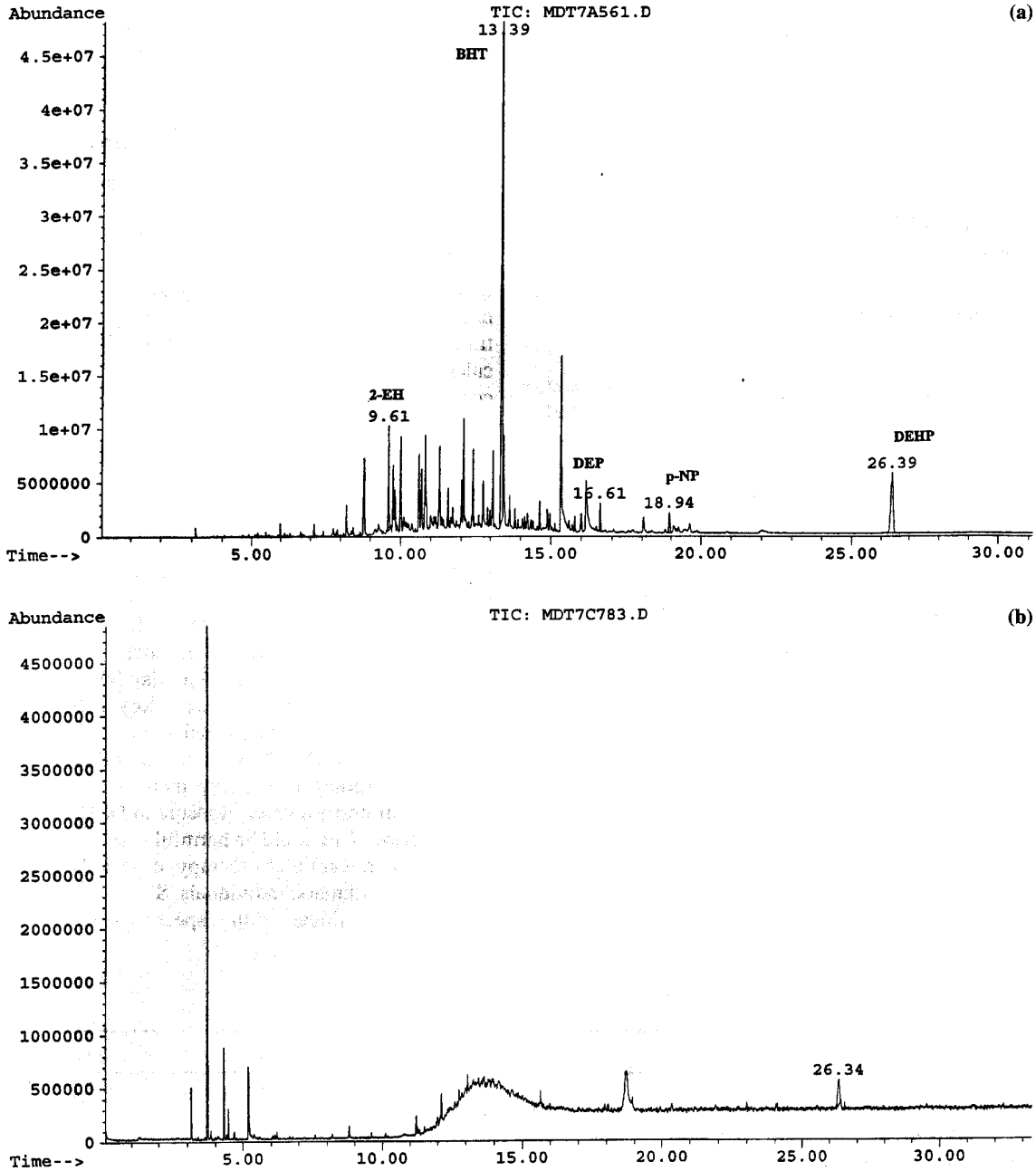

Figure 4. Direct dynamic thermal desorption DDTD GC-MS results for collection of volatile compounds onto Tenax from hospital tubing, lot no. Y6H0127. (a) Gas chromatogram for air passed through PVC tubing. (b) Gas chromatogram for control (no PVC tubing). Note the difference in scale on the *y*-axis.

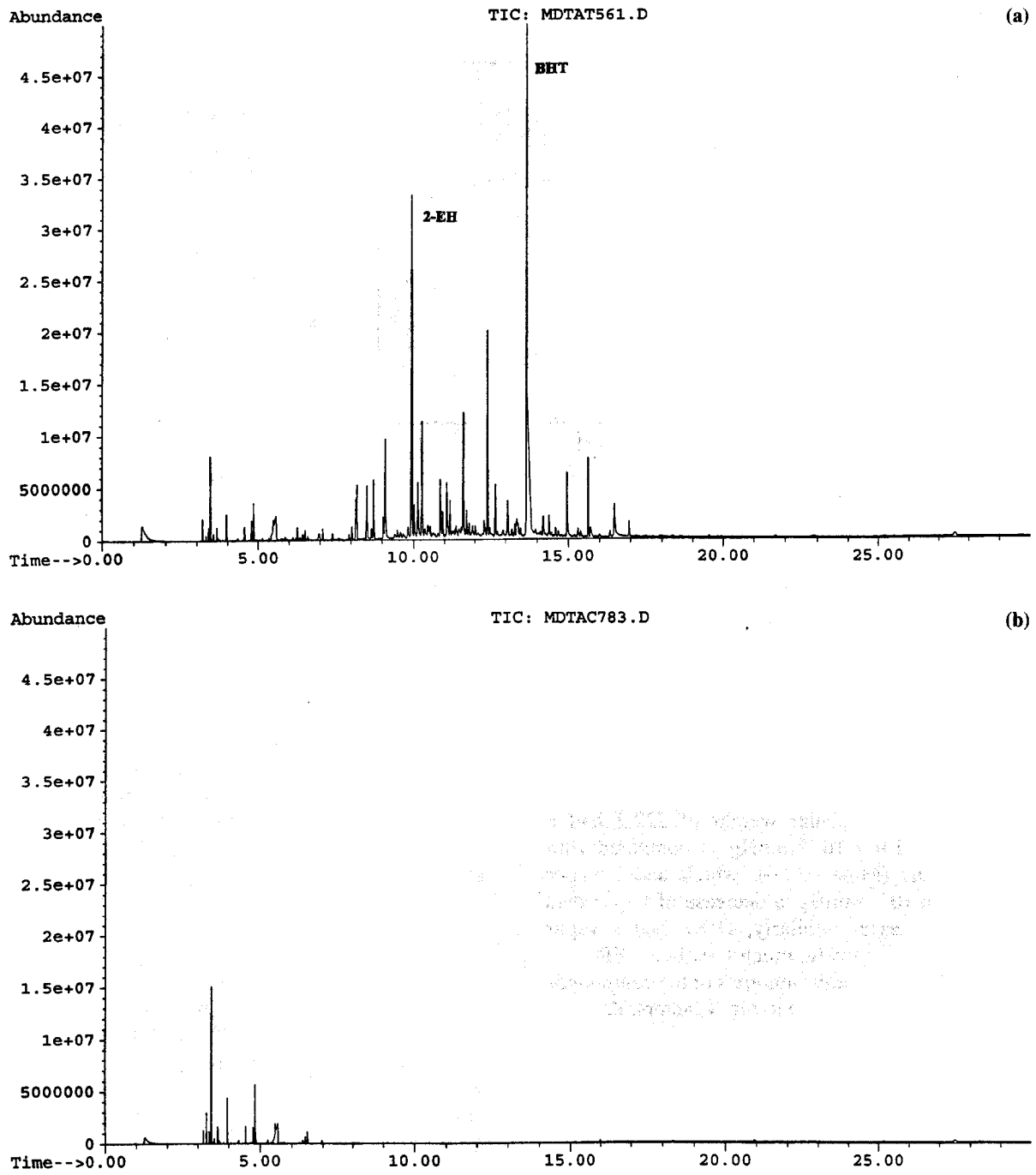

Figure 5. Direct dynamic thermal desorption GC-MS results for collection of volatile compounds onto Tenax from hospital tubing, lot no. Y6K0025. (a) Gas chromatogram for air passed through PVC tubing. (b) Gas chromatogram for control (no PVC tubing).

attributed to a variety of factors, including relative binding strengths of the compound to PVC and to Tenax, relative volatilities and the different mechanical stresses on the solid PVC samples and tubing used.

Staples *et al.* (1997) provided an extensive review of research on the environmental fate of 18 phthalate esters with alkyl chain lengths ranging from 1 to 13 hydrocarbons. Physicochemical and partitioning properties of these compounds are summarized in this review of the literature on phthalate esters. Specific parameters such as vapor pressure and octanol/water partitioning of these compounds were examined. Vapor pressure was related to the emission of these compounds into air from solid or liquid materials. Of these compounds, DEP, DEHP (two nine-carbon chains) (Hill *et al.*, 2001) and diisononyl phthalate (DINP) were evaluated for vapor pressure

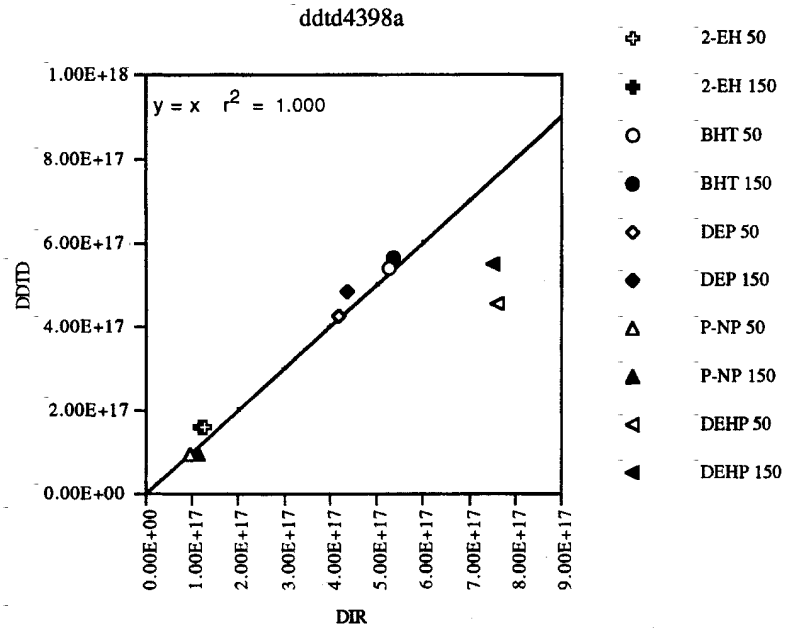

Figure 6. Calculated area to mole ratio values from Table 6 for DDTD and DIR analyses of plasticizers and additives in PVC tubing are plotted in this graph. Concentrations of 50 and 150 ppm for each standard were used. The line drawn has the theoretical slope of 1.

(mmHg) and octanol/water partition coefficients. According to Staples *et al.*, the vapor pressure of these compounds decreased by four orders of magnitude with increasing alkyl chain length. For example, DEP ($C_{12}H_{14}O_4$) with a molecular weight of 222.2 had a vapor pressure of 1.0×10^{-3} mmHg as compared with DEHP ($C_{24}H_{38}O_4$) ($M_W = 390.6$), which had a vapor pressure of 1.0×10^{-7} mmHg, a decrease of four orders of magnitude decrease. Similarly, DINP had a vapor pressure $<5.0 \times 10^{-7}$ mmHg, much less than DEP.

The variation in the relative amounts of the compounds in the present study may be due to many factors. Physical factors may include the history of the tubing prior to analysis. This history includes the manufacture of the tubing, length and conditions of storage. In addition to the physical nature of the tubing, the chemistry of the additives and the amount of manipulation of the tubing prior to analysis may have been a factor. Chemical factors include the stability of the additives in the PVC tubing over time, the volatility or vapor pressure of each additive in the tubing and the affinity of each additive for the Tenax. Finally, the flow of air through tubing (dynamic) relative to a finite moment of time in sampling (static) may affect the results.

Table 6. Comparison of amounts in moles of each compound found in air flowing through tubing relative to solid tubing samples (Lot no. Y6K0025). See Experimental section for sample mass and pre-concentration conditions

Compound	PVC (solid tubing)	Tenax (air)
	$2.7–3.9 \times 10^{-10}$	
	$5.1–5.6 \times 10^{-10}$	
	$0.096–0.14 \times 10^{-10}$	
	$0.52–0.86 \times 10^{-10}$	
	$>8.0–14 \times 10^{-10}$	

A trend is observed in the data for hospital tubing, Y6K0025, in which there is a decrease in the amount of plasticizer (DEP and DEHP) and an increase in 2-EH, the starting reagent used in the manufacture of DEHP. There was not a large amount of DEP present in either PVC tubing materials (Hill, 1997). Therefore, it was anticipated that very little DEP would be vaporized, collected and observed in the analysis of the air passing through the tubing by the pre-concentration method (Table 4). With respect to DEHP, one of the reagents used in the synthesis of DEHP is 2-EH (Kluwe, 1986; Graham, 1973; Hites, 1973). As the tubing ages (both lots of tubing were stored for an undetermined period of time), DEHP may break down to the starting materials, phthalic anhydride and 2-EH. Among the samples for the two lots of tubing, qualitatively a trend was observed in which there was an increase in 2-EH and a decrease in DEHP. To confirm the presence or absence of DEHP, in the mass spectrum for DEHP, the abundant fragment ion at *m/e* 149 represents the protonated form of phthalic anhydride (Fig. 3) (Hites, 1973). In the present study, mass spectral analysis was performed for 2-EH (Fig. 3), but not for phthalic anhydyride.

With respect to decomposition of these phthalate esters, they are suspectible to hydrolysis at slow rates. Decomposition products from hydrolysis of phthalate esters include an acid and an alcohol (Staples *et al.*, 1997). There are two steps in the hydrolysis in which the first step includes breakdown of the phthalate ester into the monoester and an alcohol. For DEHP, mono-2-ethylhexyl phthalate (MEHP) and 2-EH would be produced. The second step of hydrolysis includes breakdown of the mono-alkyl phthalate to phthalic acid and a second alcohol. Hydrolysis of the phthalate esters can be catalyzed by metal ions, anions, organic materials, acid or base (Staples *et al.*, 1997).

The values reported in this study show the presence or absence of these chemicals in the PVC tubing and not the actual amounts. For solid samples of PVC, only the fraction of a compound that was released by DDTD would be measured. For air samples, collection and recovery efficiencies are unknown. For some compounds, the calculated amount of additive found in the Tenax collected from tubing was close to or below the limit of quantification. Calculated amounts of additive from direct analysis of the tubing using DDTD were observed to be in the mid-range of the standard curves or close to the upper limits. In the analysis, standard deviations associated with the relative amount of each compound were large (Table 5), for DEHP in particular. Reasons for the variability may include the low volatility of the compound as described previously, and it may not have been thoroughly desorbed onto the column.

The observed trend for the amount of each compound desorbed from the Tenax or PVC tubing is summarized in Table 6. The amounts of DEP, *p*-NP and DEHP detected from Tenax were small compared with 2-EH and BHT. When these compounds were identified by the analysis of PVC directly using DDTD, the amounts of each compound were close to the limits of detection or lower portion of the standard curve except for DEHP.

The volatility or vapor pressure of each compound may affect the mobility of the chemical from the PVC or Tenax and limit the ability to detect the compound. It is possible that the low vapor pressure of DEHP may keep it in the PVC under the conditions used in this experiment. [When collected by thermal desorption, larger amounts of DEHP were found in the PVC compared with the amount of DEHP released from the Tenax, assuming 100% collection efficiency (Table 6).]

CONCLUSION

Environmental exposure of humans to the five compounds examined in this study may lead to chronic health effects that are difficult to determine at this time. Plastics and the additives they contain are ubiquitous in our environment, including our food (Bradbury, 1996; Lau and Wong, 1996; Ruuska *et al.*, 1987), our water (Furtmann, 1994; Group, 1986; Guisto-Norkus *et al.*, 1996; Hites, 1973), and our air (Stein *et al.*, 1987; Thuren and Larsson, 1990; Viden *et al.*, 1997). Occupational exposure to these compounds may be substantially higher for some individuals, and is already suspected to be harmful or initiate asthmatic responses in sensitive individuals. The populations most affected appear to be pre- and full-term infants requiring respiratory therapy and those genetically predisposed to allergies (Doelman *et al.*, 1990a,b; Hall, 1997; Karle *et al.*, 1997; Roth *et al.*, 1988).

The acute exposure of patients to low levels of plasticizers and other compounds studied here during short-term respiratory therapy may be insignificant when compared to total body burden from chronic environmental exposure. However, sensitive individuals, including those who have developed an allergy to a plasticizer, for example, may be at significant risk when exposed to plasticizers in the hospital.

Anecdotal observations of distress immediately following administration of oxygen are consistent with the possibility of an allergic reaction. Certainly, an asthmatic patient in respiratory distress, who is allergic to plasticizers, may not do well when the oxygen intended to provide relief is laced with a substance that causes an allergic response. The present study does not indicate that such reactions occur during respiratory therapy, only that the possibility is important to investigate further.

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REFERENCES

Astill BD, Deckardt K, Gembardt C, Gingell R, Guest D, Hodgson JR, Mellert W, Murphy SR and Tyler TR. Prechromic toxicity studies on 2-ethylhexanol in F334 rats and B6C3F1 mice. *Fundamental and Applied Toxicology* 1996; **29**: 31–39.

Astill BD, Gingell R, Guest D, Hellwig J, Hodgson JR, Kuettler K, Mellert W, Murphy SR, Sielken RL *Jr* and Tyler TR. Oncogenicity testing of 2-ethylhexanol in Fischer 344 rats and B6C3F1 mice. *Fundamental and Applied Toxicology* 1996; **31**: 29–41.

Bardana EJ *Jr* and Andrach RH. Occupational asthma secondary to

low molecular weight agents used in the plastic and resin industries. *European Journal of Respiratory Diseases* 1983; **64**: 241–251.
Bradbury J. UK panics over phthalates in babymilk formulae. *Lancet* 1996; **347**: 1541.
Colon I, Caro D, Bourdony CJ and Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environmental Health Perspectives* 2000; **108**(9): 895–900.
Doelman CJ, Dorm PJ and Bast A. Plasticizers, another burden for asthmatics? *Agent Action Supplements: Medical Airway Hyperreactivity* 1990; **31**: 81–84.
Doelman CJ, Dorm PJ and Bast A. Plasticizers and bronchial hyperreactivity. *Lancet* 1990; **335**: 725.
Dohl R, Martinati LC and Boner AL. Monitoring of bronchial asthma. *Respiratory Medicine* 1997; **91**: 581–586.
Ezrin M and Lavigne G. Failure analysis using gas chromatography/mass spectroscopy. *Society of Plastic Engineering, ANTEC Conference Proceedings* 1991; 2230–2233.
Furtmann K. Phthalates in surface-water—a method for routine trace-level analysis *F resenius. Journal of Analytical Chemistry* 1994; **348**(4): 291–296.
Graham PR. Phthalate ester plasticizers—why and how they are used. *Environmental Health Perspectives* 1973; **3**: 3–12.
Group EF. Environmental fate and aquatic toxicology studies on phthalate esters. *Environmental Health Perspectives* 1986; **65**: 337–340.
Guisto-Norkus R, Gounili G, Wisniecki P, Hubball JA, Smith SR and Stuart JD. An environmentally significant experiment using GC/MS and GC retention indices in an undergraduate analytical laboratory. *Journal of Chemical Editions* 1996; **73**(12): 1176–1178.
Gibson TP, Briggs WA and Boone BJ. Delivery of di-2-ethylhexyl phthalate to patients during hemodialysis. *Journal of Laboratory and Clinical Medicine* 1976; **87**: 519–524.
Hall IP. The future of asthma. *British Medical Journal* 1997; **314**: 45–49.
Hill SS. Analysis of contaminants in oxygen from PVC tubing used in respiratory therapy, chromatographic components in electrochemical sensors and a model for the degradation of electrical cable insulation. Ph.D. dissertation, Chapter 3, 1997.
Hill SS, Shaw BR and Wu AHB. The clinical effects of plasticizers, antioxidants, and other contaminants in medical polyvinylchloride tubing during respiratory and non-respiratory exposure. *Clinical Chimical Acta* 2001; **301**: 1–8.
Hirzy JW. Carcinogenicity of general-purpose phthalates: structure-activity relationships. *Drug Metabolism Review* 1989; **21**: 55–63.
Hites RA. Phthalates in the Charles and Merrimack Rivers. *Environmental Health Perspectives* 1973; **3**: 17–21.
Jaeger RL and Rubin RJN. Migration of a phthalate ester plasticizer from polyvinylchloride blood bags into stored human blood and its localization in human tissue. *New England Journal of Medicine* 1972; **287**: 1114–1118.
Jobling S, Reynolds T, White R, Parker MG and Sumptor JP. A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. *Environmental Health Perspectives* 1995; **103**(6): 582–587.
Karle VA, Short BL, Martin GR, Bulas DI, Getson PR, Luban NLC, O'Brien AM and Rubin RJ. Extracorporeal membrane oxygenation exposes infants to the plasticizer, di (2-ethylhexyl) phthalate. *Critical Care Medicine* 1997; **25**: 696–703.
Khaliq MA, Alam MS and Srivastava SP. Implications of physico-chemical factors on the migration of phthalate esters from tubing commonly used for oral/nasal feeding. *Bulletia of Environmental Contamination and Toxicology* 1992; **48**: 572–578.
Klotz DM, Beckman BS, Hill SM, McLachlan JA, Walters MR and Arnold SF. Identification of environmental chemicals with estrogenic activity using a combination of *in vitro* assays. *Environmental Health Perspectives* 1996; **104**(10): 1084–1089.
Kluwe WM. Carcinogenic potential of phthalic acid esters and related compounds: structure–activity relationships. *Environmental Health Perspectives* 1986; **65**: 271–278.
Labow RS, Barry YA, Tocchi M and Keon WJ. The effect of mono (2-ethylhexyl) phthalate on an isolated perfused rat heart-lung preparation. *Environmental Health Perspectives* 1990; **89**: 189–193.
Lau OW and Wong SK. Determination of plasticizers in food by gas chromatography-mass spectrometry with ion-trap mass detection. *Journal of Chromatographic Science* 1996; **737**(2): 338–342.
McMurry J. Organic Chemistry. Brooks/Cole: California, 1988; Chap. 31.
Miller JC and Miller JN. Statistics for Analytical Chemistry, Chapters 3 and 4, 1984.
Nassberger L, Arbin A and Ostelius J. Exposure of patients to phthalates from polyvinyl-chloride tubes and bags during dialysis. *Nephron* 1987; **45**: 286–290.
Oie L, Hersoug L-G and Madsen JO. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. *Environmental Health Perspectives* 1997; **105**: 972–978.
Ono K, Tatsukawa R and Wakimoto T. Migration of plasticizer from hemodialysis blood tubing. *JAMA* 1975; **234**: 948–949.
Rock G, Labow RS and Tocchi M. Distribution of di(2-ethylhexyl) phthalate and products in blood and blood components. *Environmental Health Perspectives* 1986; **65**: 309–316.
Roth B, Herkenrath P, Lehmann HJ, Ohles HD, Hömig HJ, Benz-Bohm G, Kreuder J and Younossi-Hartenstein. Di-(2-ethylhexyl)-phthalate as a plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. *European Journal of Pediatrics* 1988; **147**: 41–46.
Ruuska RM, Korkeala H and Liukkonen-Lilja H. Migration of contaminants from milk tubes and teat liners. *Journal of Food Protection* 1987; **50**: 316–320.
Schulz CO. Assessing human health risks from exposure to di(2-ethylhexyl) phthalate (DEHP) and related phthalates: Scientific Issues. *Drug Metabolism Review* 1989; **21**: 111–120.
Snell RP. Capillary GC analysis of compounds leached into parenteral solutions packaged in plastic bags. *Journal of Chromatographic Science* 1989; **27**: 524–528.
Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N and Serrano FO. The E-Screen assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. *Environmental Health Perspectives* 1995; **103**(7): 113–122.
Soto AM, Justicia H, Wray JW and Sonnenschein C. *p*-Nonylphenol: an estrogenic xenobiotic released from 'modified' polystyrene. *Environmental Health Perspectives* 1991; **92**: 167–173.
Stancel GM, Boettger-Tong HL, Chiappetta C, Hyder SM, Kirkland JL, Murthy L and Loose-Mitchell DS. Toxicity of endogenous and environmental estrogens: what is the role of elemental interactions? *Environmental Health Perspectives* 1995; **103**(7): 29–33.
Staples CA, Peterson DR, Parkerton TF and Adams WJ. The environmental fate of phthalate esters: a literature review. *Chemosphere* 1997; **35**: 667–749.
Stein VB, Thakor AM and Narang RS. Simplified method for determining polychlorinated biphenyls, phthalates, and hexachlorocyclohexanes in air. *Journal of the AOAC* 1987; **70**(4): 721–723.
Thomas JA, Darby TD, Wallin RF, Garvin PJ and Martis L. A review of the biological effects of di-(2-ethylhexyl) phthalate. *Toxicology and Applied Pharmacology* 1978; **45**: 1–27.
Thuren A and Larsson P. Determination of phthalates in aquatic environments. *Environmental Health Perspectives* 1990; **24**: 554–559.
Vainiotalo S and Pfaffli P. Air impurities in the PVC plastics processing industry. *Annals of Occupational Hygiene* 1990; **34**(6): 585–590.
Viden I and Janda V. Simple thermal desorption unit for analysis of volatile organic substances in air samples by GC-MS. *Journal of High Resolution Chromatography* 1997; **20**(3): 181–182.
Vitali M, Leoni V, Chlavarini S and Cremisini C. Determination of 2-ethyl-1-hexanol as contaminant in drinking water. *Journal of the AOAC* 1993; **76**(5): 1133–1137.