# 6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring tetrachloroethylene, its metabolites, and other biomarkers of exposure and effect to tetrachloroethylene. The intent is not to provide an exhaustive list of analytical methods, but is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods may be included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

## 6.1 BIOLOGICAL MATERIALS

Several methods are available for the analysis of tetrachloroethylene in biological media. The method of choice depends on the nature of the sample matrix; required precision, accuracy, and detection limit; cost of analysis; and turnaround time of the method. Since tetrachloroethylene is metabolized in the human body to trichloroacetic acid (TCA), TCA may be quantified in blood and urine as an indirect measure of tetrachloroethylene exposure (Monster et al. 1983). It should be pointed out that the determination of TCA may not provide unambiguous proof of tetrachloroethylene exposure since it is also a metabolite of trichloroethylene. Trichloroethanol has also been thought to be a metabolite of tetrachloroethylene, identified following occupational exposure (Bimer et al. 1996; Ikeda et al. 1972; Monster et al. 1983). However, rather than being a metabolite of tetrachloroethylene, it is more likely that trichloroethanol is formed from trichloroethylene, which is often found as a contaminant of tetrachloroethylene (Skender et al. 1991). Methods for the determination of trichloroethylene and trichloroethanol are summarized in the Toxicological Profile for Trichloroethylene (ATSDR 1993).

The main method used to analyze for the presence of tetrachloroethylene and TCA in biological samples is separation by gas chromatography (GC) combined with detection by mass spectrometry (MS) or an electron capture detector (ECD). Tetrachloroethylene and/or its metabolites have been detected in exhaled air, blood, urine, breast milk, and tissues. Preconcentration techniques are

frequently used in tetrachloroethylene analysis. Preconcentration not only increases the sensitivity but in certain instances may decrease the sample separation time. Interference in tetrachloroethylene analysis results from the widespread distribution of volatile organic compounds in the environment. The most likely sources of these interfering compounds are contamination from the vessels used to hold and prepare samples, contamination of the plumbing in the analytical instrument, and leaking of environmental contaminants into the sample vessel. Details on sample preparation, analytical method, and sensitivity and accuracy of selected methods are shown in Table 6-l.

Breath samples have been analyzed for tetrachloroethylene in several studies. Preconcentration on a solid sorbent followed by thermal desorption onto a cryogenic trap connected to the gas chromatograph was used to analyze exhaled air in several TEAM studies (Wallace 1986; Wallace et al. 1986a, 1986b, 1986c, 1986d). Vapors were thermally released directly onto the chromatographic column for separation and detection by electron impact MS (EIMS).

The methods most frequently used to determine the presence of tetrachloroethylene in biological tissues and fluids are headspace analysis and purge-and-trap, followed by GC/MS or GC/ECD. In headspace analysis, the gaseous layer above the sample is injected into the gas chromatograph. Samples may be hydrolyzed prior to analysis of headspace gases (Ramsey and Flanagan 1982). Headspace gases can be preconcentrated prior to GC analysis (Cramer et al. 1988; Michael et al. 1980) or injected directly into the gas chromatograph (Ramsey and Flanagan 1982). Sensitivity is in the low-ppb range, with generally good precision and accuracy for blood, serum, plasma, and urine (Cramer et al. 1988; Michael et al. 1980). The purge-and-trap method is used with liquid samples and involves purging the sample with an inert gas and trapping the purged volatiles on a solid sorbent. Blood and breast milk have been analyzed for tetrachloroethylene by purging onto a solid sorbent to concentrate the volatiles, followed by thermal desorption and analysis by GC/MS (Antoine et al. 1986; Pellizzari et al. 1982). However, the breast milk analysis was only qualitative, and recoveries appeared to be low for those chemicals analyzed (Pellizzari et al. 1982). Precision and sensitivity were comparable to headspace analysis, but accuracy was lower. Recovery of tetrachloroethylene from rat tissues was found to be greater when the tissues were homogenized in saline:isooctane (1:4) rather than saline alone (Chen et al. 1993).

Analysis of blood and urine for TCA has been done primarily by GC/ECD (Ziglio et al. 1984). TCA has also been determined calorimetrically by decarboxylation to chloroform and conjugation with

## Table 6-1. Analytical Methods for Determining Tetrachloroethylene in Biological Samples

| Sample Matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Exhaled air | Collected in spirometer; pre-concentrated on Tenax-GC; thermally desorbed | HRGC/MS | 0.3 ppb | 95–99 | Wallace et al. 1986a, 1986d |
| Blood | Thermally decarboxylated; subjected to static head-space analysis | GC/ECD (for metabolite TCA) | 2 ppb | 101–109 | Ziglio et al. 1984 |
| Blood | Antifoam agent added; purged and trapped on Tenax-GC/silica gel; thermally desorbed | GC/MS | 0.5 ppb | NR | Antoine et al. 1986 |
| Blood, plasma, and serum | Sample in sealed vial subjected to static head-space analysis | GC/ECD | 100 ppb | NR | Ramsey and Flanagan 1982 |
| Blood, urine, and adipose tissue | Passed inert gas over head-space of sample and trapped on Tenax-GC; thermally desorbed | HRGC/MS | NR | 100 (blood); 72 (urine); 52 (adipose tissue) | Michael et al. 1980 |

## Table 6-1. Analytical Methods for Determining Tetrachloroethylene in Biological Samples (continued)

| Sample Matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Urine | Thermally decarboxylated; reacted with pyridine | Spectrophotometry (for metabolite TCA) | <0.8 ppm | 93.5 | Pekari and Aitio 1985a |
| Urine | Enzyme hydrolysis of sample; decarboxylation of trichloroacetic acid; head-space gas analyzed | GC/ECD (for metabolite TCA) | 20 ppb | 98 | Christensen et al. 1988 |
| Urine | Hydrolyzed with $H_2SO_4$; extracted with isooctane | GC/ECD (for metabolite TCE) | 75 ppb | 98.2 | Pekari and Aitio 1985b |
| Tissue | Mixed with a proteolytic enzyme; incubated at 65°C; head-space gas analyzed | GC/ECD | NR | 100 | Ramsey and Flanagan 1982 |

## Table 6-1. Analytical Methods for Determining Tetrachloroethylene in Biological Samples (continued)

| Sample Matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Tissue | Homogenization in saline; extraction into isooctane; or direct homogenization into saline:isooctane; head-space gas analyzed | GC | 1 ng | Saline homogenization, 69-105; Saline: isooctane (1:4) homogenization, 81-99 | Chen et al. 1993 |
| Human milk | Purged warm; trapped in Tenax-GC; thermally desorbed | HRGC/MS | Qualitative identification | NR | Pellizzari et al. 1982 |

ECD = electron capture detector; GC = gas chromatography; HRGC = high resolution gas chromatography; $H_2SO_4$ = sulfuric acid; MS = mass spectrometry; NR = not reported; TCA = trichloroacetic acid; TCE = trichloroethanol

pyridine (Pekari and Aitio 1985a). The recovery and precision for this method were good, but the sensitivity was about a tenth that of GC/ECD methods (Christensen et al. 1988; Pekari and Aito 1985a).

The tetrachloroethylene metabolite, *N*-acetyl-*S*-(trichlorovinyl)cysteine (TCVC), produced from glutathione conjugation, has been measured in rat urine using a negative ion chemical ionization gas chromatographic/tandem mass spectrometric method (Bartels 1994). The detection limit of this method was reported as 0.3 ng TCVC/mL of rat urine. As discussed in Section 2.3.3, glutathione conjugation of tetrachloroethylene has not been identified in humans.

## 6.2 ENVIRONMENTAL SAMPLES

Analysis of environmental samples is similar to that of biological samples. The most common methods of analyses are GC coupled to MS, ECD, a Hall's electrolytic conductivity detector (HECD), or a flame-ionization detector (FID). Preconcentration of samples is usually done by sorption on a solid sorbent for air and by the purge-and-trap method for liquid and solid matrices. Alternatively, headspace above liquid and solid samples may be analyzed without preconcentration. Details of commonly used analytical methods for several types of environmental samples are presented in Table 6-2.

The primary methods of analyzing for tetrachloroethylene in air are GC combined with either MS or ECD. Air samples are collected on a solid sorbent, thermally desorbed to an on-column cryogenic trap and heat-released from the trapping column directly to the gas chromatograph (Bayer and Black 1987; Krost et al. 1982; Wallace 1986; Wallace et al. 1986a, 1986b, 1986c, 1986d). Grab-samples of air can also be obtained and preconcentrated on a cryogenic column (Makide et al. 1979; Rasmussen et al. 1977). The limit of detection for cryogenic trapping followed by GC/ECD or GC/MS is in the low-ppt range (Krost et al. 1982; Makide et al. 1979; Rasmussen et al. 1977; Wallace et al. 1986a, 1986d). With careful technique, precision for both GC/ECD and GC/MS is acceptable, although the relative standard deviation (RSD) can be as high as ±28% (Krost et al. 1982; Rasmussen et al. 1977; Wallace et al. 1986a, 1986b, 1986c, 1986d). Accuracy could not be compared between the two analytical methods because no recovery data were located for GC/ECD. An alternate method of analysis chemically desorbs tetrachloroethylene from activated coconut charcoal and directly injects the extract

## Table 6-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Air | Absorbed on coconut charcoal; desorbed with carbon disulfide | GC/FID (NIOSH Method 1003) | 0.4 mg/ sample | 96 | NIOSH 1984a |
| Air | Collected in stainless steel canister; preconcentrated in cooled adsorbent; thermally desorbed | GC/ECD | 1 ppt | NR | Makide et al. 1979 |
| Air | Adsorbed on Tenax-GC thermally desorbed to on-column cold trap; heat-released | HRGC/MS | 1.9 ppt | NR | Krost et al. 1982 |
| Air | Collected in stainless steel canister; preconcentrated by cryogenic trapping; thermally desorbed | GC/ECD | 0.3 ppt | NR | Rasmussen et al. 1977 |
| Air | Adsorbed on Tenax-GC; thermally desorbed to on-column cold trap; heat-released | HRGC/MS | 0.3 ppt | 95–99 | Wallace et al. 1986a |
| Air | Collected in stainless steel canister (SUMMA); cryogenic preconcentration on glass beads | Full scan GC/MS (proposed EPA Method TO-14) | 0.5 ppb | NR | Hoyt and Smith 1991 |

**Table 6-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples (continued)**

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Water | Purged and trapped in methyl silicone, [216]-diphenylene oxide polymer silica gel; thermally desorbed | GC/PI (EPA 503.1) | 0.01–0.05 ppb | 97 | APHA 1992 |
| Water | Purged and trapped on coconut charcoal/Tenax/silica gel; thermally desorbed | GC/MS (EPA Method 624) | 1.9 ppb | 101 | EPA 1982b |
| Water | Purged and trapped on coconut charcoal/Tenax/silica gel; thermally desorbed | GC/HSD (EPA Method 601) | 0.12 ppb | 106 | EPA 1982b |
| Water | Equilibrated in sealed vial at room temperature; head-space gas injection | GC/ECD | NR | 105 | Dietz and Singley 1979 |
| Water | Purged and trapped on Tenax-GC; thermally desorbed | GC/HECD; GC/FID | <0.1 ppb (HECD); 0.1 (FID) | 98 (HECD); 79 (FID) | Otson and Williams 1982 |
| Water | Purged and trapped on Tenax-GC; thermally desorbed | GC/HECD | NR | 50–90 | Wallace et al. 1986a, 1986d |
| Water | Sample directly injected | GC/UV | 1 ppb | 39 | Motwani et al. 1986 |

**Table 6-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples (continued)**

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Water | *In situ* method; concentration in LDPE coating | FEWS/FT-IR | 1 ppm | NR | Krska et al. 1993 |
| Water | Spray extraction; trapped in sorption tube; thermally desorbed | GC/MS | 10-30 ng/L | NR | Baykut and Voigt 1992 |
| Landfill leachate | Extract with pentane; analyze | GC/MS | NR | NR | Schultz and Kjeldsen 1986 |
| Liquid and solid waste | Equilibrated in sealed via headspace gas injected | GC/HSD (EPA Method 8010) | 0.03 ppb | 106 | EPA 1982c |
| Building materials and consumer products[a] | Collected by adsorption onto sorbent; thermally desorbed | HRGC/MS | 0.3 ppt | NR | Wallace et al. 1987 |
| Food | Undigested or $H_2SO_4$-digested samples at 90°C subjected to static head-space analysis | HRGC/ECD; GC/MS | 0.23 ppb | 90–100 | Entz and Hollifield 1982 |
| Food | Extraction with isooctane; cleah-up on Florisil column if needed | GC/ECD; GC/HECD | 6 ppb (ECD); 13 ppb (HECD) | >50 | Daft 1988 |

## Table 6-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples (continued)

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Olive oil | Add Dekalin to vial with olive oil; seal vial; incubate at 70°C for 60 minutes; inject sample of head-space gas | GC/ECD | 0.02 mg/kg | NR | Pocklington 1992 |
| Olive oil | Equilibrated in a sealed vial at 85°C for 30 minutes; head-space gas injection | GC/ECD | 1 pg/ sample | NR | Van Rillaer and Beernaert 1989 |
| Grains, grain-based foods | Purged and trapped on Tenax/XAD-4 resin; desorb with hexane | GC/ECD | Low- to sub-ppb | 86–100 | Heikes and Hopper 1986 |
| Lettuce | Equilibrated in sealed vial at 70°C; headspace gas injection | GC/ECD | 3-4 µg/kg | NR | Boekhold et al. 1989 |

[a]Sample is air from an environmental chamber containing the building material or consumer product.

ECD = electron capture detector; EPA = Environmental Protection Agency; FEWS = fiber evanescent wave spectroscopy; FID = flame ionization detection; FT-IR = Fourier transform infrared; GC = gas chromatography; HECD = Hall electrolytic conductivity detector; HRGC = high resolution gas chromatography; HSD = halide-sensitive detector; $H_2SO_4$ = sulfuric acid; LDPE = low-density polyethylene; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; NR = not reported; PI = photoionization; UV = ultraviolet detection

into a GC equipped with FID detection (NIOSH 1994b; Peers 1985). The sensitivity of this method is only in the low-ppm range.

Tetrachloroethylene can be detected in drinking water, groundwater, waste water, and leachate from solid waste. The primary analytical methods are separation by GC combined with detection by HECD or other type of halogen-specific detector, ECD, or MS. In most methods, tetrachloroethylene is liberated from the liquid matrix by purging with an inert gas concentrated by trapping on a suitable solid sorbent and thermally desorbed onto the gas chromatograph column. Baykut and Voigt (1992) describe a method in which tetrachloroethylene is removed from aqueous solutions using a spray extraction technique, followed by trapping on a solid sorbent, then thermal desorption onto a gas chromatograph. Detection of tetrachloroethylene is generally by HECD (or other halogen-specific detector) or MS (APHA 1992; Baykut and Voigt 1992; EPA 1982b, 1982c; Otson and Williams 1982; Wallace 1986; Wallace et al. 1986c, 1986d). The limit of detection is in the sub-ppb range for halogen-specific detectors (APHA 1992; EPA 1982b, 1982c) and in the low-ppb for MS (EPA 1982b). Accuracy is generally greater than 90% (APHA 1992; EPA 1982b, 1982c), although lower values have been reported (Wallace 1986; Wallace et al. 1986c, 1986d). Precision is ±13% (RSD) or better (APHA 1992; EPA 1982b, 1982c; Wallace 1986, Wallace et al. 1986d). Purging directly to the gas chromatograph with whole-column cryogenic trapping has been reported (Pankow and Rosen 1988). The study authors have reported excellent purging efficiency (100%) and state that sensitivity and precision should be correspondingly good, although specific values for these parameters were not reported. Headspace analysis has been used to determine tetrachloroethylene in water samples. High accuracy and precision were reported for a procedure in which GC/ECD was the analytical method (Dietz and Singely 1979). Solid waste leachates from sanitary landfills have been analyzed for tetrachloroethylene and other volatile organic carbons (Schultz and Kjeldsen 1986). Detection limits for the procedure, which involves extraction with pentane followed by GC/MS analysis, are in the lowppb and low-ppm ranges for concentrated and neat samples, respectively.

An *in situ* method for tetrachloroethylene analysis using fiber evanescent wave spectroscopy (FEWS) has been described by Krska et al. (1993). In this method, the water flows through a glass chamber containing a silver halide fiber coated with low-density polyethylene in an amorphous phase. The coating serves to concentrate the tetrachloroethylene, and the compound is detected using infrared spectrophotometry. The detection limit of this method, which was validated using headspace GC, was 1 ppm.

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No information on analysis of tetrachloroethylene in soil or sediment was located. Several procedures for determination of the chemical in plants and food were located. GC/ECD and GC/HSD are most commonly used to analyze solid samples for tetrachloroethylene contamination. Extraction, purge-and-trap, and headspace analysis have all been used to prepare samples. Analysis of headspace gases by GC coupled with ECD, MS, or HSD has proven relatively sensitive (low- to sub-ppb range) and reproducible for a variety of foods (Boekhold et al. 1989; Entz and Hollifield 1982; EPA 1982c; Pocklington 1992; Van Rillaer and Beemaert 1989). It has also been used to analyze building materials and consumer products (Wallace et al. 1987). GC/HSD of headspace gases is the EPArecommended method for solid matrices (EPA 1982c). Foods have also been analyzed for tetrachloroethylene by GC/ECD/HECD following isooctane extraction. Sensitivity was comparable to headspace methods, but reproducibility was not as good (Daft 1988). In both headspace and extraction preparation methods, increased lipid content of the matrix adversely affected accuracy and precision. A purge-and-trap technique proved useful for analyzing grains and grain-based foods with high sensitivity and good recovery (Heikes and Hopper 1986).

## 6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tetrachloroethylene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetrachloroethylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 6.3.1 Identification of Data Needs

#### Methods for Determining Biomarkers of Exposure and Effect

*Exposure.* Methods are available for measuring tetrachloroethylene in breath (Wallace et al. 1986a, 1986d), blood (Antoine et al. 1986; Michael et al. 1980; Ramsey and Flanagan 1982), urine (Michael et al. 1980), and adipose tissue (Chen et al. 1993; Michael et al. 1980; Ramsey and Flanagan 1982), and TCA in blood (Ziglio et al. 1984) and urine (Christensen et al. 1988; Pekari and Aito 1985a, 1985b). Available methods are sensitive for measuring exposure levels at which health effects have been observed to occur, for example, in workers known to be exposed to high levels of tetrachloroethylene. These methods have also been used to measure background levels in individuals believed not to have been exposed to higher-than-expected levels of tetrachloroethylene (e.g., office workers and housewives) (Wallace 1986). The methods are generally reliable, although increased precision for most methods would increase reliability. However, tetrachloroethylene is pervasive in the environment and background levels for the general population are not well defined. Levels may vary considerably within the environment, making it difficult to differentiate between normal background exposure and excess exposure. Further research on the relationship between levels found in living and working environments not suspected of having elevated levels of tetrachloroethylene and levels of the chemical and/or its metabolites in biological media would help in better defining background levels of the chemical and aid in determining if improved methods of monitoring exposure are needed.

*Effect.* There are no unique biomarkers of effect for tetrachloroethylene; however, sensitive and reliable clinical methods exist for determining damage to the liver, a target organ for tetrachloroethylene toxicity. These include measuring serum levels of liver enzymes, bilirubin, and alkaline phosphatase and urinary urobilinogen (Bagnell and Ellenberger 1977; Coler and Rossmiller 1983; Meckler and Phelps 1966; Stewart et al. 1981). Neurological effects may also result from exposure to tetrachloroethylene (Carpenter 1937; Haerer and Udelman 1964; Hake and Stewart 1977; Kendrick 1929; Koppel et al. 1985; Morgan 1969; Rowe et al. 1952; Saland 1967; Sandground 1941; Stewart et al. 1970, 1981; Wright et al. 1937). Tests for these effects are not especially sensitive, reliable, or specific and would not improve detection over the established procedures for measuring tetrachloroethylene in breath, blood, or urine.

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Methods for measuring levels of tetrachloroethylene and its metabolites that might be associated with adverse health effects are the same as those for exposure. The methods are sensitive for measuring levels of tetrachloroethylene and its metabolites in individuals not exhibiting apparent health effects resulting from the chemical (Monster and Smolders 1984; Wallace 1986) as well as in those known to be affected by absorption of excessively high levels of tetrachloroethylene. However, correlations between levels of tetrachloroethylene or its metabolites detected in biological media and specific observed effects at lower levels of absorption are not well established. Additional research in this area would allow better assessment of existing methods and would help in defining areas in which improvements are needed. Improved methods of tissue analysis, giving greater sensitivity and reproducibility, would also help in determining the quantitative relationship between the observed toxic effect on specific organs and the levels of tetrachloroethylene or its metabolites in these organs.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** Existing methods for determining tetrachloroethylene in air (Krost et al. 1982; Makide et al. 1979; Rasmussen et al. 1977; Wallace et al. 1986a) and water (APHA 1992; EPA 1982b; Otson and Williams 1982), the media of most concern for human exposure, are sensitive, reproducible, and reliable for measuring background levels in the environment. Research investigating the relationship between levels measured in air and water and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed. Methods for solid matrices vary in accuracy and precision depending on the method and the matrix (e.g., sludge, soil, sediment, building material). No detailed descriptions of methods specifically for soil were located. Soil analyses presumably were done using a method for solid waste (e.g., EPA Method 8010). Data specifically for soil might be useful in evaluating the reliability of soil data and in determining if additional methods are needed. Improved methods of detecting tetrachloroethylene in plants and foods, especially those with higher fat content, would aid in determining the contribution of tetrachloroethylene exposure from these sources. This would be especially important in determining the potential for contamination of populations living adjacent to hazardous waste sites and other potential sources of exposure to higher than background levels of tetrachloroethylene. -

### 6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of

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tetrachloroethylene and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low ppt range.