of benomyl, and the average potential respiratory exposure was 0.003 mg of benomyl/application cycle.

The data obtained from this research indicate a relatively low level of benomyl exposure. Additionally, a "worst case" approach was taken in this study, since much of the dermal exposure reported was from areas often converged with protective clothing, i.e., gloves and long-sleeved shirts. If the assumption of basic protective clothing is made, the practical exposure levels would be further reduced.

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A Multiresidue Procedure for the Determination and Confirmation of Acidic Herbicide Residues in Human Urine

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Chlorophenoxy acid herbicides (2,4-D, 2,4,5-T, 2,4-DP, 2,4-DB, and silvex), dicamba, pronamide, picloram, and PCP were determined simultaneously in human urine. Samples were hydrolyzed with mineral acid to liberate conjugated residues and to convert pronamide metabolites to 3,5-dichlorobenzoic acid. Acids were isolated from the urine hydrolysate by acid/base partitioning and derivatized with ethereal diazomethane. Pesticides were determined quantitatively by electron capture gas chromatography (EC-GC), and structures were confirmed by computer-controlled gas chromatography–mass spectrometry (GC–MS). Recoveries were 80–104% for fortifications at 0.1 mg/L, and detection limits for herbicides in urine were 0.05–0.1 mg/L by EC-GC and 0.1–0.5 mg/L by GC–MS. Derivatization with pentafluorobenzyl bromide was unacceptable for several reasons: it enhanced the electron capture response of urinary acids and the specific detection of the PFB analogues by mass spectrometry was limited by the similarity of their electron impact mass spectra.

The chlorophenoxy acid herbicides are widely used in agriculture, commerce, and homes to control terrestrial and aquatic broadleaf weeds. The halogenated benzoic acids, pyridine derivatives, and other herbicide classes supplement the biological activities of the phenoxyalkanoic compounds and provide a variety of phytotoxic responses in higher plants. Human exposure is an inevitable, but controllable result of the widespread use of these commercially important chemicals. For reliable assessment of human exposure to pesticides, analytical methods with a high degree of qualitative accuracy are required. Analysis of biological fluids by EC-GC alone provides inadequate qualitative information for positive identification of pesticide residues. Supplemental cleanup techniques increase specificity but cannot eliminate analytical ambiguity.

The chlorophenoxy acid herbicides are excreted largely unmetabolized in the urine of animals (Clark et al., 1964), and the urinary levels are well correlated with the rates of exposure (Shafik et al., 1971; Khanna and Fang, 1966). For these reasons urinalysis is useful qualitatively and quantitatively for determining occupational and extraneous exposure to these herbicides. Exposure to pentachloro- and other halogenated phenols can be determined by urinalysis, but recoveries are unacceptable without hydrolysis (Edgerton and Moseman, 1979; Shafik et al., 1971).

The objective of this investigation was to develop a generalized, multiresidue procedure for trace analysis of herbicidal acids in urine that would be readily adaptable to confirmation by mass spectrometry. Acid hydrolysis was utilized to increase the recovery of conjugated residues and to include pronamide and its metabolites in the multiresidue scheme. Finally, methyl and pentafluorobenzyl derivatives of urine extracts were examined to determine their applicability to detection by both EC-GC and GC–MS.

EXPERIMENTAL SECTION

Chemicals. Analytical reference standards of 4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid (picloram, 99%), 3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide (pronamide, 97%), 3,6-dichloro-2-methoxybenzoic acid (dicamba, 99.9%), (2,4-dichlorophenoxy)acetic acid (2,4-D,

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97%), 2-(2,4-dichlorophenoxy)propanoic acid (2,4-DP, 93.2%), 4-(2,4-dichlorophenoxy)butanoic acid (2,4-DB, 99.4%), pentachlorophenol (PCP, 99+%), (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T, 98.7%), and 2-(2,4,5-trichlorophenoxy)propanoic acid (silvex, 99%) were provided by the Quality Assurance Section, U.S. Environmental Protection Agency (Research Triangle Park, NC). α-Bromo-2,3,4,5,6-pentafluorotoluene (PFBB, 99+%) and 3,5-dichlorobenzoic acid (3,5-DCB, 99%) were obtained commercially. Pesticide residue grade solvents were used; distilled water was used for solvent partitioning. Ethereal diazomethane was prepared by alkaline hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in a commercially available, distillation apparatus designed for this purpose (Aldrich Chemical Co.). The reagent was stored at -5 °C prior to use.

Apparatus. Gas-liquid chromatography was performed on a Tracor Micro-Tek Model 220 instrument fitted with a ^{63}Ni electron capture detector operated in DC mode. A 4 m × 4 mm (i.d.) glass column packed with 80-100-mesh Gas-Chrom Q coated with 4% SE-30-6% OV-210 was used. Operating conditions were as follows: injector temperature, 240 °C; detector temperature 300 °C; column temperature 180 °C; nitrogen carrier gas flow rate 50 mL/min; purge gas flow rate 30-40 mL/min. The less volatile pentafluorobenzyl (PFB) analogues required a column temperature of 220 °C and a 90 mL/min carrier gas flow rate.

An LKB 2091 mass spectrometer interfaced to a Pye 104 gas chromatograph was used. The chromatograph, fitted with a 2 m × 4 mm i.d. glass column containing the same packing described previously, was operated under the following conditions: injector temperature, 280 °C; column oven temperature 200 °C; separator temperature 270 °C; helium carrier gas flow rate, 20 mL/min; source temperature, 300 °C. The unit resolution, magnetic sector spectrometer was interfaced to and controlled by a data system consisting of a Dec PDP 11/05 computer, Tektronix 4010 display terminal, a Versatec Matrix printer, and a commercially available, GC-MS software package. Ionization was by electron impact (70 eV) and the spectrometer scanned the mass range 35-350 amu every 3 s.

Urine Hydrolysis. One-hundred milliliters of urine, 20 mL of concentrated hydrochloric acid, and boiling stones were combined in a flask and heated in a 95 °C water bath for one h. The flask was equipped with a condenser cooled with circulating ice water (3 °C) during hydrolysis, and this condenser was not detached until the sample was thoroughly chilled in an ice bath. Smaller urine volumes were analyzed without modification of the method by diluting the sample to volume with distilled water.

Extraction and Partitioning. The hydrolysate was extracted in a separatory funnel with 3 × 40 mL of diethyl ether, and the organic layer was filtered through glass wool into a second separatory funnel. Minor emulsions, which formed during the initial extraction, separated on the glass wool, and any water collected in the lower separatory funnel was discarded. The organic layer was extracted with 25 mL of 0.05 N sodium hydroxide and 2 × 40 mL of 4% sodium bicarbonate (w/v). The combined aqueous extract was acidified by addition of 6 mL of concentrated hydrochloric acid; indicator paper was used to test the acidity of the solution. The separatory funnel was well ventilated to release the large volume of gas liberated upon acidification. Organic acids were isolated by solvent extraction with 2 × 50 mL of diethyl ether, and the combined extract was dried (sodium sulfate); the separatory funnel and drying agent were washed with 10 mL of fresh ether, and this rinse was combined with the sample. The extract was concentrated to approximately 5 mL on a rotary evaporator, transferred quantitatively to a stoppered, volumetric test tube, and reduced to approximately 0.1 mL under a stream of dry nitrogen.

Derivatization. Caution: Due to the volatility and toxicity of the reagents, a high-draft hood, gloves, and other protective clothing should be used. Samples were esterified by dropwise addition of 4 mL of ethereal diazomethane. The reaction was allowed to proceed 2 h in a sealed tube at room temperature with occasional vortex mixing. Excess diazomethane, detectable by its yellow color, was removed by concentrating the sample to approximately 0.1 mL under a stream of dry nitrogen. For EC-GC determinations, a sample aliquot equivalent to 10 mL of urine was derivatized, and this fraction was diluted to 25 mL with petroleum ether before analysis. Structural confirmation by GC-MS using a magnetic sector instrument required alkylation of the entire extract (equivalent to 100 mL of urine) and a final sample volume of 0.20 mL. Injection volumes were 6 μL for EC-GC and GC-MS; the solvent peak was vented from the GC-MS source in order to minimize contamination.

Recovery Determination. A mixed standard solution consisted of 0.10 mg/mL of each herbicide in acetone; 3,5-DCB was subsituted for pronamide. Control urine samples (100 mL) were fortified at 0.050, 0.10, or 0.50 mg/L by addition of 50, 100, or 500 μL of the mixed standard solution, respectively; a 50-μL volumetric syringe was used for the transfer. Fortified samples were subjected to hydrolysis prior to analysis.

Method Development. Preliminary experiments, not recommended analytical methodology, are described in this section. Acid-catalyzed hydrolysis of pronamide was investigated by heating pronamide (0.233 mg/L) in 2 N hydrochloric acid at 70 or 95 °C for up to 3 h. 3,5-DCB liberated was monitored; the maximum theoretical yield of dichlorobenzoic acid was 0.167 mg/L.

Control urine samples (as in Recovery Determination) were subjected to urine hydrolysis and extraction and partitioning; extracts were diluted to 10 mL with acetone, and 1-mL portions were transferred to sealable, 50-mL tubes. Pentafluorobenzyl esters were formed by using only a fraction of the extract (equivalent to 10 mL of urine) for reasons elaborated later. Samples were combined with 4.0 mL of acetone, 30 μL of 30% sodium carbonate, and 2.0 mL of freshly prepared 1% PFBB (w/v) in acetone. The mixture was thoroughly agitated and allowed to undergo reaction for 18 h at room temperature. The reaction conditions and procedure are similar to those of Chau and Terry (1976). After 3.5 mL of water was added to the reaction mixture, PFB derivatives were extracted with 5 mL of benzene. Three milliliters of the organic layer was dried by passing the solvent through 60 mm of sodium sulfate in a disposable pipet. The sample volume was adjusted to 25 mL with petroleum ether.

RESULTS AND DISCUSSION

Pentafluorobenzylation vs. Methylation. Pentafluorobenzyl bromide is useful for converting polar, acidic analytes to highly electron capturing derivatives for gas chromatography. PFB derivatives are less polar than corresponding methyl esters (or ethers), but due to higher molecules weights, they exhibit larger capacity factors desirable for separation efficiency (Chau and Terry, 1976). The analysis of chlorophenoxy alkyl acid herbicides in urine using PFB esters has been described (DeBeer et al., 1978); samples were analyzed by GC-MS in this study.

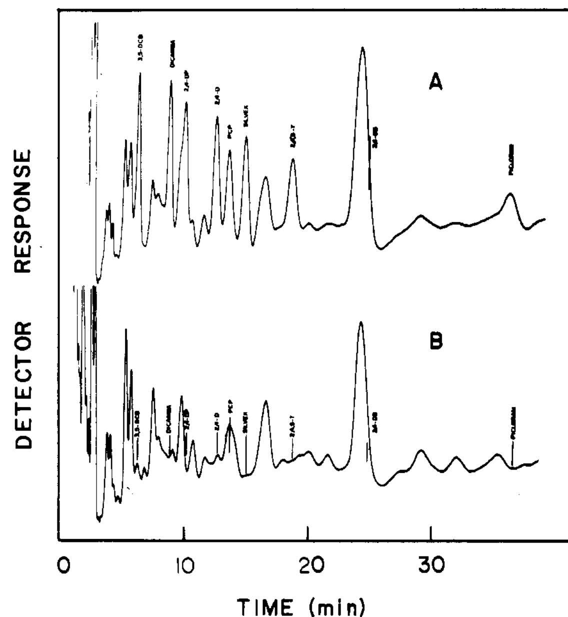

Figure 1. Electron capture gas chromatograms of urine treated with pentafluorobenzyl bromide: (A) urine fortified with 0.5 mg/L of each herbicide; (B) control urine.

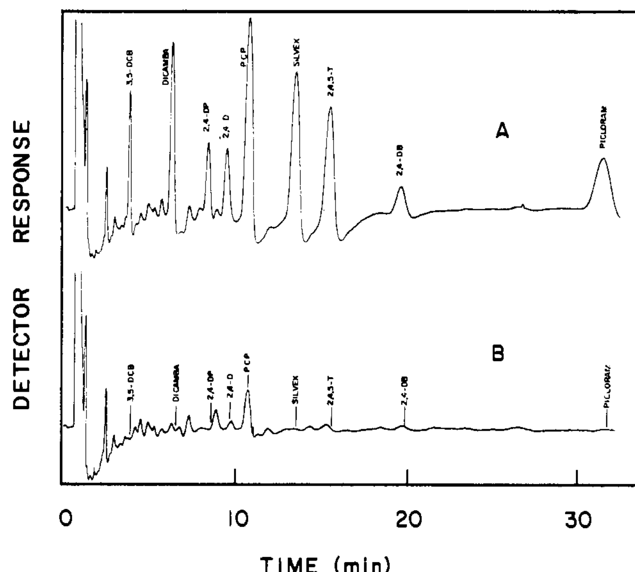

Figure 2. Electron capture gas chromatograms of urine alkylated with ethereal diazomethane: (A) urine fortified with 0.1 mg/L of each herbicide; (B) control urine.

Normal human urine contains a large number of acidic organic compounds (Tanaka et al., 1980). Derivatization of the acidic fraction of urine with PFBB converts endogenous substances, even those present at trace levels, to highly electron capturing species. Control urine treated with PFBB exhibited major interferences which increased the limits of detection for the herbicides examined; 2,4-DB, picloram, 2,4-DP, and PCP were not detectable at 0.5 mg/L when the fluorinated reagent was used (Figure 1). Matched control urines derivatized with diazomethane were relatively uncontaminated in comparison (Figure 2), and in these samples each herbicide residue was detectable at levels below 0.10 mg/L. The electron capture detector was far more selective toward the chlorinated pesticides in the urine matrix when samples were derivatized with diazomethane.

Derivatization of greater than 10% of the urine extract with PFBB resulted in poor recovery of herbicides in spite of an 18-h derivatization period. The low recoveries were apparently not associated with pH changes as addition of greater amounts of potassium carbonate did not improve yields. A large excess of this reagent was required for quantitative derivatization of herbicide standards. Treatment with over 100 μmol of PFBB quantitatively benzylated 0.1–2 μmol of dicamba and 2,4-D, but recoveries were unacceptably low above 4 μmol. Low pesticide recoveries from large urine samples may be due to an inadequate excess of the reagent. PFBB derivatization was not used routinely because of these limitations.

Table I. Retention Times and Relative Detector Responses for Methylated Herbicides and Methyl-3,5-DCB

compound	t_R', min[a]	RPH-PCP[b]	RPA-PCP[c]
3,5-DCB	3.2	0.48	0.17
dicamba	5.7	0.80	0.51
2,4-DP	7.9	0.33	0.24
2,4-D	9.0	0.33	0.36
PCP	10.3	1.00	1.00
silvex	13.1	0.73	0.80
2,4,5-T	15.1	0.75	0.95
2,4-DB	19.4	0.43	0.70
picloram	31.5	0.32	0.83

[a] Adjusted retention time, from solvent peak. [b] Peak height ratio, relative to PCP. [c] Peak area ratio, relative to PCP.

Table II. Hydrolysis of Pronamide

time, h	T, °C	% recovery[a]
1	70	2
2	70	4
1	95	31
1.5	95	37
3	95	57

[a] Percent of pronamide recovered as methyl-3,5-dichlorobenzoic acid.

Gas–Liquid Chromatography. The gas chromatography column used was effective in resolving the methylated pesticide standards, and an isothermal separation could be completed in less than 40 min (Table I). The relatively long packed column was capable of separating dicamba from its aromatic isomer in formulations, air samples, human urine, and other sample types (Draper and Street, 1982). The isomeric material, which has not been described in the literature, was not distinguishable from dicamba on other liquid phases.

The electron capture detector was most responsive to pentachlorophenol, and the least chlorinated compounds exhibited the smallest response factors (Table I). (4-Chloro-2-methylphenoxy)acetic acid (MCPA) gave only a very weak response relative to those of the herbicides studied here.

Analysis of Urine. Only a small fraction of pronamide is excreted unmetabolized in the urine, but the majority of the urinary metabolites are, like pronamide, amides that yield 3,5-dichlorobenzoic acid upon hydrolysis (Yih and Swithenbank, 1971). The hydrolysis of pronamide and its metabolites to the common product has been applied previously for analytical purposes (Adler et al., 1972). Pronamide residues were readily detected as 3,5-DCB, but hydrolysis was not complete after 1 h at 95 °C (Table II). Quantitative recovery of pronamide-related residues would require extended hydrolysis or more rigorous reaction conditions (Adler et al., 1972). As described, however, the method successfully detects urinary excretion of pronamide's metabolic products. The hydrolysis of chlorinated phenol conjugates, including those of PCP, is known to be rapid under similar conditions (Shafik et al., 1971; Edgerton and Moseman, 1979).

Table III. Recovery of Pesticides and 3,5-DCB from Urine[e]

compound	recovery, %: mean[a]	recovery, %: SD[b]	total error, %[c]
3,5-DCB	94	7	21
dicamba	92	5	18
2,4-DP	90	12	36
2,4-D	97[d]	8	22
PCP	80	6	32
silvex	88	6	25
2,4,5-T	94	7	19
2,4-DB	98	11	30
picloram	104	6	20

[a] Five replicates. [b] Standard deviation. [c] Total error (McFarren et al., 1970): excellent < 25; acceptable between 25 and 50. [d] Four replicates. [e] Apparent residues in matched controls were subtracted.

Table IV. Apparent Residues in First Void Urines of Herbicide Applicators[b]

compound	apparent residue, mg/L
pronamide	0.010 ± 0.006
dicamba	0.008[a]
2,4-DP	0.003[a]
2,4-D	0.006[a]
PCP	0.014 ± 0.007
silvex	0.002 ± 0.001
2,4,5-T	0.017 ± 0.018
2,4-DB	0.055 ± 0.006
picloram	0.008 ± 0.002

[a] One analysis; sample not obtained from pesticide applicator. [b] Five replicates were analyzed except where noted.

Relatively large urine samples were extracted to obtain sufficient material for structural confirmation with the magnetic sector mass spectrometer. The present method has been used to analyze first void urines of herbicide applicators (Draper and Street, 1982), and these samples were commonly over 200 mL, allowing duplicate analyses. Only 10 mL of urine was required, however, for analysis by EC-GC alone, and urine samples less than 100 mL can be analyzed without significantly modifying the method if they are diluted to volume with distilled water before hydrolysis. Sensitivity is not lost if the final sample volume is adjusted appropriately.

Urine samples were black after hydrolysis and contained charred particulate matter. Filtration of the ether phase through glass wool yielded a clear yellow solution free of particulates, and acid/base partitioning eliminated considerable amounts of coextracted material based on pigmentation in the discarded phases. A similar acid/base cleanup has been applied to the analysis of 2,4-D, 2,4,5-T, and dicamba in soil (Purkayastha, 1974).

Recovery of Pesticides from Urine. Mean through-the-method recoveries ranged from 80 to 104% for fortifications at 0.1 mg/L (Table III). PCP recovery, although acceptable, was significantly lower than recoveries for the carboxylic acid residues ($P = 0.05$). Total error, an index of accuracy and precision for an analytical procedure (McFarren et al., 1970), was acceptable for 2,4-DB, PCP, and 2,4-DP analyses and excellent for the other residues. Recommended detection limits were below 0.05 mg/L for most herbicides; at this fortification level recoveries varied between 70 and 120%.

An extensive survey of control urines was not undertaken. Table IV, however, contains data on the EC-GC analysis of first void urine samples from herbicide applicators known to be exposed to 2,4-D and dicamba; apparent residues of 2,4-DP were not reported either as this

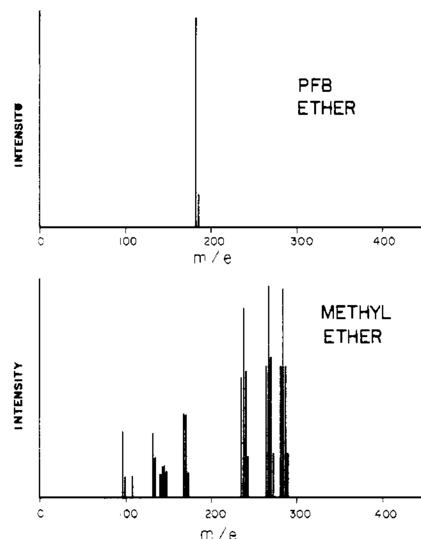

Figure 3. Electron impact mass spectra of pentachlorophenol as the PFB derivative (top) and as the methyl ether (bottom).

compound had been added as an internal standard (Draper and Street, 1982). Apparent residues in these control samples averaged between 0.003 and 0.017 mg/L for each herbicide except 2,4-DB. For these pesticides a detection limit of 0.05 mg/L is established; a detection limit of 0.1 mg/L for 2,4-DB is recommended due to matrix interference.

Qualitative Confirmation by GC-MS. The 70-eV electron impact mass spectrum of each herbicide PFB derivative exhibited the pentafluorotropilium ion, *m/e* 181, as a base peak. In the case of PCP, the spectrum contained only the base peak and its M + 1 isotopic ion (Figure 3). The influence of the PFB substituent on fragmentation patterns was evident in the chlorophenoxy, benzoic, and picolinic acid spectra as well. Few major, unique ions were present: picloram, *m/e* 196 ($C_5H_3Cl_3N_2$, 73% intensity relative to the base peak); dicamba, *m/e* 203 ($C_8H_5Cl_2O_2$, 55%) and *m/e* 189 ($C_7H_3Cl_2O_2$, 31%); 3,5-DCB, *m/e* 173 ($C_7H_3OCl_2$, 35%). Mass spectra of 2,4-D, 2,4-DB, 2,4-DP, 2,4,5-T, and silvex PFB esters were published previously (DeBeer et al., 1978). Molecular ions were weak or absent, and for two of the PFB derivatives, 2,4-DB and 2,4,5-T, unique fragment ions were only of minor intensity. The fragmentation of these derivatives has not been examined at low ionization energies or by chemical ionization, techniques which frequently enhance the relative intensity of the molecular ion.

The fragmentation of methyl analogues was more complex. Methyl-PCP yielded major fragment ions at *m/e* 278 (M^+), *m/e* 263 (C_6OCl_5), and *m/e* 235 (C_5Cl_5), and with the associated chlorine isotope clusters, a large number of ions were available for selective ion monitoring (SIM).

The major fragment and isotopic ions of each methylated herbicide are summarized in Table V. Only major ions of high mass (>*m/e* 100) were used for SIM as they tend to be more specific. The intensities (relative to the base peak) of the diagnostic ions are listed in Table V as well. Unequivocal confirmation of the herbicide structures tentatively identified in urine can be achieved by demonstrating that the diagnostic ions correspond in both retention time and relative abundance.

The mass spectrometer responded well to relatively concentrated urine extracts. The instrument, however, was not suitable for routine quantitation of herbicide residues as the detector sensitivity deteriorated with extensive use. Quadrupole mass spectrometers, which are more sensitive than magnetic sector instruments in selective ion moni-

Table V. Mass Spectra of Methylated Herbicides and Methyl-3,5-DCB

compound	*m/e* (fragment, intensity relative to base peak)[a]
2,4-D	234 (M^+, 0.90), 199 ($C_9H_8O_3Cl$, 1.0), 175 ($C_7H_5OCl_2$, 1.0), 161 ($C_6H_3OCl_2$, 0.5), 145 ($C_6H_3Cl_2$, 0.6), 133 ($C_5H_3Cl_2$, 0.5)
2,4-DB	231 ($C_{10}H_9O_2Cl_2$, 0.1), 162 ($C_6H_4OCl_2$, 0.3), 133 ($C_5H_3Cl_2$, 0.1), 101 ($C_5H_9O_2$, 1.0)
2,4-DP	248 (M^+, 0.2), 189 ($C_8H_7OCl_2$, 0.4), 162 ($C_8H_7OCl_2$, 1.0), 145 ($C_6H_3Cl_2$, 0.1), 133 ($C_5H_3Cl_2$, 0.2)
2,4,5-T	268 (M^+, 0.7), 233 ($C_9H_7O_3Cl_2$, 1.0), 209 ($C_7H_4OCl_3$, 0.7), 196 ($C_6H_3OCl_3$, 0.2)
silvex	282 (M^+, 0.3), 223 ($C_8H_6OCl_3$, 0.4), 196 ($C_6H_3OCl_3$, 1.0)
3,5-DCB	204 (M^+, 0.3), 173 ($C_7H_3OCl_2$, 1.0), 145 ($C_6H_3Cl_2$, 0.4), 109 (0.3)
dicamba	234 (M^+, 0.2), 203 ($C_8H_5O_2Cl_2$, 1.0), 188 ($C_7H_2O_2Cl_2$, 0.3)
PCP[b]	278 (M^+, 0.6), 263 (C_6OCl_5, 0.6), 235 (C_5Cl_5, 0.55), 165 (C_5Cl_3, 0.4), 130 (C_5Cl_2, 0.3)
picloram	254 (M^+, 0.2), 223 ($C_6H_2N_2OCl_3$, 0.3), 196 ($C_5H_3N_2Cl_3$, 1.0)

[a] Major fragment ions greater than *m/e* 100 are presented. Isotopic ions which are also useful for SIM can be derived from the tabulated data by considering the chlorination number of the fragment ion. [b] *m/e* 265 is the base peak.

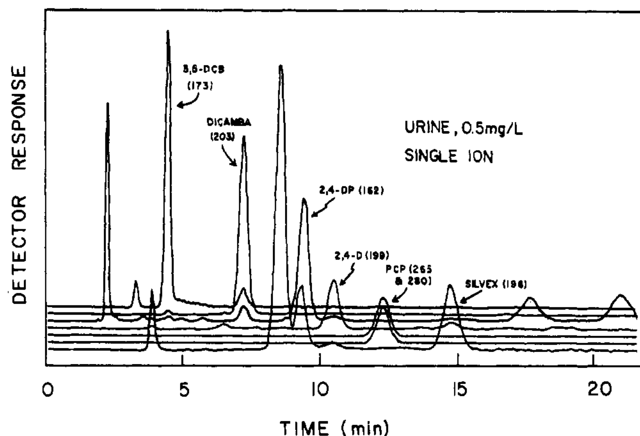

Figure 4. Computer-reconstructed ion current chromatograms of a methylated extract containing 0.5 mg/L of each herbicide: detection of 3,5-DCB (*m/e* 173), dicamba (*m/e* 203), 2,4-DP (*m/e* 162), 2,4-D (*m/e* 199), PCP (*m/e* 265 and 280), and silvex (*m/e* 196) by SIM.

toring modes (Farwell et al., 1976), may be less susceptible to contamination because smaller amounts of material are required for analysis. The advantage of operating the mass spectrometer detector in the normal mass scanning mode is that the computer can reconstruct a large number of single ion chromatograms after the chromatographic run has been completed. This capability is useful for screening urine extracts for a large number of compounds. Examples of the selective detection of herbicides in urine by GC–MS are shown in Figure 4.

CONCLUSION

A variety of herbicidal acids can be determined simultaneously with a high degree of quantitative accuracy, precision, and sensitivity with the method described. Methylation of urinary extracts was superior to pentafluorobenzylation for several reasons: the EC detector response of interfering coextractives was minimized, mass spectra were complex, increasing the number of fragments available for SIM, and derivatization was rapid and quantitative. The derivatized extract analyzed quantitatively by EC-GC could be subjected to rigorous qualitative confirmation by GC–MS after sample concentration. The procedure has been used in studies of occupational exposure to these widely used herbicides, but it shows promise as a generalized, multiresidue screen as well.

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