6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring formaldehyde, its metabolites, and other biomarkers of exposure and effect to formaldehyde. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention 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 are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Methods for the determination of formaldehyde in biological samples are given in Table 6-1. Formaldehyde has been measured in blood by gas chromatography (GC) in conjunction with mass spectrometry (MS) after derivatization of the formaldehyde to the pentafluorophenylhydrazone (Heck et al. 1985) and in rat urine by high-performance liquid chromatography (HPLC) with ultraviolet (UV) absorbance detection following formation of the 2,4-dinitrophenylhydrazone derivative (Shara et al. 1992). Although the method was used for rat urine, it would be expected that human urine could also be utilized. The determination of formaldehyde in breath has been demonstrated by Lin et al. (1995) following the formation of 2,4-dinitrophenylhydrazone using 2,4-dinitrophenylhydrazine-impregnated silica cartridges. Formaldehyde has been determined in “biologicals” (vaccines) at concentrations as low as 100 ppb following the formation of the formaldehyde phenylhydrazone (Shrivastaw and Singh 1995). It was noted by the authors that this method was free from interferences from proteins and bacterial cells so it might have applicability to biological fluids such as blood or urine. Formic acid or formate is produced from formaldehyde arising from both exogenous and endogenous sources and can be measured as reported by Baumann and Angerer (1979). Although no literature citations were found, it would seem that formate in urine and blood could be determined by a method based on ion chromatography (IC). The measurement of formaldehyde conjugates of IgE and IgG in people exposed to formaldehyde has been shown (Thrasher et al. 1989), but has not resulted in a routine method.

Table 6-1. Analytical Methods for Determining Formaldehyde and Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Venous blood	Addition of water and pentafluorophenyl-hydrazine in dilute phosphoric acid; addition of a known amount of labeled formaldehyde as internal standard; equilibration for 2 hours at 50 EC; extraction with hexane/methylene chloride.	GC/MS (SIM)	No data	No data	Heck et al. 1985
Breath	Collection of expired air into Douglas bag, then Tedlar bag; drawing of breath through DNPH-coated silica; elution with acetonitrile and addition of internal standard; evaporation of solvent and redissolution.	HPLC/UV	No data	95.6 (SD= 3.6)	Lin et al. 1995
Urine (rat)	Dilution of urine with water, addition of DNPH in 2 N HCl and pentane followed by intermittent shaking for 30 minutes; extraction with additional aliquot of pentane followed by solvent evaporation; redissolution in acetonitrile.	HPLC/UV	10 pmole/mL (0.3 µg/L, 0.3 ppb)	No data	Shara et al. 1992
Biologicals (vaccines)	Addition of 1 mL of sample to 3 mL of water, addition of phenyl hydrazine, concentrated HCl, methanol, and chloroform followed by shaking for 10–30 seconds; isolation of chloroform layer for spectrophotometric analysis.	Absorbance at 529 nm	100 ng/mL (100 ppb)	No data	Shrivastaw and Singh 1995
Blood, urine (formic acid)	Formic acid transformed by concentrated sulfuric acid into water and carbon monoxide; carbon monoxide converted to methane in chromatographic system.	GC/FID	No data	No data	Baumann and Angerer 1979

Table 6-1. Analytical Methods for Determining Formaldehyde and Metabolites in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (human serum albumin-formaldehyde conjugate; IgE, IgG)	Addition of diluted sample to coated microtiter test plates; ELISA using orthophenyldiamine as substrate.	Absorbance at 490 nm	No data	No data	Thrasher et al. 1989

DNPH = 2,4-dinitrophenylhydrazine; ELISA = enzyme-linked immunosorbent assay; FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; IgE = immunoglobulin E; IgG = immunoglobulin G; MS = mass spectrometry; SD = standard deviation; SIM = selected ion monitoring; UV = ultraviolet absorbance detection

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of formaldehyde in environmental samples are given in Table 6-2.

Formaldehyde in air can be trapped using impingers filled with water (Fan and Dasgupta 1994; Hoogenboom et al. 1987; Petreas et al. 1986); an aqueous solution of sodium bisulfite (NIOSH 1989a; Petreas et al. 1986); an acidic, aqueous solution of 2,4-dinitrophenylhydrazine (DNPH) (EPA 1988d); or buffered Girard T reagent (NIOSH 1989b). Formaldehyde released into air from textiles has been collected onto moist filter paper (Naruse et al. 1995). Cofer and Edahl (1986) have reported a sampling device that uses a nebulization/reflux approach that is essentially a modification of the impinger device capable of collecting samples at high flow rates (7–8 L/minute). Formaldehyde trapped into water or aqueous bisulfite is subjected to chemical derivatization prior to analysis (see below). Formaldehyde collected into water has been shown to degrade rapidly (a 50% loss in 50 hours) upon ambient and refrigerated storage (Daggett and Stock 1985) while those samples in bisulfite are stable for periods ranging from 1 week (Daggett and Stock 1985) to 4 weeks (Balmat and Meadows 1985). The method of EPA (1988d) traps the formaldehyde as it reacts with DNPH to form the 2,4-dinitrophenylhydrazone derivative. The formation of the formaldehyde dinitrophenylhydrazone has been extended to solid-phase samplers including DNPH-coated silica (Grosjean et al. 1993; Millipore Corporation 1992), DNPH-coated glass fiber filters (Dalene et al. 1992), and annular denuders coated with DNPH (Possanzini et al. 1987). These solid-phase samplers are much more convenient, especially for personal samples where impinger-based devices can easily be spilled. Commercially prepared DNPH-silica cartridges are available from Millipore Corporation (Milford, Massachusetts) and Supleco (Bellefonte, Pennsylvania). Nondek et al. (1991, 1992) have collected formaldehyde as dansylhydrazone through reaction of formaldehyde as it passed through dansylhydrazine-coated porous glass particles. Yet another approach is based on the collection of formaldehyde as its oxazolidine derivative using the polymeric sorbent XAD-2 coated with hydroxymethyl piperidine (NIOSH 1994a). A passive collection device is also available commercially and is based on the stabilization of formaldehyde as its adduct with sulfite after passage of formaldehyde through a membrane (3M Company 1985). Formaldehyde adsorbed to particulate matter has also been recovered using a water extraction of the particles prior to the formation of the DNPH derivative (NIOSH 1994b).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing of air through two impingers in series each of which contains 1% sodium bisulfite. Addition of chromotropic acid and concentrated sulfuric acid, heating to 95 EC for 15 minutes, cooling to room temperature (Method 3500).	Absorbance at 580 nm	0.05 µg/m^3 (0.04 ppb in 100 L sample)	No data	NIOSH 1989a
Air	Drawing of air through an XAD-2 sorbent coated with 10% 2-hydroxymethyl piperidine, elution of the oxazolidine derivative with toluene (Method 2541).	GC/FID (can use GC/NPD for improved sensitivity)	0.028 mg/m^3 (23 ppb in 36 L sample)	No data	NIOSH 1994a
Air particulates (textile or wood)	Drawing of air through 25 mm PVC filter (5 µm pore size), extraction of formaldehyde from particulates into water, derivatization with 2,4-dinitrophenylhydrazine (Method 5700).	HPLC/UV	0.076 µg/m^3 (0.062 ppb)	96 (1.1% RSD at 7 µg/sample)	NIOSH 1994b
Air	Drawing of air through a midget bubbler containing 15 mL buffered (pH = 4.5) Girard T reagent (NIOSH 3501).	DC polarography	0.3 mg/m^3 (0.24 ppm)	100	NIOSH 1989b
Air	Preparation of passive monitor (3M 3721), formaldehyde in air diffuses through a membrane and adsorbs onto bisulfite-impregnated paper, desorption with water, addition of chromotropic acid and concentrated sulfuric acid.	Absorbance at 580 nm	<34 µg/m^3 (<0.028 ppm)	100 (±5%)	3M Company 1985
Air	Drawing of sample through impinger containing 2N HCL/0.05% 2,4-dinitrophenylhydrazine and isooctane; removal of isooctane layer, extraction of aqueous layer with 70/30 hexane/ methylene chloride, combining of organic layers and evaporation of solvent; redissolution in methanol (TO5-1).	HPLC/UV	1.2–2.4 µg/m^3 (1–2 ppb)	>75 (15–20% RSD)	EPA 1988d
Air	Drawing of air through DNPH-coated silica SPE, elution with acetonitrile.	HPLC/UV	0.49 µg/m^3 (0.40 ppb)	96 (7.1% RSD)	Grosjean et al. 1993

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing of air through DNPH-coated silica; elution with acetonitrile.	HPLC/UV	<1.2 µg/m^3 (< 1 ppb)	>95 for sampling rates up to 2 L/min	Millipore Corporation 1992
Air (tropospheric)	Drawing of filtered air through a nebulization/reflux concentrator (scrubber) at rate of 7–8 L/min where formaldehyde is reacted to form DNPH derivative.	HPLC/UV	0.12 µg/m^3 (0.1 ppb)	90–96	Cofer and Edahl 1986
Air	Drawing of air through impinger filled with 1% sodium bisulfite; addition of CTA, concentrated sulfuric acid; equilibration for 1 hour.	Absorbance at 580 nm	No data	98.7±4.7	Petreas et al. 1986
Air	Drawing of air through impinger containing water; addition of pararosaniline (PRA) hydrochloride, sodium sulfite, and equilibration for 60 minutes at room temperature.	Absorbance at 570 nm	No data	91.9±6.9	Petreas et al. 1986
Air	Drawing of air through glass fiber filter impregnated with DNPH. After collection, elution of derivative with acetonitrile and elution through a cation exchange column to remove excess reagent; evaporation of solvent and redissolution in toluene containing internal standard.	GC/TSD	10 µg/m^3 (8.1 ppb)	92 at 600 ng (5% RSD)	Dalene et al. 1992
Air	Drawing of air through tube that contains a smaller, concentric tube made of Nafion (semipermeable) through which water flows in the opposite direction and serves to trap formaldehyde; addition of 1,3-cyclo-hexanedione, in acidified ammonium acetate to form dihydropyridine derivative in flow injection analysis system.	Fluorescence (FIA)	0.011 µg/m^3 (9 ppt)	. 50 (%RSD at 0.07 ppb = 1.5%)	Fan and Dasgupta 1994
Air	Drawing of air through impingers containing pH 7 phosphate buffer and EDTA; addition of bisulfite, reaction of excess bisulfite with 5,5'-dithiobis(2-nitrobenzoic acid) (indirect measure of formaldehyde).	Absorbance at 412 nm	12 µg/m^3 (0.01 ppm in 88 L)	99.9 (1.7% RSD)	Hoogenboom et al. 1987

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing of air through microcartridges packed with porous glass particles impregnated with dansylhydrazine; cartridge placed in-line with HPLC mobile phase.	online HPLC/Fluorescence	0.01 µg/L (0.01 ppb in 1 L)	No data	Nondek et al. 1992
Air (off-gassing from textiles)	Placement of filter paper moistened with distilled water into a vial and incubation of the open vial with textiles at 40EC for 24 hours in 12.7 L chamber; addition to vial of solution containing ammonium acetate, water, acetic acid, and acetylacetone and incubation at 40EC for 30 min.	Absorbance at 414 nm	< 15 ppm	No data	Naruse et al. 1995
Atmospheric water	Reaction of formaldehyde in water with ammonium acetate and 2,4-pentanedione in FIA system to form 3,5-diacetyl-1,4-dihydrolutidine.	FIA/fluorescence	3 µg/L (3 ppb)	No data	Dong and Dasgupta 1987
Drinking water	Reaction of 1 L water with DNPH in 2M acid, extraction with chloroform, solvent exchange to methanol.	HPLC/UV	20 µg/L (20 ppb)	>90 at 20–200 µg/L	Tomkins et al. 1989
Drinking water	Buffering a volume of water to pH 3 followed by derivatization at 40 EC for 1 hour with DNPH. Derivative recovered using C_{18} SPE and elution with methanol (Method 554).	HPLC/UV	8.1 µg/L	96 (7.9% RSD) at 250 µg/L.	EPA 1992b
Fog water	Free formaldehyde: addition of 200 µL of DNPH solution in 2N HCl was added to 200 µL of sample followed by addition of 400 µL of iso-octane and reaction for 45 minutes; direct analysis of an aliquot of organic layer. Total formaldehyde: addition of NaOH to increase pH to 13 to decompose formaldehyde-bilsulfite adduct followed by addition of DNPH in 2.7 N HCl and isooctane; direct analysis of an aliquot of the organic layer.	HPLC/UV	3 µM (90 ppb)	No data (analytical variability stated as ±1 µM)	Facchini et al. 1990

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Maple syrup	Distillation of 3 mL of water from 20 g of sample, addition of Nash reagent (ammonium acetate, acetic acid, acetyl acetone) followed by heating for 30 minutes at 37 EC (Method 964.21).	Absorbance at 415 nm.	<1 ppm (<1 mg/L)	No data	Helrich 1990
Milk	Addition of acidified DNPH and hexane to 2 mL of sample, reaction with stirring for 30 minutes at room temperature; filtration through Celite, washing with hexane; evaporation of solvent; redissolution in acetonitrile.	HPLC/UV	Estimated at 0.009 mg/kg (9 ppb)	89.9±3.9 (0.1 µg/mL)	Kaminski et al. 1993b
Fish flesh	Heating of 100 g of fish to 200 EC and purging of volatiles through two impingers in series, each containing cysteamine solution; equilibration for 30 minutes to form thiazolidine derivative; extraction with methylene chloride, cleanup using silica-gel; addition of internal standard.	GC/NPD	5.8 pg (for GC detection only; not a method LOD)	No data	Yasuhara and Shibamoto 1995
Coffee	Addition of 0.75 g cysteamine to 250 mL of brewed or reconstituted instant coffee to liquid-liquid continuous extractor; adjustment of pH to 8 and extraction with 70 mL chloroform for 3 hours; removal of water using sodium sulfate, addition of internal standard, volume adjustment.	GC/NPD	No data	>100 at 1 ppm	Hayashi et al. 1986

CTA = chromotropic acid; DNPH = 2,4-dinitrophenylhydrazine; EDTA = ethylene diaminetetraacetic acid; FIA = flow injection analysis; GC = gas chromatography;; HPLC = high-performance liquid chromatography; LOD = level of detection; NPD =nitrogen-phosphorus detector; PRA = pararosaniline; RSD = relative standard deviation; SPE = solid phase extraction; TSD = thermionic specific detection; UV = ultraviolet absorbance detection

Most of the measurement methods reported rely on spectrophotometry or chromatography, either GC or HPLC, although one of the NIOSH methods (Method 3501, NIOSH 1989b) is based on polarography. There are many spectrophotometric methods available. Method 3500 (NIOSH 1989a) is often used as a reference method during the development of new methods. This method relies on the reaction of the formaldehyde-bisulfite adduct with chromotropic acid (4,5-dihyroxynaphthalene-2,7-disulfonic acid) in the presence of concentrated sulfuric acid to form a highly colored product that is measured by its absorbance at 580 nm. Phenols in 8-fold excess over formaldehyde produce a -10 to -20% bias; small negative interferences can also result from ethanol and higher molecular-weight alcohols, olefins, aromatic hydrocarbons, and cyclohexanone (NIOSH 1989a). Little interference is seen from other aldehydes.

The method of Fan and Dasgupta (1994) relies on the reaction of formaldehyde with 1,3-cyclohexane-dione in acidified ammonium acetate to form the fluorescent dihydropyridine derivative in a flow injection analysis system. Formaldehyde trapped in water can be reacted with pararosaniline and sodium sulfite under mild conditions (neutral pH, room temperature equilibration) to produce a colored product that is measured at 570 nm (Petreas et al. 1986). The presence of bisulfite is an interference in this reaction so the method cannot be used to sample atmospheres that contain sulfur dioxide. In addition, the method is reported to suffer from interferences resulting from the presence of other aldehydes and phenol (Hoogenboom et al. 1987). The indirect method of Hoogenboom et al. (1987) relies on the reaction of excess bisulfite in an aqueous solution of formaldehyde with 5,5'-dithiobis(2-nitrobenzoic acid) to form a colored product, the absorbance of which is measured at 412 nm. The method reported by Naruse et al. (1995) relies on the formation of a colored product obtained by reacting the aqueous formaldehyde with acetylacetone and ammonium acetate in acetic acid. Absorbance is measured at 414 nm.

The separation of dinitrophenylhydrazones using HPLC and absorbance detection is widely used for the measurement of formaldehyde and other carbonyl compounds (EPA 1988d; Grosjean et al. 1993; Millipore Corporation 1992; NIOSH 1994b). The reactivity of carbonyl compounds other than formaldehyde with DNPH requires the use of a chromatographic method to resolve the derivatives of the other compounds from that of formaldehyde. Ozone present in the atmosphere being sampled reacts with DNPH and the DNPH derivative of formaldehyde (Arnts and Tejada 1989), especially when using DNPH-coated silica gel cartridges. Ozone can be scrubbed from the sample stream by passing the air through a copper tube coated with potassium iodide before passing the air through the DNPH-coated silica (Millipore Corporation 1992). In some cases, the DNPH derivatives are separated using GC, but

this mode of analysis requires an additional cleanup step to remove the excess DNPH reagent (Dalene et al. 1992). Caution must be used to avoid exposure of DNPH-silica cartridges or eluted samples to aldehyde and ketone sources. Laboratory air often holds high concentrations of acetone. Labeling inks, adhesives, and packaging containers (including vials with plastic caps) are all possible sources of contamination (Millipore Corporation 1992). Field blanks should always be used.

Methods for the collection and determination of formaldehyde in water show great similarity to those methods for air described above. The methods of Tomkins et al. (1989) and EPA (1992b) for formaldehyde in drinking water and the method of Facchini et al. (1990) for formaldehyde in fog water all rely on the formation of the DNPH derivative followed by HPLC. The method of Dong and Dasgupta (1987) relies on the reaction of formaldehyde in atmospheric water with a diketone (2,4-pentanedione) and ammonium acetate to form a fluorescent derivative that is measured spectrophotometrically in a flow injection analysis system.

A few methods for the determination of formaldehyde in foods were found in the literature. The method of Kaminski et al. (1993b) for formaldehyde in milk relies on the formation of the DNPH derivative with analysis by HPLC and absorbance detection. Formaldehyde in maple syrup (Helrich 1990) is determined spectrophotometrically after the reaction of formaldehyde with acetyl acetone (Nash reagent or 2,4-pentanedione) in the presence of ammonium acetate in an acidic solution. Formaldehyde in fish flesh (Yasuhara and Shibamoto 1995) and in coffee (Hayashi et al. 1986) has been determined through the formation of the thiazolidine derivative (a reaction product of formaldehyde with cysteamine) followed by GC in conjunction with nitrogen-phosphorus detection. Yasuhara and Shibamoto (1995) noted that the accuracy of formaldehyde determination can be affected by the adsorption of formaldehyde onto glass surfaces and the generation of artificial formaldehyde during heating of nitrogen-containing compounds such as trimethylamine oxide.

Two other methods for the determination of formaldehyde in gases and liquids have been described but are too complex, given the simplicity of the other methods available. One method is based on enzymatic processes (Barzana et al. 1989; Ho and Richards 1990) followed by spectrophotometry; the other is based on pH changes associated with formaldehyde metabolism by genetically altered cells (Korpan et al. 1993).

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 formaldehyde 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 formaldehyde.

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 for the determination of formaldehyde in blood (Heck et al. 1985), breath (Lin et al. 1995), and urine (Shara et al. 1992) have been published. However, formaldehyde concentration in body fluids or expired air is not expected to be a reliable biomarker of exposure, even for acute exposure, because of its high reactivity and rapid metabolism. Methods for the detection of formate, the principal metabolite of formaldehyde, in urine are also available, but urinary levels of formate did not appear to be consistently associated with exposure levels in studies of students exposed to formaldehyde in anatomy laboratories (Einbrodt et al. 1976; Gottschling et al. 1984). One plausible contributing factor to the lack of consistency in the use of formate concentrations as a measure of exposure is that the metabolism of other chemicals can lead to the formation of formate. Further research to increase the sensitivity or reliability of methods to quantify formaldehyde or formate does not seem warranted.

In contrast, DNA-protein cross links in white blood cells (Shaham et al. 1996a) and the presence of serum IgG antibodies to formaldehyde conjugated to human serum albumin (Carraro et al. 1997) are

potentially useful biomarkers of intermediate- or chronic-duration exposure to formaldehyde that may be developed further with additional research.

Methods to detect DNA-protein cross links have been published (Cohen et al. 1990; Shaham et al. 1996a; Zhitkovich and Costa 1992) that reportedly have greater sensitivity than earlier methods that relied on alkaline elution techniques (Brutlag et al. 1969). Although the formation of DNA-protein cross links is not specific to formaldehyde (i.e., other agents can form them), Shaham et al. (1996a) demonstrated that cultured human white blood cells showed increasing quantities of DNA-protein cross links when cultured in media with increasing formaldehyde concentrations and that a small group of formaldehyde-exposed persons had a significantly greater mean amount of DNA-protein cross links in their white blood cells than did a group of non-exposed persons. Additional research to apply these methods to larger groups of occupationally exposed and non-exposed persons may help to determine the reliability of this variable as a biomarker of exposure and to determine the extent to which individuals vary in this response to formaldehyde. Additional research to apply the DNA-protein cross link methods to nasal biopsy specimens may lead to an increased sensitivity of this potential biomarker of exposure and effect.

Carraro et al. (1997) developed an indirect competitive immunoenzyme assay to detect serum IgG antibodies against formaldehyde conjugated to human serum albumin. This technique was used to compare the presence or absence of the antibodies in 219 healthy subjects who differed in smoking habits (tobacco smoke is a significant source of formaldehyde exposure) and occupational exposure to formaldehyde. The indirect competitive immunoenzyme assay was developed and applied as a qualitative method. Additional research is needed to determine if the method can be modified to provide a reliable and precise measure to quantify exposure level or exposure duration.

Effect. As discussed in the previous section, DNA-protein cross links and anti-formaldehyde-human serum albumin IgG antibodies are potential biomarkers of effect and exposure. Whereas detection of these biomarkers can represent biological responses to repeated exposure to formaldehyde (the first is not specific to formaldehyde, but the second is), it is uncertain to what degree their detection indicates that adverse health effects will occur. Further research on relationships between formaldehyde-induced upper respiratory tract tissue damage and/or dysfunction and: (1) DNA-protein cross links in either white blood cells or nasal biopsy tissue; or (2) levels of formaldehyde-specific IgG antibodies may help in determining if improved detection methods are needed.

Various methods have been published to examine nasal lavage fluid for cellular and chemical contents that may be indices of acute allergic or inflammatory responses to formaldehyde or other respiratory irritants (Pin et al. 1992; Prat et al. 1993; Wang et al. 1995). Increased eosinophil concentration and increased albumin and total protein levels have been found in nasal lavage fluid taken from subjects exposed to 0.4 ppm formaldehyde for 2 hours (Krakowiak et al. 1998; Pazdrak et al. 1993). Although these variables are not expected to be specifically influenced by formaldehyde, they appear to provide biomarkers of acute respiratory irritation from airborne formaldehyde or other upper respiratory irritants. Further research on relationships between concentrations of these variables in nasal lavage fluid and prevalence or severity of respiratory symptoms in humans exposed acutely to varying concentrations of formaldehyde may help to confirm their use as biomarkers of effect.

Histological changes in nasal biopsy tissue samples have been observed in several cross-sectional studies of formaldehyde-exposed and non-exposed workers (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Each of these studies used a morphological grading method that assigned an increasing point value for histological changes ranging in severity from loss of ciliated cells to the presence of malignant cells. Prevalence of different types of changes and mean histological scores were compared between exposed and non-exposed groups. As with the use of cellular and biochemical changes in nasal lavage fluid, the changes are not expected to be only due to formaldehyde, but appear to provide biomarkers of upper respiratory tract tissue damage. Further research on the possible progression of nasal tissue damage in workers with increasing duration of exposure may help in determining if methods for detecting and quantifying nasal epithelial tissue damage need further improvement.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for the determination of formaldehyde in air, water, and a limited number of foods. Regarding methods for air, very low limits of detection (LODs) are possible. The chromotropic acid method (NIOSH 3500) (NIOSH 1989a) has an LOD of 0.04 ppb. Typical LODs possible using dinitro phenyl hydrazine (DNPH) derivatization, either from an impinger-based sample collection procedure or through derivatization on DNPH-coated silica, are 1–2 ppb (EPA 1988d), 0.4 ppb (Grosjean et al. 1993), and less than 1 ppb (Millipore Corporation 1992). Other methods that form fluorescent derivatives, such as the method of Nondek et al. (1992), can provide greater sensitivity (LOD reported to be 0.01 ppb) and are applicable; however, they require specialized equipment not available in most laboratories. Assuming an intermediate inhalation exposure minimal

risk level (MRL) of 0.01 ppm, all of the above methods are adequate. If a chronic-duration inhalation MRL of 0.0008 ppm (0.8 ppb) is assumed, the methods of NIOSH (1989a), Grosjean et al. (1993), and Nondek et al. (1992) are adequate. For monitoring of air, formaldehyde concentrations at the intermediate (0.01 ppm) and acute (0.05 ppm) MRLs, the above methods, in addition to those of Millipore Corporation (1992) and EPA (1988d), are adequate. No additional methods for formaldehyde in air are needed.

Methods for the determination of formaldehyde in drinking water are available and they utilize the same detection methods as those utilized for the analysis of formaldehyde in air, with LODs reported to be 20 ppb (Tomkins et al. 1989) and 8.1 ppb (EPA 1992b). The MRL for chronic oral exposure to formaldehyde is 0.2 mg/kg/day. If a 70-kg person is assumed, the maximum intake is 14 mg/day. If a daily intake of 2 L of water or 2 kg/day of food per day is assumed, then any analytical method must have an LOD of less than 7 mg/L for water or 7 mg/kg (ppm) for food. The cited methods for detecting formaldehyde in water have LODs far below the needed value and are sensitive enough to measure background levels in the environment; no additional methods for formaldehyde detection in water are required. Other than for milk (Kaminski et al. 1993b, LOD=9 ppb), no methods for formaldehyde detection in food were found. Additional methods for detection of formaldehyde in foods are needed. Methods for the detection of formaldehyde in soil are not adequately described in the available literature.

6.3.2 Ongoing 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 formaldehyde and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low-parts-per-trillion (ppt) range.

The information in Table 6-3 was found as a result of a search of Federal Research in Progress (FEDRIP 1996).

Table 6-3. Ongoing Studies on Formaldehyde

Investigator	Affiliation	Research description	Sponsor
Creighton University		Studying products of altered lipid metabolism, including formaldehyde, associated with exposures to TCDD, endrin, and lindane in pregnant mice. Specifically, they are concerned with the exposures of the fetus to these products and will be determining formaldehyde concentrations in maternal serum and amniotic fluid.	NIEHS
Albion Instruments	Salt Lake City, UT	Investigating the utility of solid-state lasers for monitoring escaped clinical gases.	DHHS
Spectral Sciences, Inc.	Burlington, MA	Development of diode laser-based remote monitoring of trace gas concentrations over long open-air paths. The target analytes include those covered by the Clean Air Act (CAA), formaldehyde among them.	DOE
Southwest Sciences	Santa Fe, NM	Diode laser-based sensors for gases, including formaldehyde, in harsh high-temperature, high-pressure environments.	DOE

DHHS = Department of Health and Human Services; DOE = Department of Energy; NIEHS = National Institute of Environmental Health