ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR FORMALDEHYDE

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ADDENDUM FOR FORMALDEHYDE

Supplement to the 1999 Toxicological Profile for Formaldehyde

Background Statement

This addendum to the Toxicological Profile for Formaldehyde supplements the profile that was released in 1999.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986, which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1999.

Chapter numbers in this addendum coincide with the Toxicological Profile for Formaldehyde (1999). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

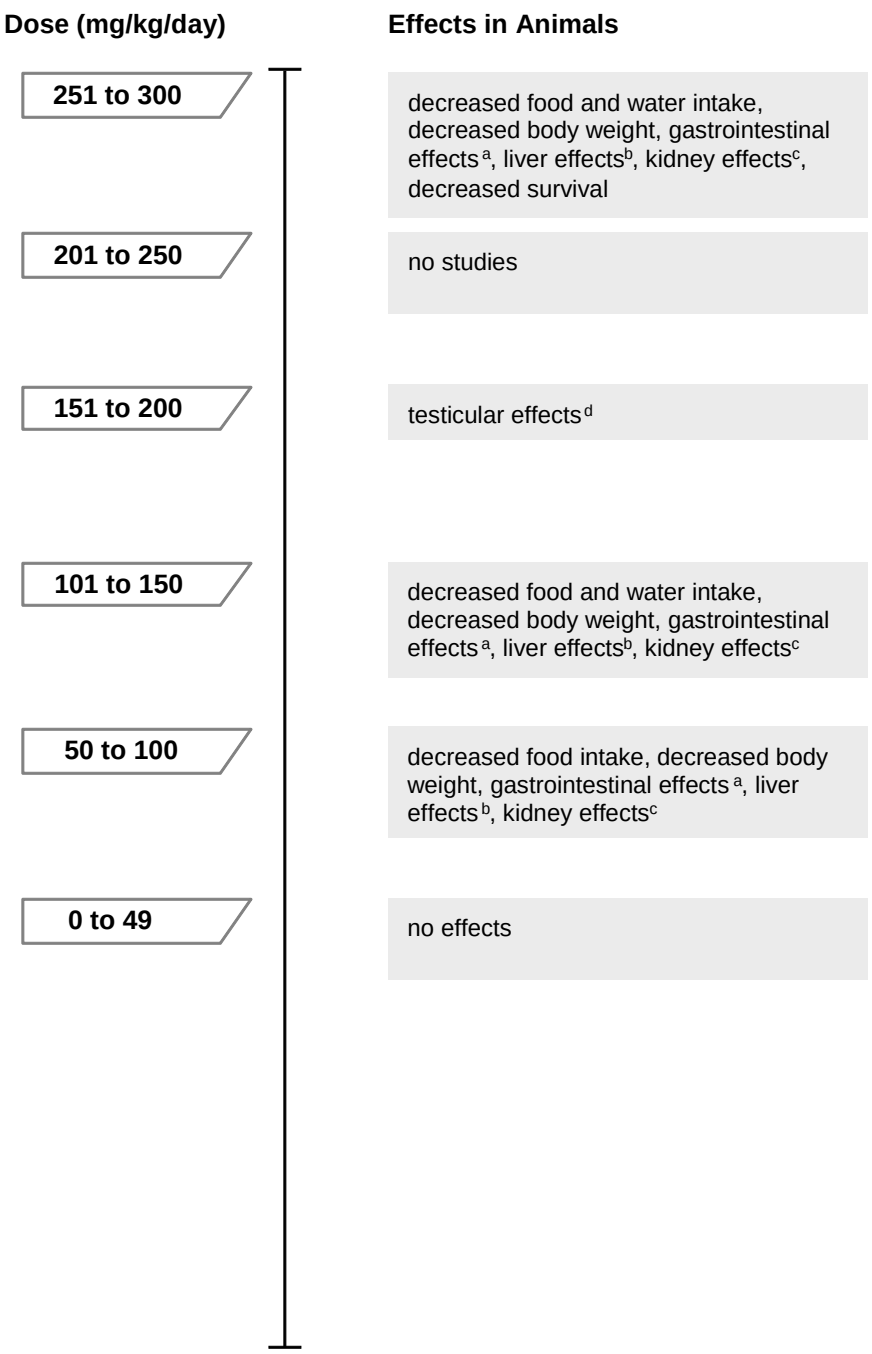
Figure 2-1 illustrates the health effects of breathing formaldehyde in humans and laboratory animals and the range of air concentrations at which these effects were seen. Figure 2-2 shows the health effects of formaldehyde ingestion in laboratory animals and the dose ranges at which these effects occur.

Figure 2-1. Health Effects

Concentration in Air (ppm)	Effects in Humans	Effects in Animals
>50	no studies	bloody nasal discharge, pulmonary edema
11 to 50	no studies	nasal and eye irritation, nasal ulceration, change in pulmonary function[c], neurological effects[d], liver effects[e] decreased body weight, decreased fetal weight, nasal tumors, reduced survival
6.0 to 10.9	nasal, eye, throat and skin irritation, headache, nausea, discomfort in breathing, cough	nasal and eye irritation, nasal ulceration, change in pulmonary function[c], liver effects[e], testicular effects[f], nasal tumors, reduced survival
2.0 to 5.9	nasal, eye and throat irritation, eczema or skin irritation, change in pulmonary function[a]	nasal and eye irritation, throat irritation, change in pulmonary function[c], decreased body weight, enhanced allergic responses, neurological effects[g], liver effects[e], testicular effects[f]
0.6 to 1.9	nasal and eye irritation, eczema, change in pulmonary function[a]	change in pulmonary function[c], neurological effects[g]
0.1 to 0.5	nasal and eye irritation, neurological effects[b], increased risk of asthma and/or allergies	change in pulmonary function[c], enhanced allergic responses, neurological effects[g]

[a] changes in pulmonary variables from spirometry testing (FEV, FVC)
[b] decreased performance on short-term memory tests
[c] decrease breathing rate and/or increased airway resistance
[d] listlessness, hunched appearance, uncoordinated movement, ataxia
[e] altered serum biochemistry and/or liver histopathology
[f] decreased testicular weight, testicular atrophy, altered sperm motility/morphology, decreased serum testosterone, decreased diameter of seminiferous tubules
[g] decreased motor activity, altered open field behavior, impaired learning and memory

Figure 2-2. Health Effects of Ingesting Formaldehyde



[a] erosions and ulcers, histopathological changes
[b] altered serum biochemistry and histopathology
[c] occult blood, changes in urine density and volume, kidney weight and histopathology
[d] altered sperm morphology

2.2.1.2 Systemic Effects

Acute Controlled Exposure Human Studies. Several published studies of respiratory function and/or irritation of the nose, eyes, and throat are available involving acute controlled exposure of volunteers, generally at formaldehyde concentrations ≤3 ppm. Reviews of these studies include those by Arts et al. (2006a, 2006b) and Lang, 2008. Controlled exposure human studies have found that short-term inhalation exposures to concentrations ranging from 0.4 to 3 ppm can produce symptoms of mild to moderate irritation of the eyes, nose, and throat. The odor threshold for formaldehyde in humans has been reported to be 1 ppm (Leonardos et al. 1969), but others have noted that it may range as low as 0.05 ppm (Arts et al. 2006a).

In a controlled study, Lang et al. (2008) exposed 21 healthy subjects (11 males and 10 females, mean age of 26.3 years) to different concentrations of formaldehyde 4 hours/day, 5 days/week for 10 weeks. The subjects experienced various exposure conditions, including continuous formaldehyde concentrations of 0, 0.15, 0.3, and 0.5 ppm in the presence and absence of 12–16 ppm ethyl acetate as a masking agent and formaldehyde peak concentrations of 0.6 and 1 ppm (occurring 4 times) accompanying the continuous formaldehyde concentrations of 0.3 and 0.5 ppm, respectively. The 2-week exposure sequences were randomized with the exposure concentrations, and the daily effect measures were conducted in a double-blind fashion. Increased blinking frequency and slight to moderate conjunctival redness were observed at a continuous formaldehyde concentration of 0.5 ppm, accompanied by peak at a concentration of 1 ppm. No treatment-related effects were observed on nasal flow and resistance, pulmonary function, or reaction times to visual or acoustic stimuli. The subjective complaints of the volunteers were ocular and nasal irritation occurring at lower concentrations (0.3 ppm) of formaldehyde exposure, and were not analogous to objective test measures of eye and nasal irritations and were believed to be strongly influenced by personality factors such as anxiety and smell. Arts et al. (2006a) reviewed respiratory irritation data for several sensory irritant chemicals, including formaldehyde. They concluded that objective measures of

irritation often differed from subjective measures and were affected by the perception of odor intensity, exposure history, and individual bias related to knowledge of chemical effects (Arts et al. 2006a). Xu et al. (2002) exposed eight human subjects to 0, 1.65, 2.99, or 4.31 ppm formaldehyde through a pair of goggles (eyes-only exposure) for 5 minutes. Each formaldehyde concentration produced an increase in eye blinking. This effect was concentration-related and peaked at approximately 1 minute of exposure. In a controlled study no statistically significant effects were observed in lung function tests in 10 volunteers exposed to up to 2 ppm formaldehyde for 3 hours (Kulle et al. 1993). Furthermore, no statistically significant exposure-related effects on acute or subacute changes in lung function measurements were observed among 15 healthy subjects (Schachter et al. 1986) or 15 mild asthmatics (Witek et al. 1987) exposed in environmental chambers to formaldehyde from 0 to 2 ppm for 40 minutes. In similar studies, formaldehyde was administered in controlled environments at different concentrations, and no significant adverse effects were observed in 10 healthy subjects exposed up to 2 ppm for 3 hours (Kulle et al. 1987), or in 21 healthy subjects exposed to 0.5 ppm for 4 hours with a formaldehyde peak concentration of 1 ppm occurring once per hour (Lang et al. 2008). Similar results were reported by Ezratty et al. (2007), where 12 human subjects with allergic asthma exposed to 0 or 0.4 ppm formaldehyde for 1 hour showed no asthmatic response. Furthermore, Krakowiak et al. (1998) detected no adverse pulmonary effects in 10 formaldehyde-exposed textile or shoe manufacturing workers with purported bronchial asthma and 10 non-exposed healthy subjects exposed to 0.4 ppm for 2 hours.

Acute Occupational Exposure Human Studies. Inconsistent effects have also been found in numerous assessments of pulmonary function variables in formaldehyde-exposed workers during workday shifts. For example, Bracken et al. (1985) measured no significant changes in pulmonary function variables (FVC, FEV_1, and $FEFR_{25–75}$) during a workshift in which 10 laboratory technicians were exposed to estimated average formaldehyde concentrations ranging from 0.106±0.02 to 0.269±0.05 ppm. Akbar-Khanzadeh et al. (1994) found no statistically significant differences in workshift changes in pulmonary function variables (FVC, FEV_1, FEV_3, and $FEFR_{25–75}$) in a group of

34 students exposed for 2-3-hour periods to an estimated time-weighted average (TWA) concentration of 1.24±0.61 ppm (range 0.07-2.94 ppm) in a gross anatomy laboratory, as compared to a non-exposed group of 12 subjects serving as controls. However, the exposed group showed an average 1.2% decline in FEV_3 during exposure, compared to a 1.3% increase in FEV_3 for the controls during a comparable period. In another group of 50 students exposed to formaldehyde-containing embalming fluid in a 3-hour gross anatomy laboratory and a control group of 36 non-exposed students in a 3-hour physiotherapy laboratory, pulmonary function variables increased during the 3-hour periods, but the average increases in FEV_1 and $FEFR_{25–75}$ for the exposed group (2.7 and 2.2%, respectively) were statistically significantly less than the average increases (5.2 and 9.3%, respectively) for the control group (Akbar-Khanzadeh and Mlynek 1997). Estimates of breathing zone formaldehyde concentrations in the anatomy laboratory ranged from 0.3 to 4.45 ppm, with a mean of 1.88±0.96 ppm. In both studies by Akbar-Khanzadeh and colleagues, eye and nose irritation were reported by >70% of exposed subjects. Kriebel et al. (2001) evaluated pulmonary function and respiratory symptoms in 38 anatomy students (9 men and 29 women, mean age 24.9 years) exposed to 1.1+0.56 ppm formaldehyde for 2.5 hours/week for 14 weeks. The highest short-term exposure level was 10.91 ppm for a 12-minute interval. During the first 4 weeks of the exposure period, mean PEFR was slightly reduced immediately following a 2.5-hour formaldehyde exposure (-1% per ppm, as determined by multivariate modeling). Eye, nose, and throat irritations were the most common symptoms reported. The intensity of reported symptoms also declined after 4 weeks, suggesting development of respiratory tolerance to formaldehyde exposure. Delfino et al. (2003) conducted a panel study of 22 asthmatic children (10–16 years old) living in a Los Angeles community with high traffic density. Children recorded daily symptoms and PEFR for 3 months. Formaldehyde concentrations were measured at a single central monitoring site. Although formaldehyde concentrations fluctuated only between 0.004 and 0.01 ppm, there was a significant relationship between daily fluctuations and reported symptoms. The adjusted odds ratio (OR) for bothersome or more severe asthma with an inter-quartile range (IQR) increase (0.003 ppm) in formaldehyde was 1.37 (95% CI 1.04–1.8), with a 1-day lag. There was no relationship with PEFR. A limitation of the study was the use of a central monitoring site as an

indicator of exposure. For children, domestic concentrations are likely to be the main predictor of personal exposure to formaldehyde. Ambient air fluctuations in formaldehyde may have been an indicator of other chemicals (e.g., traffic-related pollutants).

Repeated Exposure Human Studies. Studies of formaldehyde-exposed humans with repeated exposure under occupational, or residential conditions provide confirmatory evidence that formaldehyde can be irritating to the upper respiratory tract (Kim et al. 1999; Takahashi et al. 2007; Wei et al. 2007). Earlier studies provided limited evidence that pulmonary functions may be adversely affected by repeated exposure to formaldehyde (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Krzyzanowski et al. 1990; Malaka and Kodama 1990).

Takahashi et al. (2007) surveyed 143 medical students exposed to 2.4±0.49 ppm formaldehyde (1.79–3.78 ppm) for 15 hours/week for 2 months. Clinical symptoms included skin irritation (27%), eye soreness (68%), lacrimation (60%), eye fatigue (45%), rhinorrhea (38%), and throat irritation (43%). Students with a history of allergic rhinitis (31 of 143 students) complained of rhinorrhea and sneezing more often than students without a history of allergic rhinitis. One hundred sixty seven medical students exposed to formaldehyde from 0.16-9.2 ppm (0.194-11.245 mg/m^3) during cadaver dissection practice revealed clinical symptoms that included eye soreness (92.8 %); lacrimation (74.9 %); headaches (51.5 %); and rhinorrhea (50.3 %) (Kim et al.1999). Wei et al. (2007) reported similar clinical symptoms in medical students exposed to a peak concentration of 0.89 mg/m^3 (0.72 ppm) of formaldehyde for 6-8 hours/day for 3 months. Takigawa et al. (2005) demonstrated that installation of ventilation fans to a gross anatomy laboratory reduced the median personal formaldehyde exposure from 3.31 mg/m^3 (2.70 ppm) to 0.875 mg/m^3 to (0.715 ppm) and reduced the intensity of skin eczema and eye, nose, and throat irritation. Clinical findings of upper respiratory tract inflammation were reported in 12 of 29 (41%) workers exposed to a mean formaldehyde concentration of 0.87 mg/m^3 (0.71 ppm) -range 0.52–1.56 ppm-

or for a mean exposure duration of 12.7 years (Lyapina et al. 2004). The clinical observations included hypertrophy or atrophy of the upper respiratory mucous membranes, chronic pharyngitis, rhinitis, rhinosinusitis, and rhinopharyngitis. A history of frequent viral or bacterial inflammatory relapses of the upper respiratory tract was also reported in these formaldehyde-exposed workers.

Earlier, Holmstrom and Wilhelmsson (1988) examined respiratory symptoms and pathophysiolgical effects of workers exposed to formaldehyde and wood dust. Furthermore, Holmstrom et al. (1989) investigated histological changes in nasal tissue specimens from a group of 70 workers exposed to formaldehyde alone, and exposed to formaldehyde in combination with wood dust from a chemical plant that produced formaldehyde, and formaldehyde resins for impregnation of paper. Included in this study were 100 furniture factory workers working with particle board and glue components and a referent group of 36 office workers in the same village as the furniture factories (Holstrom et al. 1989c). The 36 office workers are referred to as a referent group, because they received low-level formaldehyde exposures. Mean durations of employment in the groups were 10.4 years (standard deviation [SD] 7.3, range 1-36 years) for the chemical workers, 9.0 years (SD 6.3, range 1–30 years) for the furniture workers, and 11.4 years (SD 5.4, range 4-18 years) for the referent group. Estimates of personal breathing zone air concentrations ranged from 0.04 to 0.4 ppm of formaldehyde (median 0.24±0.13 ppm) for the chemical workers, from 0.16 to 0.4 ppm (median 0.20±0.04 ppm) for the furniture workers, and from 0.07 to 0.13 ppm in the late summer for the office workers, with a year-round office worker median reported as 0.07 ppm with no standard deviation. The mean wood dust concentration in the furniture factory was reported to have been between 0.81 ppm and 1.6 ppm (1 and 2 mg/m^3). In the Holmstrom and Wilhelmsson (1988) study, three physical examinations were performed on each participant on separate days: (1) mucociliary clearance of indocyanine green and spirometry; (2) medical examination including rhinomanometry; and (3) olfactory (sensitivity) test using binary pyridine dilutions. There were no differences between groups in tobacco usage, and none of the participants were occupationally exposed to solvents. The symptoms questionnaire revealed that a significantly greater percentage of formaldehyde-

exposed workers suffered from nasal discomfort (64 vs 25%; $p<0.001$); eye discomfort (24 vs 6%; $p<0.05$); lower airway discomfort (44 vs 14%; $p<0.01$); and frequent headache (24 vs 6%; $p<0.05$). Other specific symptoms (e.g., nasal obstruction, watery discharge) occurred more frequently in the formaldehyde-exposed group ($p<0.05$; data not presented) than the other groups. The latencies for nasal and lower airway symptoms in the formaldehyde-exposed group were 4.3 and 3.0 years, respectively. During time away from work (e.g., weekends and vacations) symptoms improved in approximately 67% of the formaldehyde-exposed workers. Mucosal swelling was more pronounced in the formaldehyde-exposed group in comparison to referents, as evidenced by a greater improvement in rhinomanometry values in response to administration of a decongestant. Mucociliary clearance was pathologically slow in 20% of formaldehyde-exposed workers, compared to 35% of the referents ($p<0.05$). In addition, formaldehyde-exposed workers suffered from a greater loss of smell compared to the referent group ($p<0.01$). In spirometric tests, the formaldehyde-exposed group exhibited FVC values that were significantly lower than the expected values (4.979 vs. 5.556 L; $p<0.001$). However, FEV was not affected by formaldehyde exposure. The results of rhinomanometry, spirometry, and olfactory tests indicated that the workers' symptoms did not become more severe with increasing duration of exposure (Holmstrom and Wilhelmsson, 1988).

The following studies of baseline pulmonary function variables (e.g., FVC, FEV_1, $FEFR_{25–75}$) have found no abnormal average values for groups of workers repeatedly exposed to formaldehyde or no statistically significant exposure-related differences compared to referent, non-exposed workers: (1) 10 laboratory technicians employed for an average 7.7 years in workplaces with estimated mean concentrations ranging from 0.106±0.2 to 0.269±0.05 ppm (Bracken et al. 1985); (2) 109 particleboard workers employed for an average 10.3 years (range <1–20 years) in a plant with estimated TWA concentrations ranging from 0.17 to 2.93 ppm (mean 0.69 ppm) (Horvath et al. 1988; (3) 64 embalmers (embalming for an average of 10 years) and 12 embalming apprentices (employed <1 year) estimated to have been exposed to formaldehyde concentrations ranging from 0.08- 0.81 ppm (mean 0.36±0.19 ppm) (Holness and

Nethercott 1989); and (4) 16 health professional working in a pathology laboratory for >4 years (formaldehyde concentrations were not reported) (Ostojic et al. 2006).

Fransman et al. (2003) conducted a study of respiratory symptom prevalence in 112 plywood workers employed for an average duration of 4.7±3.5 years. Measured formaldehyde exposure levels ranged from 0.008- 0.6 ppm (0.01–0.74 mg/m^3). The geometric mean concentration of inhalable dust was 0.57 ppm (0.7±1.9 mg/m^3). Personal exposure concentrations of bacterial endotoxin, abietic acid, α-pinene, β-pinene, and δ-carene were also measured. Reported attacks of shortness of breath with wheezing in the past 12 months were increased in plywood workers employed for >6.5 years (34.2%) compared to the general population (15%, n=415) (adjusted OR 2.6, 95% confidence interval [CI] 1.1–5.8). Reports of being awakened by shortness of breath were also increased in these workers (23.1%) compared to the general population (8.7%) (adjusted OR 3.8, 95% CI 1.4–10). Eleven workers with high exposure to formaldehyde reported more respiratory symptoms (36.4% woken with shortness of breath) than workers with low exposure (n=38, 7.9%) (adjusted OR 9.5, 95% CI 1.2–74.7). However, these findings should be interpreted with caution due to the small number of workers assigned to these exposure categories and the potential for exposure misclassification due to the small number of personal exposure measurements obtained for analysis (n=22). No clear association between the measured concentrations of inhalable dust bacterial endotoxin, abietic acid, α-pinene, β-pinene, and δ-carene and the prevalence of respiratory symptoms was found (Fransman et al. 2003). Mean values of FVC, FEV_1/FVC, and maximum expiratory flow rate were significantly lower in a group of 37 anatomy and histopathology workers compared to values for a control group of 37 non-exposed workers from the same college (FVC 2.18 vs. 2.63 L; FEV_1/FVC 0.607 vs. 0.787; flow rate 1.55 vs. 2.71 L/second) (Khamgaonkar and Fulare 1991). Employment durations were not reported in this study, but estimated formaldehyde air concentrations ranged from 0.036 - 2.27 ppm (mean 1.0±0.55 ppm) in the anatomy and histopathology workplaces compared to 0-0.52 ppm (mean 0.1±0.11 ppm) in the control workplaces. The investigators suggested

that the apparent bronchoconstrictor effect of formaldehyde was due either to a direct effect of formaldehyde, or to a reflex response caused by irritation of the nose and throat.

Similarly, Pourmahabadian et al. (2006) reported that FVC and FEV_1 were reduced by 18 and 21%, respectively, in 124 pathology laboratory workers exposed to formaldehyde compared to an unexposed hospital staff (post-shift measurements). Pre-shift measurements of FVC and FEV_1 were also decreased by 14 and 16%, respectively. The differences between pre- and post-shift measurements were greatest for pathology workers than for the staff working in the surgery and endoscopy departments. Formaldehyde exposure concentrations were not directly measured for this study. However, formaldehyde measurements from seven other area hospitals suggested that concentrations in pathology laboratories were higher than other hospital departments. Formaldehyde-exposed workers reported asthma symptoms and signs of eye and nasal irritation (Pourmahabadian et al. 2006).

Mean baseline PEFR declined by about 2% over a 10-week period in a group of 24 physical therapy students who dissected cadavers for 3-hour periods per week (Kriebel et al. 1993). Estimates of breathing zone formaldehyde concentrations ranged from 0.49 - 0.93 ppm (geometric mean 0.73±1.22 ppm). PEFR was the only pulmonary function variable measured in this study, and it was measured before and after each exposure period. Post-exposure PEFR means were 1-3% lower than pre-exposure PEFR means during the first 4 weeks, but this difference was not apparent during the last 6 weeks. Fourteen weeks after the end of the 10-week period, the mean PEFR for the group returned to the pre-exposure baseline value. Similar findings were reported in a more recent study of 38 students exposed to 1.1±0.56 ppm formaldehyde for 2.5 hours/week for 14 weeks (Kriebel et al. 2001). The highest short-term exposure level for this group was 10.91 ppm for a 12-minute interval. During the first 4 weeks of the exposure period, mean PEFR was slightly reduced immediately following a 2.5-hour formaldehyde exposure (-1% per ppm determined by multivariate modeling). No difference in PEFR was observed during the last 10 weeks of the exposure period.

Mild nasal epithelial lesions observed in formaldehyde-exposed workers have been observed consistently across four studies (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989), and the lesions do not appear to be confounded by exposure to wood dust (see Edling et al. 1988; Holmstrom et al. 1989). Furthermore, these studies are consistent with results from animal toxicity, pharmacokinetic, and anatomical airflow studies indicating that at concentrations $\leq$1 ppm, inhaled formaldehyde gas does not reach lower regions of the respiratory tract.

Franklin et al. (2000) reported that residential formaldehyde concentrations of >0.05 ppm did not affect pulmonary function variables (FVC or FEV_1) in healthy children (n=224, 6-13 years old). Nitric oxide exhalation was increased in children exposed to >0.05 ppm formaldehyde compared to children exposed to <0.05 ppm. This effect may represent a subclinical inflammatory response in the airways of healthy children. No concentration range or upper concentration limit was provided for exposed children in this study.

The formaldehyde/asthma hypothesis was investigated in young children from 6 months to 3 years of age in a population-based control study at an Australian hospital (n=88, mean age 25 months) involving age-matched controls (n=104). Although the diagnosis of asthma in this age group was difficult, each of the cases had an episode of acute wheeze sufficient to be treated at the emergency department of the hospital. Passive residential sampling for formaldehyde was performed in both winter and summer months. The association between formaldehyde exposure and asthma in children was tested by including formaldehyde as a categorical or continuous variable in multivariate linear regression models. The model was adjusted for known asthma risk factors and other confounding variables. The investigators concluded that children who are exposed to indoor air formaldehyde concentrations > 0.049 ppm (60 $\mu g/m^3$) are 39% more likely to have an asthmatic attack than children not exposed to such levels (Rumchev et al. 2002).

Venn et al. (2003) performed a similar case-control study of 193 children between the ages of 9 and 11 with persistent wheezing, and 223 healthy controls. Indoor air samples were collected in the homes from the kitchen, living room and the child's bedroom. There were no differences in formaldehyde concentrations in homes between the cases and controls. The investigators concluded that domestic volatile organic compounds are not a primary determinant of risk of severity of childhood wheezing, but formaldehyde exposure may enhance the symptoms severity, and the risk of wheezing was increased by dampness (on a four category scale of % wood moisture equivalent). The investigators also concluded that wheezing was more frequent among the cases at night due to formaldehyde exposure and dampness with an OR 1.45 (1.06 to 1.98) and 1.97 (1.0 to 3.53), respectively (Venn et al. 2003).

Garrett et al. (1999) conducted a cross-sectional survey of 80 homes in Australia. The survey included a total of 148 children, 53 of whom were reported to be asthmatic. The children in this study were between 7 and 14 years of age. Passive residential sampling for formaldehyde was performed four times between March 1994 and February 1995 (median 0.0126 ppm, maximum 0.111 ppm). An association between exposure to indoor formaldehyde and atopy was observed. However, no significant increase was observed between the adjusted risk of asthma or respiratory symptoms and increasing formaldehyde concentration. The authors suggested that low-level exposure to indoor formaldehyde may provide an increased risk of allergic sensitization to common aeoroallergens in young children (Garrett et al. 19991). In another cross-sectional case-control study, Tavernier et al. (2006) investigated the home environment of 105 asthmatic children between 4 and 7 years of age, and 95 healthy controls. There were no differences in formaldehyde residential air concentrations between cases and controls. No analyses were conducted within the asthmatic group. Furthermore, Jaakkola et al. (2004) reported an association between the presence of particle board in homes and asthma-like symptoms in children. No formaldehyde air levels were reported in this study.

Recently, McGwin et al. (2010) conducted a meta-analysis of seven peer reviewed studies that compared formaldehyde exposure in children with and without asthma. They calculated summary ORs employing either the fixed, or random effects model and found a significant association between formaldehyde exposure and childhood asthma. For each 10 $\mu g/m^3$ unit increase in formaldehyde, the asthma risk was 1.03 (95% CI: 1.02 – 1.04) by use of the fixed effects model, whereas the random effects model reported a higher OR (OR= 1.17; 95% CI: 1.02–1.04). The authors also reported a list of limitations found in their analysis of these studies. These limitations included selection bias, self-reported information, seasonal variations in formaldehyde measurements in indoor air, and the fact that some studies reported adjusted estimates, whereas others did not. However, subject to these limitations, the authors suggested that there is a positive association between indoor inhalation of formaldehyde and induction of asthma in children. Moreover, they suggested that further epidemiological investigations of the formaldehyde/asthma hypothesis in children are necessary (McGwin et al. 2010).

Acute Inhalation Animal Studies. Animal studies have shown evidence and confirmed that the upper respiratory tract is a critical target for inhaled formaldehyde and that exposure-response relationships for upper respiratory tract irritation and epithelial damage exist in several species. Acute animal studies have also shown that inhaled formaldehyde at certain exposure concentrations damages epithelial tissue in specific regions of the upper respiratory tract in rats, mice, and monkeys (Ohisuka et al. 2003; Thomas et al. 2007) and that formaldehyde is a more potent sensory irritant in mice (Nielsen et al. 1999) than in rats (Chang et al. 1983).

Ohtsuka et al. (2003) found strain differences in the upper respiratory toxicity of rats exposed to 15 ppm–20 ppm formaldehyde 3 hours/day for 5 days. The incidence and severity of clinical signs (i.e., abnormal respiration, nasal discharge, and sneezing) and the nature and extent of histopathological changes (i.e., degeneration, desquamation, and neutrophil invasion) were greater in F-344 rats than in Brown Norway rats.

Increased epithelial cell proliferation was observed in the nasal epithelium but not in the lung parenchyma of rats exposed to10 ppm of formaldehyde for 3 hours during exercise or at rest (Mautz 2003). In this study, formaldehyde exposure also induced degenerative proliferation in the tracheal epithelium during exercise. These results indicate that very limited amounts of formaldehyde reach the lungs with exposure to 10 ppm (Mautz, 2003).

Intermediate Inhalation Animal Studies. Results from intermediate-duration inhalation studies with rats (Ozen et al. 2003), Rhesus monkeys (Monticello 1989), Cynomolgus monkeys (Rusch et al. 1983), mice (Maronpot et al. 1986), and hamsters (Rusch et al. 1983) indicate that the nasal epithelium is the most sensitive target of inhaled formaldehyde.

Ozen et al. (2003) exposed groups of male Wistar rats to 0, 5, or 10 ppm formaldehyde 8 hours/day, 5 days/week for 4 or 13 weeks. Rats from all exposure groups experienced unsteady breathing, increased nose cleaning, excessive licking, frequent sneezing, and nasal mucosal hemorrhages. Trace element levels of zinc and iron were altered in lung tissue from formaldehyde-exposed rats. However, the significance of these changes is not known, because measures of pulmonary function or lung histopathology were not evaluated.

No treatment-related histopathological changes to the lungs or trachea were observed in female C3H/He mice exposed to 0.08, 0.4, or 2 ppm formaldehyde 16 hours/day, 5 days/week for 12 weeks (Fujimaki et al. 2004, 2005). Similarly, no histopathological changes were observed in male and female Wistar rats exposed to 2.6 or 4.6 ppm of formaldehyde 10 minutes/day, 7 days/week for 90 days (Pitten et al. 2000). Nasal cavity tissues were not examined in these studies, and clinical signs of nasal or eye irritation were not reported.

No histological evidence of adverse effects on cardiovascular tissues was found in an acute study of rats exposed up to 5.4 ppm formaldehyde 2 hours/day for 10 days (Malek et al. 2003c). Gulec et al. (2006b) suggested that formaldehyde inhalation may produce oxidative stress in the heart (0, 10, or 20 ppm formaldehyde, 8 hours/day, 5 days/week for 4 or 13 weeks). However, increased superoxide dismutase activity appears to prevent elevated lipid peroxidation from occurring.

Hematological Effects. Petushok (2000) found evidence of lipid peroxidation-i.e., increased thiobarbituric acid reactive substances and catalase activity-in the blood of rats exposed to 8 ppm (10 mg/m^3) of formaldehyde for 7 hours/day for 5 days. No changes in glutathione levels, glutathione reductase activity, or glutathione peroxidase activity were observed.

Musculoskeletal Effects. No histopathological changes were reported in skeletal muscle of rats exposed to formaldehyde up to 5.4 ppm for 2 hours/day for 10 consecutive days (Malek et al. 2003c). Several investigators have studied the potential of formaldehyde to produce oxidative stress in the liver of animals (Petushok 2000; Kum et al. 2007; Sogut et al. 2004). Petushok (2000) showed evidence of lipid peroxidation (increased thiobarbituric acid reactive substances and catalase activity) in the liver of rats exposed to 8 ppm (10 mg/m^3) 7 hours/day for 5 days. Glutathione levels and glutathione reductase activity were increased, but the activity of glutathione peroxidase was similar to that of controls. Kum et al. (2007) reported no changes in liver weight or liver biochemistry parameters (superoxide dismutase and catalase activities and glutathione and malondialdehyde levels) in adult rats exposed to 6 ppm formaldehyde 8 hours/day for 6 weeks. An increase in liver weight (18%) and a decrease in liver superoxide dismutase activity were observed in 4-week-old rats from this study (6 ppm formaldehyde, 8 hours/day for 6 weeks). Decreases in absolute liver weight and altered liver biochemistry parameters were observed for developing rats under the same exposure conditions. The investigators suggested that the decrease in liver weight is likely related to the observed decrease in body weight seen in these groups (relative liver weight was not reported). Catalase activity and malondialdehyde levels were increased in

prenatally exposed rats. However, glutathione levels were reduced in rats exposed during the postnatal period. These results suggested that oxidative stress may result from formaldehyde exposure in the developing rat liver. However, no histopathological examination of the liver was performed for this study. Sogut et al. (2004) also suggested that hepatic oxidative stress may result from formaldehyde inhalation in rats. Glutathione levels were decreased in liver homogenates from rats exposed to 10 or 20 ppm formaldehyde 8 hours/day, 5 days/week for 4 weeks. Xanthine oxidase activity was also decreased, but only at the higher concentration of formaldehyde (20 ppm). Malondialdehyde levels, nitric oxide concentrations, and myeloperoxidase activity in rat liver were not altered by formaldehyde inhalation for 4 weeks (Sogurt et al. 2004).

No histological liver changes were found in rats exposed to up to 5.4 ppm, 2 hours/day for 10 days (Malek et al. 2003c) or 4.6 ppm, 10 minutes/day, 7 days/weeks for 90 days (Pitten et al. 2000). Mild infiltration of mononuclear cells into the portal space, hepatocellular regeneration in the periportal area, and dilation and congestion of sinusoids and centrilobular veins were observed in the liver of rats exposed to 1.5 ppm formaldehyde for 18 weeks in the use of three different exposure scenarios (4 hours/day for 4 days/week, 2 hours/day for 4 days/week, or 2 hours/day for 2 days/week) (Fazeli et al. 2006). No evidence of necrosis was found. The frequency and daily duration of exposure were not related to the nature or severity of histologic changes in the liver. The weight of available evidence suggests that airborne formaldehyde may produce toxic effects on the liver only at high concentrations that may exceed metabolic and binding capacities in the respiratory tract.

Renal Effects. No evidence from histological examinations, or blood chemistry monitoring for formaldehyde-induced kidney effects has been found in acute-or intermediate-duration inhalation studies with animals (rats, Rhesus monkeys, or mice) (Malek et al. 2003c; Pitten et al. 2000), or in chronic inhalation studies with rats and mice (Kamata et al. 1997; Kerns et al. 1983). Kum et al. (2007) found that the serum urea concentration was increased in rats exposed to 6 ppm formaldehyde 8 hours/day for

6 weeks, and no changes were observed in serum protein, albumin, or creatinine in comparison to control animals. Kidney weight and biochemistry parameters (superoxide dismutase and catalase activities and glutathione and malondialdehyde levels) were also similar to control animals (Kum et al. 2007).

Endocrine Effects. No human studies were located in the literature regarding inhalation exposure to formaldehyde and adverse endocrine effects. Furthermore, there is no evidence from histological examinations, or organ weight measurements for formaldehyde-induced effects on endocrine organs (e.g., pancreas, pituitary, adrenals, thyroid) in acute, or intermediate-duration inhalation studies with rats, mice, or Rhesus monkeys (Appelman et al. 1988; Malek et al. 2003c; Pitten et al. 2000; Woutersen et al. 1987), or in chronic inhalation studies with rats or mice (Kamata et al. 1997; Kerns et al. 1983).

Sorg et al. (2001) reported that exposure of rats to 0.7 or 2.4 ppm formaldehyde, 1 hour/day, 5 days/week for 4 weeks increased basal corticosterone levels in the serum. Exposure of female mice to 0.08, 0.4, and 2 ppm formaldehyde, 16 hours/day, 5 days/week for 12 weeks produced increases in the number of corticotrophin-releasing hormone-immunoreactive neurons in the hypothalamus. This effect was observed at exposure levels of 0.4 and 2 ppm formaldehyde. Similarly, increases in adrenocorticotropin hormone-immunoreactive cells in the anterior pituitary gland were observed in mice exposed to formaldehyde at 0.08, 0.4, and 2 ppm (Sari et al. 2004). An increase in adrenocorticotropin hormone mRNA levels was also seen in the pituitary gland. It was indicated that this upregulation of the hypothalamus-pituitary-adrenal pathway is not clearly adverse and may represent an adaptive response to formaldehyde exposure. Sari et al. (2004) reported that the upregulation response was impaired in allergy-model mice (sensitized with ovalbumin) exposed to 0.4 and 2 ppm. However, the importance of this pathway to the overall health status of the animal is unclear.

Dermal Effects. Occupational exposures to formaldehyde have been associated with dermal irritation and the diagnosis of allergic contact dermatitis by patch testing. Reported historical percentages of

subjects with skin problems showing positive responses to formaldehyde in patch tests performed by dermatologists using aqueous solutions with 1 or 2% formaldehyde include 8.1% in Pennsylvania between 2004 and 2005 (Anderson et al. 2007), 7.8% in North America between 1992 and 1994 (Marks et al. 1995), 1.6% in a 1983–1984 Swedish study (Meding and Swanbeck 1990), 2.6% in a 1988–1989 European study (Mennè et al. 1994), and 3.7% in a 1990–1994 Polish study (Kjec-Swierczynska 1996).

Takahashi et al. (2007) conducted a prospective study of clinical symptoms and skin test reactions in 143 medical students exposed to 2.4 ppm+0.49 ppm formaldehyde, 15 hours/week for 2 months. Skin irritation was reported in over 25% of students after repeated exposure to formaldehyde. Students with a history of atopic dermatitis (22 of 143 students) complained of skin irritation and redness more often than students without a history of atopic dermatitis. Positive patch testing was reported for only 2 of 60 students (3.3%) (1 male with allergic hand dermatitis due to direct contact with a cadaver and 1 female with an atopic background and symptoms). Negative patch test findings were also reported for 58 students similarly exposed to formaldehyde 2–4 years previously.

Body Weight Effects. Body weight effects have not been associated with formaldehyde exposure in humans, but exposure-response relationships have been described in animal studies. Body weight decreases ≥10% of control values were observed in formaldehyde-exposed animals in the following studies: (1) male rats exposed to 2 ppm, 6 hours, 5 days/week for 28 months (Kamata et al. 1997); (2) developing female rats exposed to 6 ppm, 8 hours/day for 6 weeks (Kum et al. 2007); (3) male rats exposed to 5 or 10 ppm, 8 hours/day, 5 days/week for 4 or 13 weeks (Ozen et al. 2003); (4) male rats exposed to 9.9 or 19.9 ppm, 8 hours/day, 5 days/week for 4 or 13 weeks (Ozen et al. 2002); and (5) female mice exposed to 5 or 10 ppm, 6 hours/day, 5 days/week for 2 weeks (Jung et al. 2007). No body weight effects were observed in rats exposed to formaldehyde up to 5.4 ppm, 2 hours/day for 10 days (Malek et al. 2003c) in rats exposed up to 4.6 ppm, 10 minutes/day, 7 days/week for 90 days (Pitten et al.

2000) or in mice exposed up to 2 ppm, 16 hours/day, 5 days/week for 12 weeks (Fujimaki et al. 2004, 2005; Sari et al. 2004).

2.2.1.3 Immunological and Lymphoreticular Effects

There are only a few recently available case reports of bronchial asthma suggestive of respiratory tract sensitization to formaldehyde gas, including a textile worker (Kim et al. 2001). This case of formaldehyde-exposed workers displayed marked changes in FEV_1 or airflow rates in response to acute challenges with formaldehyde gas at exposure levels <3 ppm. Vandenplas et al. (2004) reported a case of a persistent asthma following exposure to a high concentration of formaldehyde; the asthma was not considered to arise through an immunological mechanism. Inhalation challenge with concentrations up to 3 ppm did not result in a change in FEV_1, and the observed increase in IgE antibodies to formaldehyde was transient. Furthermore, 10 formaldehyde-exposed textile or shoe manufacturing workers with purported bronchial asthma were challenged with 0.41 ppm formaldehyde for 2 hours and showed no changes in FEV_1 (Krakowiak et al. 1998).

Several studies have examined serum for the presence of formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed humans (Doi et al. 2003; Kim et al. 1999; Wantke et al. 1996a). In general, the studies do not provide consistent evidence for a formaldehyde-induced allergic respiratory syndrome, but they provide suggestive evidence that children may have an increased tendency to develop specific antibodies after exposure to low levels of formaldehyde from indoor air (Wantke et al. 1996a).

Doi et al. (2003) examined the prevalence of IgE specific antibody sensitization to formaldehyde in Japanese children with asthma. Low levels of formaldehyde- IgE specific antibody were detected in only 2 of 150 children (122 children with asthma and 33 nonallergic children). One of these children was

reported to have severe asthma and frequent symptoms of mucosal irritation, while the other was reported to have mild asthma and only rare symptoms of mucosal irritation.

Ezratty et al. (2007) evaluated the effects of formaldehyde exposure on allergenic responses in 12 human subjects with intermittent asthma and allergy to grass pollen. Subjects were exposed to 0 or 0.4 ppm formaldehyde for 1 hour in a double-blind crossover study. Exposures were separated by 2 weeks, and the order of exposure to either formaldehyde, or purified air was randomized. Exposure to formaldehyde for 1 hour had no effect on FEV_1 or PEFR in human subjects with allergic asthma. Formaldehyde exposure did not affect the bronchial allergen responses to grass pollen or methacholine provocation. The levels of inflammatory markers measured in sputum (differential cell counts, interleukin [IL]-1, IL-4, IL-5, IL-8, and IL-10, granulocyte-macrophage colony stimulating factor [GMCSF], monocyte chemotactic protein-1 [MCP-1], tumor necrosis factor [TNF]-α, interferon[IFN]-γ, eotaxin-1, and eosinophilic cationic protein [ECP] levels) were similar in subjects exposed to either formaldehyde or purified air (Ezratty et al. 2007).

Casset et al. (2006) evaluated the effects of acute formaldehyde exposure (0.08 ppm for 30 minutes, mouth-breathing only) on the bronchial response to mite allergen in 19 subjects with mild asthma and allergic sensitization to house dust mites (confirmed by skin prick testing and IgE-specific antibodies to *Dermatophagoides pteronyssinus*). Formaldehyde exposure did not affect baseline pulmonary function or the nonspecific bronchial reactivity to methacholine. The immediate bronchial response to dust mite allergen occurred at a lower allergen concentration when subjects were pre-exposed to formaldehyde compared to air. The late-phase reaction, expressed as the maximum decrease in FEV_1 from baseline, was enhanced when subjects were exposed to formaldehyde. ECP concentrations in sputum were higher following exposure to formaldehyde than for exposure to air. Although this study suggests that formaldehyde could affect allergen responses in sensitized individuals, it is unlikely that low

concentrations of formaldehyde would reach the lower airways under conditions where nose-breathing is allowed (Casset et al. 2006).

Matsunaga et al. (2008) performed a cross-sectional epidemiology study to evaluate the possible relationship between formaldehyde exposure and allergic disorders in 998 pregnant Japanese women. Subjects were considered to have asthma, atopic eczema, or allergic rhinitis if they received medical treatment for these disorders during the 12 months prior to initiation of the study. Formaldehyde exposure determined by passive sampling devices worn for 24 hours was categorized into four groups based on the 30th, 60th, and 90th percentile values (<0.018, 0.018–0.027, 0.028–0.046, and >0.047 ppm). The prevalence of asthma, atopic eczema, and allergic rhinitis in the study population was 2.1, 5.7, and 14.0%, respectively. No association was found between formaldehyde exposure and the prevalence of asthma or allergic rhinitis. There was a tendency for a positive relationship between the formaldehyde concentration and atopic eczema. When the exposure data were categorized into two groups by use of a cutoff point at the 90th percentile, formaldehyde concentrations of >0.047 ppm were associated with an increased prevalence of atopic eczema in the multivariate model that controls for age, gestation, parity family history, cigarette smoking, mold, domestic pets, mite antigen level in house dust, family income, education, and season of data collection (adjusted OR 2.25, 95% CI 1.01–5.01).

In another study, Garrett et al. (1999) evaluated the risk of allergy in children exposed to residential concentrations of formaldehyde. The authors used a cross-sectional survey of 80 homes in Australia (148 children, 53 of whom were asthmatic). Passive residential sampling for formaldehyde was performed 4 times between March 1994 and February 1995, and the median level of formaldehyde was 0.0126 ppm, while the maximum level was 0.111 ppm. Formaldehyde exposure categories were <0.02, 0.02–0.04, and >0.04 ppm (<0.02, 0.020–0.050, and >0.050 mg/m^3) on the basis of the highest recorded levels. Respiratory questionnaires were completed by parents, and skin-prick testing was performed with 12 environmental allergens. No significant increase was observed between the adjusted risk of asthma or

respiratory symptoms with increasing formaldehyde concentration. A trend was observed between the formaldehyde exposure category and the proportion of atopic children. Logistic regression analysis using adjustments for parental asthma (i.e., family history) and sex gave an adjusted OR of 1.42 (0.99–2.04) for an increase in atopy associated with the highest recorded formaldehyde concentration of 0.02 ppm (0.02 mg/m^3). The analysis was not adjusted for passive smoking, presence of pets, nitrogen dioxide levels, or airborne fungal spores or dust mites, because these factors did not influence the outcome of the analysis and were not considered to be confounding factors. The number of positive skin-prick tests and the average size of the allergen wheal were increased in the highest formaldehyde exposure category >0.04 ppm (>0.050 mg/m^3) compared to the lowest formaldehyde exposure group (> 0.02 ppm [<0.02 mg/m^3]).

No histopathological effects on lymphoreticular tissues (e.g., spleen, thymus, lymph nodes) were observed in rats exposed up to 5.4 ppm formaldehyde, 2 hours/day for 10 days (Malek et al. 2003c), or in rats exposed to up to 15 ppm formaldehyde, 6 hours/day, 5 days/week for 28 months (Kamata et al. 1997).

Ohtsuka et al. (2003) evaluated the inflammatory response in the nasal mucosa of F-344 and Brown Norway rats exposed to 15 to 20 ppm formaldehyde aerosol, 3 hours/day for 5 days. Strain differences were observed in clinical signs (abnormal respiration, nasal discharge, and sneezing) and the incidence and severity of histopathological effects in the nasal mucosa (degeneration and desquamation of epithelial cells with neutrophil invasion). These effects were more pronounced in F-344 rats than in Brown Norway rats. The expression levels of T helper cell 1 (Th1)-related cytokines (INF-γ and IL-2) were reduced in nasal mucosa of Brown Norway rats, but not of F-344 rats, compared to untreated controls. The expression of Th2-related cytokines (IL-4 and IL-5) in the nasal mucosa was not altered by formaldehyde treatment in either rat strain. The altered cytokine levels in this study do not clearly explain the strain differences in nasal mucosa toxicity, and the biological significance of these changes is unknown.

Jung et al. (2007) investigated the pulmonary inflammatory response in female mice exposed to 0, 5, or 10 ppm formaldehyde for 6 hours/day, 5 days/week for 2 weeks, and the authors observed a 10% decrease in body weight in mice treated with 5 or 10 ppm. However, lung, liver, kidney, spleen, and thymus weights of the treated animals were similar to those of controls. Histopathological analysis of the lung tissues demonstrated eosinophils and mononuclear cell infiltration of the alveolar cell walls and alveolar spaces in formaldehyde exposed mice. Exposed mice had a higher number of CCR3+ eosinophils in bronchoalveolar lavage fluid than control mice and showed upregulated gene expression of CC-chemokine receptor-3 (CCR3), eotaxin, intercellular adhesion molecules (ICAM-1), and proinflammatory cytokines (IL-1, IL-4, and IL-5) in mouse lung. Formaldehyde exposure also produced an increase in the serum levels of IgG1, IgG3, IgA, and IgE compared to controls. Gene expression of thioredoxin (TRX), a redox-regulating antioxidant protein, was suppressed in formaldehyde-exposed mice, and levels of intracellular reactive oxygen species levels were increased. These results were consistent with the observed increase in the number of CCR3+-expressing eosinophils, and the results suggest that reactive oxygen species were generated from eosinophils recruited to the inflammatory sites of the airways (Jung et al. 2007).

In another study, Franco et al. (2006) examined the pulmonary inflammatory response in rats exposed to formaldehyde (concentration not measured) for 90 minutes/day for 4 days. Formaldehyde exposure produced an increase in leukocytes in bronchoalveolar lavage fluid, peripheral blood, and spleen, but the exposure did not alter cell counts in bone marrow. Formaldehyde also reduced the contractile response to methacholine in isolated rat bronchi. Lung histopathology showed mast cell degranulation and neutrophil invasion resulting from formaldehyde exposure. Mechanistic experiments suggest that leukocyte infiltration and bronchial hyporesponsivness may involve nitric oxide, airway sensory fibers, and mast cell mediators.

Fujimaki et al. (2004, 2005) evaluated the effect of formaldehyde exposure on allergic inflammatory responses in the lung by comparing non-immunized mice to allergy model mice (immunized with ovalbumin). Female C3H/He mice were exposed to formaldehyde concentrations of 0, 0.08, 0.4, or 2 ppm, 16 hours/day, 5 days/week for 12 weeks. Formaldehyde exposure did not alter body weight or thymus weight in non-allergy or allergy model female mice. Spleen weight was reduced in non-immunized mice exposed to 0.4 or 2 ppm formaldehyde, but it was unchanged in allergy-model mice. No histopathological evidence of inflammation was noted in the lungs or trachea of formaldehyde-exposed mice (nasal tissues were not examined). In non-immunized mice, formaldehyde inhalation did not alter the cell profile in bronchoalveolar lavage fluid. The number of macrophages and eosinophils was increased in allergy-model mice exposed to 2 ppm compared to allergy model controls. However, the level of IL-1β was reduced in these mice. Immunization with ovalbumin increased the production of nerve growth factor in bronchoalveolar lavage fluid and plasma, but exposure to 0.08 or 0.4 ppm formaldehyde (but not 2 ppm) reduced nerve growth factor levels compared to immunized control mice. Formaldehyde exposure did not alter the total number of spleen cells or the number of CD3-positive T cells, CD19-positive B cells, or the CD4/CD8 T cell ratio. The spleen cell proliferative response to mitogens or ovalbumin was not changed by formaldehyde exposure. An increase in INF-γ production was increased in cultured spleen cells from non-immunized mice exposed to 2 ppm formaldehyde for 12 weeks. Ovalbumin-stimulated monocyte chemo-attractant protein (MCP-1) was increased in allergy-model mice exposed to 0.4 or 2 ppm formaldehyde. Plasma levels of anti-ovalbumin IgG1 and IgG3 were decreased in mice exposed to 0.4 ppm. Substance P levels in the plasma increased in a dose-dependent fashion in non-immunized mice, but not in allergy-model mice. To summarize, alterations in some immune parameters were noted for both allergy and non-allergy model mice; however, a clear pattern of effects contributing to allergic sensitivity was not found. Some changes in cytokines and neuropeptides were noted, but tests of immune function were not performed. No IgE-mediated allergic inflammatory response was observed in these studies (Fujimaki et al. 2004, 2005).

Fujii et al. (2005) also demonstrated that formaldehyde inhalation may alter the intensity of the allergic contact hypersensitivity response to other chemicals. The effect of formaldehyde inhalation on the contact hypersensitivity of 2,4,6-trinitrochlorobenzene was determined in mice. Mice were sensitized by epicutaneous application of 20 μL of 2% 2,4,6-trinitrochlorobenzene on the right earlobe and challenged by applying 20 μL of 0.5% 2,4,6-trinitrochlorobenzene on the left earlobe on day 7 only or on days 7, 14, 21, 28, and 35 (chronic model). Mice were exposed to 0.2 ppm formaldehyde for 4 weeks prior to sensitization or during the challenge or elicitation phase. Ear swelling response was measured, and skin lesions were excised following sacrifice for histopathological examination. Draining lymph node cells were collected and cultured. Surface markers and cytokine production of T cell subsets were assessed. Ear swelling was decreased after a 7-day formaldehyde exposure during the challenge or elicitation phase followed by a single challenge dose. This was accompanied by a decrease in edema in the subcutaneous adipose tissue, an increased percentage of IL-4-producing $CD4^+$ T cells, and a decreased percentage of IFN-γ-producing $CD8^+$ T cells. Formaldehyde exposure for 4 weeks prior to sensitization resulted in an increased ear swelling response. Formaldehyde exposure also increased ear swelling during the challenge phase if the challenge occurred weekly over a 5-week period (chronic model). A decreased percentage of $CD4^+$, CD25, and$^+$ T cells, an increased percentage of $CD8^+$ and T cells, and an increase in the accumulation of mast cells in the elicited area of skin were also observed (Fujii et al. 2005).

In a similar study, Sandikci et al. (2007) exposed rats of four different life stages to 0 or 6 ppm formaldehyde 8 hours/day for 6 weeks. Life stage groups included prenatal exposure beginning on gestational day 1, early postnatal exposure beginning on the first day after birth, 4-week-old rats, and adult rats. Rats were sacrificed at 3, 6, 10, and 18 weeks after the exposure period for the prenatal, postnatal, 4-week-old, and adult rat groups, respectively. T lymphocytes in the peripheral blood and bronchus-associated lymphoid tissue were identified by demonstration of alpha-naphthyl acetate esterase activity. Formaldehyde exposure increased the proportion of alpha-naphthyl acetate esterase positive T cells in peripheral blood regardless of age. These cells were also increased in the bronchus-associated

lymphoid tissue in 4-week-old and adult rats. These results suggest that repeated inhalation exposure to formaldehyde may alter systemic cellular immunity.

2.2.1.4 Neurological Effects

Bach et al. (1990) conducted a study to determine if humans reacted acutely to formaldehyde exposure and if previous chronic exposure to formaldehyde adversely affected the responses observed in an acute formaldehyde challenge. Thirty-two men who worked at local formaldehyde-related factories were selected from 108 workers with more than 5 years of occupational exposure, and 29 matched controls were randomly selected from a group of 546 males with similar age, education, and smoking habits. Both groups were exposed to formaldehyde at concentrations of 0, 0.12, 0.32, or 0.98 ppm for 5.5 hours in a controlled atmospheric environment. The subjects underwent a series of performance tests during the exposure period; the tests were designed to access the subject's distractibility, short-term memory, and capability to understand and perform certain tasks. Headaches and physical tiredness occurred more often in the controls than in the workers previously exposed to formaldehyde. In both the occupationally exposed and the non-exposed subjects, decreased performances in several tests were statistically significant, and they correlated with increasing acute exposure concentrations of formaldehyde. The occupationally exposed subjects showed significantly decreased performance, as compared to non-exposed subjects, only in a digit span test, but not in variables for a graphic continuous line test, an addition test, or a digit symbol test. The authors demonstrated that under controlled environmental conditions, exposure to formaldehyde at concentrations of 0.32 ppm and 0.98 ppm may cause acute CNS effects (Bach et al., 1990).

Neurobehavioral effects, including altered motor activity and impaired learning and memory, have been noted in animal studies following acute- (Lu et al. 2008; Malek et al. 2003a, 2003b, 2003c, 2004; Morgan et al. 1986; Usanmaz et al. 2002; Wood and Coleman 1995) and intermediate-duration (Pitten et al. 2000;

Usanmaz et al. 2002) exposure to formaldehyde. No histopathological alterations in the brain or spinal cord were found in these studies. Alterations in brain structure were observed in neonatal rats exposed to formaldehyde during the first 30 days after birth (Aslan et al. 2006; Sarsilmaz et al. 2007). These studies are discussed in Section 2.2.1.6.

Open field behavior was evaluated in rats exposed to 0, 0.1, 0.5, or 5 ppm formaldehyde for 2 hours (Malek et al. 2003b). Rats were exposed to 0, 1, 2.5, or 5 ppm for 2 hours (Malek et al. 2003a), and male mice were exposed to 0, 0.1 1, 2, 3, or 5.2 ppm for 2 hours (Malek et al. 2004). These acute formaldehyde exposures resulted in a decrease in spontaneous motor activity and changes to some exploratory behaviors (i.e., sniffing, rearing) 2 hours after the end of exposures in rats and mice. Some of the exploratory behavioral parameters remained altered 24 hours after the end of the exposure (Malek et al. 2003a, 2004). Kun Ming male mice exposed to formaldehyde at 0, 0.81, or 2.4 ppm for 6 hours/day for 7 days and trained for 30 minutes in a Morris water maze following exposure showed a significant decrease in maze performance (increased escape latency and decrease spatial memory) in the 2.4 ppm formaldehyde-exposed group, as compared to the control group (Lu et al. 2008). Moreover, oxidative stress on the brains of the mice assessed by glutathione and super dismutase changes and increased expression of genes associated with learning and memory processes of animals were also observed in the 2.4 ppm exposure group.

Usanmaz et al. (2002) evaluated the neurotoxicity of acute- and intermediate-duration formaldehyde exposures in mice. Mice were exposed to formaldehyde concentrations of 1.8, 2, 3.2, 4.5, 6.4, 7.8, 9.7, and 14.8 ppm for 3 hours (1-day exposure), 2 ppm for up to 3 weeks (3 hours/day, 5 days/week), or 3.2 ppm for up to 2 weeks (3 hours/day, 5 days/week). Spontaneous motor activity was reduced by a single 3-hour exposure to formaldehyde at concentrations >1.8 ppm and by repeated exposure to 2 ppm for 3 weeks or 3.2 ppm for 2 weeks. The wet-dog shake, a pro-convulsive behavior, was increased at concentrations of 1.8, 3.2, and 6.4 ppm for a 3-hour exposure, but the same was not observed at higher

acute concentrations or following repeated exposure to 2 ppm for 3 weeks or 3.2 ppm for 2 weeks. Pentylenetetrazole-induced seizures were more severe in mice exposed to 1.8 ppm formaldehyde for 3 hours, as compared to controls. No change in seizure parameters was seen following a 3-hour exposure to 6.4 ppm, and a decrease in the incidence of seizures was observed at 14.8 ppm, compared to controls. Repeated exposure to formaldehyde did not alter the pentylenetetrazole-induced seizure response in mice (Usanmaz et al. 2002).

Malek et al. (2003c), using a water maze study design, evaluated the effect of acute formaldehyde inhalation on learning and memory in rats. Rats were exposed to 0, 0.1, 0.5, or 5.4 ppm formaldehyde 2 hours/day for 10 days. A pre-trial period occurred 2 days prior to exposure, when rats were placed in the water labyrinth and manually assisted with learning the swimming route to the finish. Animals were tested in the water labyrinth each day during the 10-day exposure period (2 hours after exposure). Control rats required increasingly shorter swimming times to reach the finish over the 10-day course of the experiment. In male rats, the mean swimming time was increased in rats exposed to 0.5 or 5.4 ppm formaldehyde, while the error frequency was increased in all formaldehyde treatment groups (0.1, 0.5, or 5.4 ppm) compared to controls. The mean swimming time was also increased in female rats exposed to formaldehyde at 0.5 or 5.4 ppm. However, female rats exposed to 0.1 ppm of formaldehyde showed faster swimming times than control rats on several days during the exposure period. The error frequency in female rats was increased in all formaldehyde-exposed groups, as compared to controls. No histopathological alterations were observed in the heart, thymus, pancreas, liver, kidney, skeletal muscle, or spleen. Focal microatelectasis (absence of gas from part or all of the lungs due to failure of expansion and resorption) of the lungs (i.e., changes to alveolar structure) was noted in 20-30% of rats from both control and formaldehyde-treatment groups (Malek et al. 2003c).

In another study, Pitten et al. (2000) evaluated maze performance in rats exposed to 0, 2.6, or 4.6 ppm formaldehyde 10 minutes/day, 7 days/week for 90 days. Maze performance was evaluated every 10th day

during the 90-day exposure period and a 30-day post-exposure period. Rats from both formaldehyde exposed groups made more errors in maze performance during the exposure period than control rats. No difference in maze performance was seen among treatment groups by 4 weeks after cessation of exposure. The time required to find food in the maze was longer for rats in both formaldehyde-exposed groups during exposure, as compared to control rats. No alterations in general locomotion were observed, and no histopathological changes were noted in the liver, trachea, lungs, kidney, heart, spleen, pancreas, testicles, cortex, brainstem, cerebellum, or spinal cord (Pitten et al. 2000).

2.2.1.5 Reproductive Effects

Several comprehensive reviews have concluded that formaldehyde does not produce significant reproductive and developmental toxicity. In a review of available reproductive and developmental toxicity data for humans and laboratory animals, the World Health Organization (WHO) concluded, "There is no convincing evidence that formaldehyde is a teratogen in either animals or human beings. Formaldehyde has not produced any adverse effects on reproduction in test animals or human beings" (WHO 1989). IARC (2006) reached a similar conclusion in a more recent review. Reports of higher rates of spontaneous abortion in female occupational workers were characterized as inconsistent, and effects on pregnancy and fetal development in animals were not seen at exposures below maternally toxic concentrations. Collins et al. (2001) performed a review of the reproductive and developmental toxicity data for formaldehyde in animals. They concluded that animal studies demonstrated that formaldehyde is unlikely to reach the reproductive system at concentrations sufficient to cause damage due to rapid biotransformation of formaldehyde by the respiratory tract (Collins et al. 2001). In addition, human studies were considered to be limited by study design flaws and reporting and publication bias.

Taskinen et al. (1999) performed a retrospective study of time to pregnancy in 699 female wood workers from Finland who had given birth between 1985 and 1995. A questionnaire was used to obtain

information on exposure, pregnancy history, time-to-pregnancy, and potential confounders. Daily formaldehyde exposure concentrations were estimated for each person based on the results of the questionnaire and industrial hygiene measurements from the workplace. The three formaldehyde exposure categories were determined with mean measured concentrations of 0.07, 0.14, and 0.33 ppm for the low, medium, and high categories, respectively. The highest formaldehyde exposure category was associated with delayed conception, as measured by an adjusted fecundability density ratio (FDR, ratio of average incidence densities of pregnancies for exposed women, compared to unexposed women, adjusted for confounding factors) (FDR= 0.64; 95% : CI 0.43–0.92, p=0.02, n=39). Further analyses of this group indicated that the use of gloves was an important protective factor to dermal exposure to formaldehyde. In fact, women in the high exposure group who did not wear gloves had a significantly lower FDR (0.51; 95% CI: 0.28–0.92, n=17), compared to the unexposed formaldehyde group. Instead, women in the high exposure group who used gloves had a non-significant decrease of FDR (0.79; 95% CI: 0.47–1.23). These results suggest that dermal exposure to formaldehyde plays a significant role in the potential effects on female fertility. Exposure to organic solvents, dusts, and wood dusts were not associated with prolonged time to pregnancy (FDR values for exposure categories did not differ from unity). It was suggested that formaldehyde exposure may also be related to the risk of spontaneous abortion; however, a dose-response relationship for this effect was not apparent. Exposure to high concentrations of formaldehyde was associated with increased risk of endometriosis (OR= 4.5; 95% : CI 1.0–20.0). The authors concluded that a woman's occupational exposure to formaldehyde has an adverse effect on fertility (Taskinen et al. 1999). However, the findings of this study may have several limitations-for example, the small number of women in the high formaldehyde exposure group (n=39), the fact that exposure to organic solvents was not associated with FDR, and importantly, the finding that dermal exposure is suggested to play a significant role in reduced fertility outcome , however,the dose absorbed by the dermal exposure route was not estimated.

Saillenfait et al. (1989) examined the effects of maternal exposure to inhaled formaldehyde on embryonic and fetal toxicity in Sprague-Dawley rats. Groups of 25 dams were exposed to 0, 5, 10, 20, and 40 ppm formaldehyde in inhalation chambers on gestational days 6-20. Dams were weighed on gestational days 0, 6, and 21, and they were randomly assigned to experimental groups so that their body weights on gestational days 0 and 6 were similar to those of dams in different dose groups. All dams survived the experiment, and on gestational day 21, dams were sacrificed, and their uteri were excised and examined. Maternal weight gain, percentage of pregnancy, litter sex ratio, fetal mortality, fetal weight, cleft palate malformation, and alterations of soft and skeletal tissues were assessed. Dams exposed to 40 ppm formaldehyde had a 51% reduction in weight gain in comparison to controls ($p<0.01$), but the former showed no other clear or overt signs of toxicity. The authors observed no significant differences between treatment groups in the incidences of pregnancies, number of implantations, or resorptions, numbers of dead, or live fetuses, fetal sex ratios, or the incidences of external, visceral, or skeletal abnormalities. Fetal body weights of male offspring from dams exposed to 20 ppm formaldehyde were 5% lower than those of controls ($p<0.05$). Furthermore, fetal body weights of male and female offspring from dams exposed to 40 ppm formaldehyde ($p<0.01$) were about 21% lower than those of offspring of controls. Therefore, maternal exposure to formaldehyde at 40 ppm for 6 hours/day during gestational days 6–20 was not teratogenic nor embryotoxic, but exposue at 20 ppm was slightly fetotoxic, as indicated by lower fetal body weights (Saillenfait et al., 1989).

Senichenkova (1991) examined the embryotoxic effect and fetal and juvenile offspring development from mongrel female white rat dams exposed to 0 or 0.4 ppm formaldehyde for 4 hours/day on gestational days 1-19. The results showed that prenatal exposure to formaldehyde does not affect the embryonic mortality and does not decrease the crown-tail (craniocaudal) lengths or the weights of embryos. However, examination of internal organs of the prenatal formaldehyde-exposed group revealed decreased fetal hyoid ossification and increased incidence of total anomalies, with absence of testes as the predominant

anomaly (Senichenkova 1991). Senichenkova (1991) also examined the postnatal behavior of offspring after prenatal exposure to formaldehyde. The authors observed a significant increase in motor activity and exploratory activity in the formaldehyde-exposed group, as manifested by increased numbers of squares visited and increased frequency of rearings on postnatal days 2 and 3 in comparison to controls.

In a similar study of pregnant mongrel female mice exposed to 0 or 0.4 ppm formaldehyde for 4 hours/day on gestational days 1-19, decreased fetal hyoid ossification and increased incidence of total anomalies, with absence of testes as the predominant anomaly, were found in the formaldehyde-exposed group (Senichenkova and Chebotar 1996). These investigators observed that when maternal iron deficiency anemia was induced in pregnant mongrel mice, the embryo toxic effect of environmental xenobiotics studied was significantly increased (Senichenkova and Chebotar 1996).

Kitaev et al. (1984) exposed mature female Wistar rats to formaldehyde at concentrations of 0, 0.4, or 0.8 ppm for 4 hours/day, 5 days/week for 123 days. The female rats were mated with male rats on day 120 of exposure and embryos were removed on day 2 or 3 of gestation. The dams exposed to 0.8 ppm had a significant increase in embryo degeneration on the 3rd day. The dams exposed to 0.8 ppm of formaldehyde revealed an increase in follicle stimulating hormone (FSH) concentrations in blood samples in comparison to controls. The duration of the estrus cycle in dams was not affected by prolonged formaldehyde exposure, nor was the weight of the uterus in animals exposed to 0.4 ppm. Initially, these authors observed an increase in the weight of the ovaries at the lower dose, but when the animals were exposed to formaldehyde at 0.8 ppm, the weight of the ovaries fell below that of the control animals. The authors suggested that the increase in ovary weight at exposure to 0.4 ppm corresponded to the increase in blood LH and progesterone levels (Kitaev et al. 1984).

In a study of humans, Maroziene and Grazuleviciene (2002) conducted a population-based, cross-sectional study in Lithuania to evaluate the relationship between ambient air pollution and the occurrence

of low birth weight and pre-term delivery. The study findings related to low birth weight are presented in Section 2.2.1.6. The study included all singleton newborns born in 1998 in the City of Kaunas (n=3,988). Maternal characteristics were obtained from the Lithuanian National Birth Register, and residential concentrations of formaldehyde were estimated from data collected at 12 community monitoring stations. The mean formaldehyde concentration during the study period was 2.6 ppb, SD=1.9 ppb (3.14 $\mu g/m^3$ SD=2.36 $\mu g/m^3$). Exposure concentrations were grouped into three categories, and the exposure variable was applied as both categorical and continuous parameters through use of multivariate logistic regression. No significant association was observed between formaldehyde exposure and premature birth (Marzoiene and Grazuleviciene, 2002).

Collins et al. (2001) performed a meta-analysis of eight studies that evaluated spontaneous abortions related to formaldehyde exposure. Inconsistent findings were reported in the original studies, and the meta-analysis was adjusted for reporting and publication bias. The meta-analysis concluded that there was no evidence of increased risk of spontaneous abortions among workers exposed to formaldehyde (meta-relative risk=0.7, 95% CI 0.5–1.0) (Collins et al, 2001).

Zhou et al. (2006) evaluated the testicular toxicity of formaldehyde in male rats exposed to 0 or 8 ppm formaldehyde, 12 hours/day for 2 weeks. Formaldehyde exposure produced a decrease in testicular weight and histopathological changes, including atrophy of the seminiferous tubules, a decrease in spermatogenic cells, azoospermic lumina, disintegration of seminiferous epithelial cells, which were shed into the lumina, and edematous interstitial tissue with vascular dilation and hyperemia. Formaldehyde exposure also produced a decrease in sperm motility and an increase in the percentage of abnormal sperm. The activities of glutathione peroxidase and superoxidase dismutase and the level of testicular glutathione were decreased, while malondialdehyde levels were increased in formaldehyde-exposed rats compared to controls. Administration of 30 mg/kg/day vitamin E during the formaldehyde exposure period prevented

the biochemical changes and the histopathological and sperm motility/morphology changes induced by formaldehyde in male rats (Zhou et al. 2006).

Similar results were reported by Ozen et al. (2002), who observed decreased testicular weight in rats exposed to 0, 9.9, or 19.9 ppm (0, 12.2, or 24.4 mg/m^3) formaldehyde 8 hours/day, 5 days/week for 4 or 13 weeks. This decrease in testicular weight may be related to overall growth retardation, because decreases in body weight gain (>10%) were seen at both formaldehyde concentrations after 4 and 13 weeks of exposure. Altered concentrations of trace metals were found in the testes of formaldehyde-exposed rats (decreased zinc and copper, increased iron). However, the relevance of these changes is unclear, because no further evaluation of testicular structure or function was performed in this study.

In another study, Ozen et al. (2002) examined male reproductive effects in rats exposed to 0, 5 ppm, or 10 ppm formaldehyde, 8 hours/day, 5 days/week for 91 days. Serum testosterone levels and the diameters of seminiferous tubules were reduced in both exposure groups compared to controls. Immunoreactive heat shock protein 70 was detected in the spermatogonia of formaldehyde exposed rats (5 and 10 ppm), but not in control rats. The spermatocytes and spermatids located in the adluminal portion of the seminiferous epithelium showed high-density immunohistochemical staining for heat shock protein 70 in formaldehyde-exposed rats (5 and 10 ppm) and low density staining in control rats. Survival was not affected by formaldehyde exposure in this study. However, formaldehyde-exposed rats experienced decreased food and water consumption, unsteady breathing, increased nose cleaning, excessive licking, frequent sneezing, and nasal mucosal hemorrhages (Ozen et al. 2005).

Adult male Wistar rats exposed to formaldehyde at concentrations of 10 or 20 ppm, 8 hours/day, 5 days/week for 4 weeks were found to have concentration-related reduced body weight gains and decreased Leydig cell quantities in comparison to control animals (Sarsilmaz et al. 1999). Leydig cells were examined for histological changes. The percentage of normal Leydig cells was decreased in both

formaldehyde exposed groups compared to controls. The histological changes consisted of nuclear damage to the Leydig cells (Sarsilmaz et al. 1999).

2.2.1.6 Developmental Effects

Maroziene and Grazuleviciene (2002) conducted a population-based cross-sectional study in Lithuania to evaluate the relationship between ambient air pollution and the occurrence of low birth weight and pre-term delivery. The findings related to pre-term delivery are presented above in Section 2.2.1.5. The study included all singleton newborns born in 1998 in the City of Kaunas (n=3,988). Maternal characteristics were obtained from the Lithuanian National Birth Register, and residential concentrations of formaldehyde were estimated from data collected at 12 community monitoring stations. The mean formaldehyde concentration during the study period was 2.6 ppb, SD=1.9 ppb (3.14 µg/m^3) (SD=2.36 µg/m^3). Exposure concentrations were grouped into three categories, and the exposure variable was applied as both categorical and continuous parameters by use of multivariate logistic regression. The crude and adjusted ORs for low birth weight increased with formaldehyde exposure. After adjustment for low birth weight risk factors (maternal age, marital status, education, season of birth, parental smoking), the risk of low birth weight remained increased for the medium (OR 1.86, 95% CI 1.10–3.16) and high (OR 1.84, 95% CI 1.12–3.03) formaldehyde exposure categories (concentrations for categories were not specified). Further adjustment for gestational age slightly increased the OR. However, the estimate remained statistically significant only for the high exposure group (OR 2.09, 95% CI 1.03–4.26) (Maroziene and Grazuleviciene 2002).

Kum et al. (2007) evaluated the potential for liver toxicity in female rats exposed to 0 or 6 ppm formaldehyde 8 hours/day for 6 weeks beginning on gestation day 1 or post-parturition day 1. Body weight and liver weight were decreased in rats exposed to 6 ppm formaldehyde during the prenatal or early postnatal periods. Catalase activity and malondialdehyde levels in the liver were increased

following prenatal exposure to formaldehyde. Glutathione levels were decreased in the early postnatal exposure group. Sandikci et al. (2007) used the same study design to evaluate immune system effects in rats exposed during the prenatal, or the early postnatal periods. Exposure to 6 ppm formaldehyde increased the proportion of α-naphthyl acetate esterase positive T cells in peripheral blood, suggesting that systemic cellular immunity may be affected in developing rats. A similar response was seen in young (4-week-old) and adult rats.

The results of studies in neonatal rats have suggested that exposure to formaldehyde can affect brain development (Aslan et al. 2006; Sarsilmaz et al. 2007). Aslan et al. (2006) showed alterations in volume and cell number of the hippocampal formation of the brain in neonatal male rats exposed to 6 or 12 ppm formaldehyde, 6 hours/day, 5 days/week for the first 30 days of life. The brains of rats were examined immediately following the exposure period or 60 days later. The morphology of granule cells in the dentate gyrus was not altered by formaldehyde treatment. However, the volume of the dentate gyrus was increased in both formaldehyde-exposed groups of 30-day-old rats compared to controls. The low concentration of formaldehyde also produced an increase in the dentate gyrus volume in 90-day-old rats compared to the controls or the high concentration group. A volume reduction in the granule cell layer was seen in the high concentration group at 90 days, as compared to rats examined at 30 days. There was no effect of formaldehyde treatment on granule cell number immediately following exposure; however, exposure to the high concentration resulted in a decrease in the granule cell number 60 days later, as compared to controls and the low concentration group (Aslan et al. 2006).

Sarsilmaz et al. (2007) demonstrated similar effects in the cornu ammonis region of the hippocampus following exposure of neonatal rats to 6 or 12 ppm formaldehyde for 6 hours/day, 5 days/week for the first 30 days of life. The brains of rats were examined immediately following the exposure period or 60 days later. Formaldehyde exposure did not alter the appearance of pyramidal cells in the hippocampus. There were concentration-related volume changes in the cornu ammonis and the whole

hemisphere of the brain. Immediately following the exposure period, the low concentration of formaldehyde increased the cornu ammonis volume, while the high concentration decreased the cornu ammonis volume. Both low and high concentrations reduced the whole hemisphere volume immediately following the exposure period, but they increased the whole hemisphere volume 60 days later, as compared to controls. Rats in the high exposure group had fewer pyramidal cells than rats from the low exposure group or controls at 30 or 90 days after birth.

Songur et al. (2005) demonstrated that formaldehyde exposure alters trace element levels in the neonatal rat lung following exposure to 6 ppm or 12 ppm formaldehyde 6 hours/day, 5 days/week for 30 days beginning the first day after birth. Superoxide dismutase activity and copper and iron levels were reduced, while zinc levels were increased in lung samples from neonatal rats exposed to formaldehyde. These changes were observed immediately following the exposure period and 30 days later. Survival was not affected by formaldehyde exposure in neonatal rats. However, food and water consumption and body weight measurements were reduced during the exposure period compared to controls. Clinical signs of toxicity included sneezing, dyspnea, polypnea, increased nose cleaning, excessive licking, blinking of the eyes, and nasal bleeding. At the end of the 30-day post-exposure period, body weights were similar to those of controls (Songur et al. 2005).

2.2.1.7. Genotoxicity

In vivo Exposure Studies. Results from human *in-vivo* exposure genotoxicity studies are mixed (Table 2-1). Several human occupational exposure studies have described increased sister chromatid exchange (SCEs) in lymphocytes (Shaham et al. 2002; Ye et al. 2005), while a shorter-term exposure (8 weeks) study of anatomy students did not report exposure-related increased SCEs in lymphocytes (Ying et al. 1999). With the exception of one short-term (10-day, 4 hours/day) experimental exposure study (Speit et al. 2007a), all other human occupational exposure studies have reported an increased frequency of

micronuclei in nasal mucosa (Burgaz et al. 2001; Ye et al. 2005), buccal mucosa (Burgaz et al. 2002), and peripheral lymphocyte cells (Orsiere et al. 2006; Sari-Minodier et al. 2001) in exposed workers compared to controls. In other studies of formaldehyde workers, no evidence was found of DNA damage (Orsiere et al. 2006) or changes in DNA-repair enzyme activity (Schlink et al. 1999) in lymphocytes.

Table 2-1. Genotoxicity of Formaldehyde *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human (peripheral lymphocytes) 30 medical students <1 ppm 15 months	Chromosomal aberrations	–	Vasudeva and Anand 1996
Human (peripheral lymphocytes) 18 workers (16 control subjects) TWA=0.985 mg/m^3 mean=8.6 years	Sister chromatid exchange	+	Ye et al. 2005
Human (peripheral lymphocytes) 23 students (pre-exposure control) TWA=0.508 mg/m^3 8 weeks (3 hours x 3 times/week)	Sister chromatid exchange	–	Ying et al. 1999
Human (peripheral lymphocytes) 90 pathology workers (52 controls subjects) unspecified concentrations mean=15.4 years	Sister chromatid exchange	+	Shaham et al. 2002
Human (nasal mucosa) 18 workers (16 control subjects) TWA=0.985 mg/m^3 mean=8.6 years	Micronucleus increase	+	Ye et al. 2005

Table 2-1. Genotoxicity of Formaldehyde *In Vivo*

Species (test system)	End point	Results	Reference
Human (peripheral lymphocytes) 59 laboratory workers with 0.5–34 years of previous exposure (37 control subjects) 2.0 ppm for 15 minutes or 0.1 ppm for 8 hours	micronucleus increase	+	Orsiere et al. 2006
Human (buccal mucosa) 10 days (4 hours/day) experimental exposure 0.15–0.5 ppm with 4 peaks of 1.0 ppm for 15 minutes each	Micronucleus increase	–	Speit et al. 2007a
Human (peripheral lymphocytes) 10 occupationally exposed women (27 control subjects) unspecified concentrations; mean=9 years	Micronucleus increase; chromosome aberrations	+	Sari-Minodier et al. 2001
Human (nasal mucosa) 23 laboratory workers (25 control subjects) 2–4 ppm; mean=5.06 years	Micronucleus increase	+	Burgaz et al. 2001
Human (buccal mucosa) (18 control subjects) Group I: 22 shoe workers TWA=11.39–58.07 ppm Mean=7.68 years Group II: 28 pathology workers TWA=2–4 ppm mean=4.70 years	Micronucleus increase	+	Burgaz et al. 2002

Table 2-1. Genotoxicity of Formaldehyde *In Vivo*

Species (test system)	End point	Results	Reference
Human (peripheral lymphocytes) 59 laboratory workers with 0.5–34 years of previous exposure (37 control subjects) 2.0 ppm for 15 minutes or 0.1 ppm for 8 hours	DNA damage	–	Orsiere et al. 2006
Human (embalming student exposure/peripheral lymphocytes)	DNA-repair enzyme activity	–	Schlink et al. 1999
Rat (lung cells)	DNA damage	+	Sul et al. 2007

– = negative result; + = positive result

In other mammalian *in-vivo* studies, inhalation exposure to formaldehyde has been found to increase DNA-protein cross links in the monkey respiratory tract (Casanova et al. 1991) and rat nasal mucosal cells following 6-hour exposures. Acute inhalation exposure (6 hours) to formaldehyde was also found to induce chromosomal aberrations in pulmonary lavage cells in rats (Dallas et al. 1992) and spleen lymphocytes in mice. Inhalation exposure to formaldehyde in rats caused increased DNA damage in lung cells following a 2-week exposure (Sul et al. 2007) and p53 suppressor gene mutations in nasal cells after 2 years of exposure (Recio et al. 1992). Other reports present negative findings for chromosomal aberrations in the bone marrow after a 6-hour inhalation exposure to formaldehyde (Dallas et al. 1992) and for chromosomal aberrations, mitotic activity, and SCEs in lymphocytes of rats exposed for 5 days (6 hours/day). *In-vivo* formaldehyde exposure resulted in mortality and sterility and caused lethal mutations in Drosophila melanogaster, (Valencia, et al. 1989 and Woodruff et al. 1985).

In vitro Exposure Studies. As summarized in Table 2-2, formaldehyde has been found to be mutagenic in *Salmonella typhimurium* in most studies without metabolic activation, but not mutagenic in a few other studies.

Table 2-2. Genotoxicity of Formaldehyde *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human (peripheral blood lymphocytes)	Micronuclei	No data	+	Iarmarcovai et al. 2007
Human (leukocytes)	DNA damage	No data	+	Frenzilli et al. 2000
Human (blood cultures)	DNA protein cross links; sister chromatid exchange	No data	+	Schmid and Speit 2007
Human (blood cultures)	Micronuclei	No data	–	Schmid and Speit 2007
Chinese hamster (V79 cell HPRT locus culture)	Sister chromatid exchange; DNA protein cross links	No data	+	Merk and Speit 1999
Chinese hamster (V79 cell HPRT locus culture)	Mutations	No data	–	Merk and Speit 1999
Chinese hamster (V79 cell culture)	Sister chromatid exchange; DNA protein cross links; micronuclei	No data	+	Merk and Speit 1998
Chinese hamster (V79 cell HPRT locus culture)	Mutations	No data	–	Merk and Speit 1998
Chinese hamster (V79 cell culture)	DNA strand breaks	No data	–	Speit et al. 2007b
Chinese hamster (V79 cell culture)	Sister chromatid exchange; DNA protein cross links; micronuclei	No data	+	Speit et al. 2007b
Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Miyachi and Tsutsui 2005
Non-mammalian cells:				
Neurospora crassa	Mutation	No data	(+)	de Serres and Brockman 1999

[a]Test compound was formalin.

– = negative result; + = positive result; (+) = weakly positive; DNA = deoxyribonucleic acid

A number of human cell lines have been tested, with formaldehyde giving positive results without metabolic activation, resulting in mutations, DNA damage, DNA-protein cross links, increased micronuclei, chromosomal aberrations, and SCEs (Emri et al. 2004; Frenzilli et al. 2000; Iarmarcovai et al. 2007; Schmid and Speit 2007; Shaham et al. 2003; see Table 2-2). Using a sensitive technique to detect total DNA-protein cross links, Shaham et al. (1996) reported that 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. Although DNA-protein cross links are known to be formed by other agents, such as ionizing radiation and alkylating agents, Shaham et al. (1996) suggested that levels of DNA-protein cross links in white blood cells may provide an indicator of formaldehyde-induced tissue damage and a biomarker of occupational exposure to formaldehyde. Statistically significant higher levels of DNA-protein cross links in formaldehyde-exposed workers compared to unexposed workers ($p<0.01$) were later reported in an extending study (Shaham et al. 2003). The authors examined peripheral blood lymphocytes of 186 workers exposed to formaldehyde and in 213 unexposed workers for DNA-protein cross links as well as p53 protein. Pantropic (wild type + mutant) p53 >150 pg/ml was higher in exposed workers with DNA-protein cross links above the median (median DNA-protein cross links >0.187). The adjusted OR to have pantropic p53 150 pg/mL in workers with DNA-protein cross links above the median was 2.5 (95% CI 1.2–5.4). The adjusted OR was still significant when stratified by gender in the female group (OR 2.8; 95% CI 1.1–7.1), but not significant in the male group (OR 1.9; 95% CI 0.5–7.2).

Formaldehyde Genotoxicity Conclusions. In summary, the majority of tests show that formaldehyde *in vivo* and *in vitro* exposure can induce genotoxic effects in various organisms and cell types. The weight of evidence indicates that formaldehyde itself (not a metabolite) is capable of directly reacting with DNA and producing genotoxic effects in portal-of-entry tissues, especially when biotransformation capacities are exceeded. More extensive evaluations of the genotoxic potential of

formaldehyde are available in IARC (2006) and WHO (1989). Environment Canada/Health Canada (2001) and WHO (2002) concluded that overall, formaldehyde is weakly genotoxic, with effects most likely to be observed *in vivo* in cells from tissues or organs with which the aldehyde comes into first contact.

2.2.1.8 Cancer

Human Studies Overview. The finding of nasal tumors in rodents exposed to high levels of airborne formaldehyde led to a concern about cancer effects in occupationally exposed workers. There are now more than 60 epidemiology studies examining the potential for occupational formaldehyde exposure to cause cancer in humans. The studies include cohort mortality studies of formaldehyde-exposed industrial workers, cohort mortality studies of formaldehyde-exposed professionals or medical specialists, and case-control studies that looked for associations between occupational exposure to formaldehyde and cancers of the nose, pharynx, or lung. More recent reviews have been published by Duhayon et al. (2008), Golden et al. (2006), IARC (2006), and NTP (2005). In addition, several meta-analyses of the data have been published (Bosetti et al. 2008; Collins et al. 1997; Luce et al. 2002; Partanen 1993).

Although some of the epidemiological studies have found some evidence for extra-respiratory site cancers in groups of formaldehyde-exposed workers, the data are not consistent across studies, and adjustment for potential confounding cancer risk factors has not often been possible. IARC (2006) concluded that while a number of studies have found associations between formaldehyde exposure and cancer at other sites, including the oral cavity, oro- and hypopharynx, pancreas, larynx, lung, and brain, the overall evidence in humans does not support a causal role for formaldehyde in these cancers.

Increased incidences of leukemia rates have been reported in some studies of anatomists, pathologists, and embalmers (Blair et al. 1990; Hauptman et al. 2009), and such incidences have also been observed in

cohort studies of industrial workers. Two updated large industrial studies showed an association between some measures of formaldehyde exposure and relative risk from leukemia (Hauptmann et al. 2003; Pinkerton et al. 2004). However, another large industrial follow-up study did not find any association between exposure to formaldehyde and leukemia (Coggon et al. 2003). In addition, a follow-up of the Hauptmann et al. (2003) cohort study revealed that whereas a statistically significant association between death from leukemia and peak exposure to formaldehyde remained, the overall association of formaldehyde exposure with leukemia had diminished with the additional 10 years of follow-up (Freeman et al. 2009). The authors noted that although this decline over time may suggest that the previous results could be due to chance, the largest risks occurred closer in time to relevant exposure, a fact that is consistent with known leukemogenic agents. A re-analysis of the Hauptmann et al. (2003) data by Marsh and Youk (2004) did not support a causal association between formaldehyde exposure and mortality from leukemia. External comparisons provided by Marsh and Youk (2004) suggested that elevated risks occurred because slight to moderate excesses in mortality were compared to statistically significant baseline category deficits in deaths. Collins and Lineker (2004) conducted a meta-analysis of 18 epidemiology studies of formaldehyde exposed workers reporting rates of leukemia development. These investigators did not find any firm support to establish a relationship between formaldehyde exposure and risk of leukemia (Collins and Lineker 2004). Several studies have examined the biological plausibility of formaldehyde-induced leukemia, and have concluded that there is inadequate biological evidence to support a possible mechanism of action for hypothesis (Cole and Axten 2004; Golden et al. 2006; Heck and Casanova 2004). In contrast to the results of these studies, IARC (2009) concluded that “there is sufficient evidence for a causal association of formaldehyde with leukaemia.”

Many reviewers have agreed that cancer of the respiratory tract, particularly the upper respiratory tract, is more biologically plausible than formaldehyde-induced cancer at distant sites (NTP 2010). This is probably based on the reactivity of formaldehyde, the capacity of tissues to bio-transform formaldehyde, and the results from chronic rodent inhalation studies showing that formaldehyde-induced non-neoplastic

and neoplastic effects are restricted to the upper respiratory tract with exposures to concentrations <5-10 ppm. Accordingly, the reviews and meta-analyses of the human data have focused primarily on the findings for respiratory cancer deaths in occupationally exposed humans.

The following six mortality studies of cohorts of formaldehyde exposed industrial workers are included in recent reviews and the meta-analyses: (1) 26,561 former U.S. workers involved in formaldehyde production, resin making, and several other activities using formaldehyde (Hauptmann et al. 2004; Marsh and Youk 2005; Marsh et al. 2007a); (2) 7,660 workers in six British plants using formaldehyde (Coggon et al. 2003); (3) 11,030 workers in three U.S. garment facilities (Pinkerton et al. 2004); (4) 1,332 Italian workers involved in resin making (Bertazzi et al. 1986, 1989); (5) 3,929 foundry workers exposed to formaldehyde (Andjelkovich et al. 1994, 1995); and (6) 7,345 workers in a Connecticut chemical plant that included some of the workers from the Blair et al. (1986) study (Marsh et al. 2002, 2007b).

In the industrial worker cohort studies, the range of standardized mortality ratios (SMR) relevant to exposure to airborne formaldehyde were as follows (a zero reflects a finding of no deaths from the subject cancer):

lung cancer: 0.9 -0.4 (lung cancer deaths were reported in each cohort);

nasopharyngeal cancer: 0-4.04 (only the Blair et al. [1986, 1990], Hauptmann et al. [2004] cohort had nasopharyngeal cancer deaths: eight observed versus two expected);

nasal cancer: 0-1.9 (Andjelkovich et al. [1994, 1995]; Bertazzi et al. [1986, 1989]; Stayner et al. 1988, however, did not report nasal cancer deaths); and

buccal cavity and/or pharynx cancer: 0.95–1.69 (only Bertazzi et al. [1986, 1989] did not report buccal cavity and/or pharynx cancer).

Meta-analyses performed by use of human occupational studies have arrived at different conclusions regarding the association between formaldehyde exposure and respiratory tract cancer (Bosetti et al. 2008; Luce et al. 2002). In both analyses, aggregate relative risks for lung cancer deaths calculated for

formaldehyde-exposed medical and non-medical professionals were at or below those expected. Aggregate relative risks for lung cancer in industrial worker studies showed a small excess relative risk (1.1) in both analyses, but no evidence for an exposure-related increase in relative risk in a comparison of the "low/medium" relative risks (1.2) with those of the "substantial" exposure class (1.0 or 1.1). Small excess aggregate relative risks for occupationally exposed workers in all of the studies existed for cancer of the nose and nasal sinuses (1.1 [95% CI, 0.8–1.4], Blair et al. 1990; 1.1 [95% CI, 0.8–1.5], Partanen 1993), and cancer of the nasopharynx (1.2 [95% CI, 0.8–1.7], Blair et al. 1990) and 2.0 [95% CI, 1.4–2.90], Partanen 1993). Relative risks for both types of cancer increased with increasing exposure intensity. The meta-analyses by Collins et al. (1997) and Bosetti et al. (2008) arrived at the conflicting conclusion that the available studies do not support a causal relationship between formaldehyde exposure and nasopharyngeal cancer. Collins et al. (1997) analyzed data from essentially the same case-control studies as Blair et al. (1990) and Partanen (1993), but the authors included a few cohort mortality studies that were not available or were included in the earlier meta-analyses (e.g., Andjelkovich et al. 1994, 1995; Gardner et al. 1993). Collins et al. (1997) noted that nasopharyngeal cancer rates were elevated in a minority of the available studies, that most studies did not find any nasopharyngeal cancers, and that many studies did not report on nasopharyngeal cancer. Unlike the calculation techniques used in the previous meta-analyses, a calculational technique was used to adjust for underreporting of expected mortality rates in the calculation of "weighted meta-relative risks". Meta-relative risks (with 95% CIs) for nasopharyngeal cancer were 1.0 (0.5–1.8) for the 14 cohort studies included in the analysis, 1.2 (0.4–2.5) for the six industrial worker cohort studies, and 1.3 (0.9–2.1) for the seven case-control studies. Collins et al. (1997) concluded from their review of the available studies that exposure estimates for the case-control studies were both lower and less certain than exposures in the industrial worker cohort studies and that their analysis does not support an exposure-response relationship between formaldehyde and nasopharyngeal cancer.

Bosetti et al. (2008) pooled the results of epidemiology studies published through February 2007, including 30 publications describing seven cohorts of industrial workers and nine cohorts of professionals exposed to formaldehyde. Nine deaths from nasopharyngeal cancer in three cohorts of industry workers gave a pooled relative risk of 1.33 (95% CI 0.61–2.53), a relative risk that declined to 0.49 after excluding six cases from one U.S. plant. Pooled relative risk values for cancers of the lung, sinus and nasal cavity, oral cavity and pharynx, brain, lymphatic and hematopoietic systems, and leukemia were not elevated in industrial workers (pooled SMR and relative risk values <1.1). In professionals exposed to formaldehyde, pooled relative risk values for brain cancer, lymphatic and hematopoietic cancers, and leukemia were 1.56 (95% CI 1.24–1.96), 1.31 (95% CL 1.16–1.48), and 1.39 (95% CI 1.03–1.79), respectively. Bosetti et al. (2008) concluded that the meta-analysis showed no appreciable excess risk for oral and pharyngeal, sinonasal, or lung cancer. The non-significant increase in relative risk from nasopharyngeal cancer was attributed to a cluster of deaths at a single U.S. formaldehyde related plant. Brain and lymphohematopoietic cancers were slightly elevated in professionals exposed to formaldehyde, but the cancers were not increased in industrial workers, suggesting that lifestyle or other occupational characteristics of pathologists, anatomists, and embalmers may play a role in the observed excess risk for these cancers (Bosetti et al. 2008).

Luce et al. (2002) performed a pooled analysis of 12 case-control studies of sinonasal cancer in seven countries. Occupational exposures to formaldehyde, silica dust, textile dust, coal dust, flour dust, asbestos, and human-made vitreous fibers were assessed by use of a job-exposure matrix. The meta-analysis included 195 cases of adenocarcinoma, 432 cases of squamous cell carcinoma, and 3,136 controls. Odds ratios calculated by unconditional logistic regression were adjusted for age, study, wood dust, and leather dust. A significantly increased risk of adenocarcinoma was suggested for males (91 exposed cases, OR 3.0, 95% CI 1.5–5.7) and females (5 exposed cases, OR 6.2, 95% CI 2.0–19.7). There was significant heterogeneity in the findings for men, with a significantly better fit observed for the regression model that included interaction terms between exposure effects and study. A review of this

study by IARC (2006) concluded that adjustment for extensive heterogeneity in this model may have led to inappropriately narrow confidence limits, because random effects are not accounted for. IARC (2006) also indicated that a residual confounding by wood dust was possible in this study, despite attempts to control for it, due to the high correlation between exposure to wood dust and formaldehyde and the strong association between adenocarcinoma formation and wood dust exposure. IARC (2006, 2009) concluded that "there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans".

Recent reviews of the available epidemiology studies arrive at differing conclusions. NTP (2005) indicated that formaldehyde is reasonably anticipated to be a human carcinogen. IARC (2006) concluded, "[the] results of the study of industrial workers in the U.S., supported by largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans". IARC's overall evaluation that formaldehyde is carcinogenic to humans (Group 1) was based on specific evaluations that there is sufficient evidence in both humans and experimental animals for the carcinogenicity of formaldehyde (IARC 2006). Duhayon et al. (2008) concluded that "human studies fail to raise a convincing conclusion concerning the carcinogenicity of formaldehyde and are not helpful to delineate a possible dose-response relationship". Earlier, EPA (1991) classified formaldehyde in Group B1 a probable human carcinogen, based on an evaluation of limited human evidence and sufficient laboratory animal evidence. However, this assessment has not been updated to consider more recent epidemiological data. Environment Canada/Health Canada (2001) and WHO (2002) concluded that there is little evidence of a causal association between exposure to formaldehyde and lung cancer, but the data for nasal and nasopharyngeal cancer are less clear. Case-control studies demonstrating increases in cancers of the nasal or nasopharyngeal cavities fulfil, at least in part, traditional criteria of causality. However, excesses of cancers of the nasal or nasopharyngeal cavities have not been observed consistently in cohort studies. An evaluation of the mode of carcinogenic action for inhaled formaldehyde was proposed by Environment Canada/Health Canada (2001) and WHO (2002).

The sustained increase in epithelial cell regenerative proliferation resulting from cytotoxicity is considered a requisite precursor in the mode of induction of nasal tumors in rats. Mutation for which the formation of DNA-protein crosslinks serves as a marker of potential may also contribute to the carcinogenicity of the compound in the nasal cavity of rats. The hypothesized mode of induction of formaldehyde-induced tumors was determined to satisfy several criteria for weight of evidence (i.e., consistency, concordance of exposure-response relationships across intermediate end points, and biological plausibility and coherence of the database) and was considered likely relevant to humans, at least qualitatively.

Cohort Mortality Studies. Marsh and Youk (2005) performed a re-evaluation of the mortality risks from nasopharyngeal cancer observed in Hauptmann et al. (2004). Because 6 of the 10 reported cases of nasopharyngeal cancers occurred at a single manufacturing plant located in Connecticut, the re-analysis calculated U.S. and local county (regional) SMRs and internal cohort relative risk values. A significant excess was observed in the regional SMR for the Connecticut manufacturing plant, where six cases of nasopharyngeal cancers were observed (SMR 10.32, 95% CI 3.79–22.47). However, the mortality from nasopharyngeal cancers was lower than expected for the other nine manufacturing plants combined (i.e., SMR<1.00). The relative risk analysis demonstrated that the exposure-response relationship was driven by the nasopharyngeal cancer risk at the Connecticut plant and the highest peak exposure category (≥4 ppm). For the remaining nine plants, the relative risk values were below 1 for the highest peak exposure categories, and no evidence of an exposure response relationship was observed. Marsh et al. (2007a) also performed an interaction assessment to determine the appropriateness of the model chosen by Hauptmann et al. (2004) and a sensitivity analysis to explore the degree of instability in the risk assessments for nasopharyngeal cances in relation to the highest peak exposure. The results of the interaction assessment suggested that the model used by Hauptmann et al. (2004) did not account for the important interaction between plant group and the exposure variable that may prohibit the generalization of formaldehyde effects within and beyond the cohort. In addition, the sensitivity analysis demonstrated

considerable uncertainty in the risk estimates for nasopharyngeal cancer, especially at the Connecticut plant (Marsh et al 2007a).

Several additional studies have been performed to further investigate the cancer mortality in the cohort of 7,345 former workers employed at the Wallingford, Connecticut manufacturing plant (Marsh et al. 1994, 1996, 2002, 2007b). In the most recent follow-up study of this population, "vital status for 98% of the cohort and cause of death for 95% of 2,872 deaths were determined through 2003" (Marsh et al. 2007). Lagged and un-lagged exposure measures were determined from reconstructed worker exposures. Marsh et al. (2007) "observed no new deaths for nasopharyngeal cancers, and only one new death for all other pharyngeal cancer deaths, which yielded SMRs of 4.43 (95% CI 1.78–9.13; 7 deaths) and 1.71 (95% CI 1.01–2.72, 16 deaths), respectively." After the use of interaction models for this nested case-control study for this cohort, the results showed that nasopharyngeal and all other pharyngeal cancers were not elevated in subjects exposed to formaldehyde alone (Marsh et al. 2007). These authors indicated that risks of nasopharyngeal cancers increased in areas where people worked in silver smithing facilities, including brass plating and other jobs related to silver or brass (Marsh et al. 2007). Five of seven cases of nasopharyngeal cancer worked in silver smithing or other metal working industries, while this was relatively rare in the remaining study population (OR 7.311, 95% CI 1.08–82.1). Other metal work was also associated with a moderate increase in the relative risk of all other pharyngeal cancers (OR 1.4, 95% CI 0.31–5.1). These findings suggested that secondary work in the metal industry may have contributed to the elevated findings of nasopharyngeal cancers at the Wallingford, Connecticut plant compared to the other nine manufacturing plants (Marsh et al. 2007).

For the final analysis, death certificates were available for a large percentage (92%) of the identified decedents. A trained nosologist coded the underlying cause of death for all death certificates, using the coding rules in effect at the time of each death. Therefore, the assignment of the cause of death should have been comparable to that used for the standard (comparison) population. The analysis controlled for

potential confounding effects from age, race, sex, and calendar year. Several weaknesses of this study were also noted. In general, PMR studies have a relatively weak design compared to other types of studies. The analysis included only those deaths reported to the Bureau of Funeral Directing and Embalming, and the completeness of this reporting is not known. The authors indicate that deaths at ages >65 years were substantially under-reported. Consequently, the causes of death in the analysis could have differed systematically from the causes found in the total population of deceased embalmers (e.g., for chronic conditions that led to death at older ages). The total U.S. population was used as the external comparison population, even though rates from New York State would probably be stable enough to provide expected values. Possible regional differences in cancer incidence (rather than occupational exposures) could have affected the observed pattern of mortality excesses and deficits. Study weaknesses included that cancer deaths are often reported inaccurately on death certificates. Exposure levels for formaldehyde were unknown, and no analyses that combine the white and black decedents (with appropriate adjustment) were presented, even though there were similarities in the pattern of excess deaths. A combined analysis presumably would have greater statistical power. Lastly, the expected number of deaths for nasal cancer, which was an end point of particular interest, was only 0.7, so that the study had low statistical power to detect an excess of this cancer.

Pinkerton et al. (2004) extended the follow up of vital status for the garment workers cohort (Stayner et al. 1985a, 1985b, 1988) for an additional 16 years (to 1998). Mortality from all causes and all cancers was less than expected, compared to U.S. mortality rates (SMRs <1). Mortality from buccal cavity cancer, which was elevated in the original study, was only slightly elevated in the follow-up study (four deaths, SMR 1.33, 95% CI 0.36–3.41). No nasal or nasopharyngeal cancers were found, although the study had limited statistical power to detect an excess for rare cancers. Mortality from cancer of the trachea, bronchus, and lung was not increased (147 deaths, SMR 0.98, 95% CI 0.82–1.15). Excess mortality from leukemia and myeloid leukemia was observed, with mortality from myeloid leukemia highest in workers exposed for ≥10 years, with ≥20 years since the first exposure (eight deaths, SMR

2.55, 95% CI 1.1–5.03). Coggon et al. (2003) followed the British chemical worker cohort (Acheson et al. 1984; Gardner et al. 1993) for an additional 11 years through 2000. Mortality from all cancers was slightly elevated (1,511 deaths, SMR 1.1, 95% CI 1.04–1.16) compared to the national population. Mortality from lung cancer was increased in men exposed to the highest concentration of formaldehyde (>2 ppm) (272 deaths, SMR 1.58, 95% CI 1.4–1.78). The increase in lung cancer mortality remained elevated after adjustment for local geographic variations in mortality (SMR 1.28, 95% CI 1.13–1.44). Two deaths from sinonasal cancer (2.3 expected) and one death from nasopharyngeal cancer (2.0 expected) were observed. Mortality from brain cancer and leukemia were lower than expected (SMRs <1) for the entire cohort and among the highest exposure group.

A statistically significant excess in mortality from respiratory system cancer was observed in the whole cohort compared to national data (874 deaths, SMR 1.16, 95% CI 1.08–1.24) (Marsh et al. 2001). The analysis was based on 630 cases (96% were carcinoma of the trachea bronchus or lung) and 570 controls. Exposure to formaldehyde was estimated through use of industrial hygiene data and a job-exposure matrix. The conditional logistic regression analysis that was adjusted for smoking did not demonstrate any clear exposure-response trend with cumulative (<2 ppm-years) or average concentration of formaldehyde exposure (<0.14 ppm) (Youk et al. 2001). Adjustment of the regression model for exposure to respirable particles and smoking provided suggestive evidence that increased risk of mortality from respiratory track cancer may be associated with the highest average intensity of formaldehyde exposure (Stone et al. 2001). Cumulative exposure to formaldehyde was not associated with respiratory tract cancer risk in this model.

Armstrong et al. (2000) interviewed 282 Chinese residents of Malaysia (195 males, 87 females) who had a confirmed diagnosis of nasopharyngeal carcinoma and an equal number of age- and gender-matched controls. Occupational history, diet, alcohol consumption, and tobacco use were determined. Univariate and multivariate methods were used to evaluate exposure to 20 kinds of workplace substances, solar and

industrial heat, and cigarette smoke. Formaldehyde exposure was determined by industrial hygiene investigation and use of a job-exposure matrix. Only 9.9% of cases and 8.2% of controls were exposed to formaldehyde. The adjusted ORs (adjusted for smoking and diet) were <1 for any versus no occupational exposure to formaldehyde and for a 10-fold increase in exposure hours. No association was observed between formaldehyde exposure and nasopharyngeal cancer (Armstrong et al. 2000).

Hildesheim et al. (2001) performed a case-control study of nasopharyngeal cancer diagnosed at two hospitals in Taiwan (375 cases, 325 age- and gender-matched controls). Occupational history for cases and controls was obtained by personal interview, and formaldehyde exposure was estimated by industrial hygiene investigation and use of a job-exposure matrix. Information was also collected regarding potential confounding factors, such as cigarette smoking and diet. Blood samples were collected and analyzed for antigen class I/II genotype, polymorphism in cytochrome P450 2E1 genotype, and anti-Epstein Barr virus (EBV) antibodies known to be associated with nasopharyngeal cancer. Individuals exposed to formaldehyde for >10 years had a relative risk of 1.6 (95% CI 0.91–2.9), which was increased when the analysis was restricted to individuals who were seropositive for EBV (relative risk 2.7, 95% CI 1.2–5.9). However, no exposure-response relationship was observed with increasing duration of exposure or cumulative exposure. The observed associations were not significantly affected by further adjustment for exposure to wood dust or organic solvents (Hildesheim et al. 2001).

In another study, investigators used data from five cancer registries in the United States to perform a multi-center population-based case-control study to examine the association between occupational exposures to formaldehyde and wood dust and nasopharyngeal cancer (Vaughan et al. 2000). Telephone interviews were conducted with 196 cases with epithelial nasopharyngeal cancers and 244 controls to collect demographic data and information on lifetime occupational history, history of chemical exposure, medical history, family history of cancer, and use of medication, alcohol, and tobacco. Exposures to formaldehyde and wood dust were estimated by industrial hygiene investigation and use of a job-exposure

matrix. The epithelial nasopharyngeal cancers were classified into one of three histological groups: epithelial, not otherwise specified (NOS) (n=24), undifferentiated or nonkeratinizing (n=54), or squamous cell (n=118). Potential exposure to formaldehyde was assessed in 40.3% of cases and 32.4% of controls. The adjusted OR for occupational exposure versus no exposure was 1.3 (95% CI 0.08–2.1) for all cancers. Trends were observed between increased nasopharyngeal cancer risk and increased duration of exposure and cumulative formaldehyde exposure. The OR associated with an exposure duration >18 years was 2.7 (95% CI 1.0–4.5). The OR associated with cumulative exposure to >1.10 ppm-years compared to those considered unexposed was 3.0 (95% CI 1.3–6.6). There was no evidence of an association between formaldehyde exposure and the undifferentiated or nonkeratinizing histological subcategory. The ORs for formaldehyde were unaffected by the addition of wood dust to the logistic regression models (Vaughan et al. 2000).

NTP (2005) noted that formaldehyde is reasonably anticipated to be a human carcinogen, and IARC (2006) indicated that the results of the study of former industrial workers from 10 U.S. formaldehyde related plants, supported by largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans. More recently, IARC concluded that there is sufficient evidence in humans for a causal association of formaldehyde with leukemia (IARC 2009). IARC's overall evaluation that formaldehyde is carcinogenic to humans (Group 1) was based on specific evaluations that there is sufficient evidence in both humans and experimental animals for the carcinogenicity of formaldehyde. Furthermore, EPA in 1991 and Integrated Risk Information System (IRIS) in 2010 classified formaldehyde as a Group B1–probable human carcinogen on the basis of limited evidence of carcinogenicity in humans and sufficient carcinogenicity evidence in laboratory animals. Duhayon et al. (2008) concluded that "human studies fail to raise a convincing conclusion concerning the carcinogenicity of formaldehyde and are not helpful to delineate a possible dose-response relationship."

Environment Canada/Health Canada (2001) and WHO (2002) have evaluated the mode of carcinogenic action for inhaled formaldehyde. The sustained increase in epithelial cell regenerative proliferation resulting from cytotoxicity is considered a requisite precursor in the mode of induction of nasal tumors in rats. Mutation, for which the formation of DNA-protein crosslinks serves as a marker of potential, may also contribute to the carcinogenicity of the compound in the nasal cavity of rats. The hypothesized mode of induction of formaldehyde-induced tumors was determined to satisfy several criteria for weight of evidence (i.e., consistency, concordance of exposure-response relationships across intermediate end points, and biological plausibility and coherence of the database) and was considered likely relevant to humans, at least qualitatively. A biologically motivated case study was also provided that evaluated cancer risks by use of a two-stage clonal growth model. Estimates of carcinogenic risks using the human two-stage clonal growth model were developed for typical environmental exposures (i.e., continuous exposure throughout an 80-year lifetime to concentrations of formaldehyde ranging from 0.001 ppm to 0.1 ppm [0.0012-0.12 mg/m^3]). The human clonal growth model predicted non-zero additional risks throughout the exposure ranges examined.

2.2.2 Oral Exposure

Most of the available reports of controlled studies of health effects from oral exposure to formaldehyde have not provided information regarding how frequently dosing solutions were analyzed for formaldehyde content. Earlier, some studies reported how frequently formaldehyde solutions were prepared, but other study reports provided no information regarding solution-preparation frequency, conditions of storage, or analysis of test material for formaldehyde content (e.g., Soffritti et al. 2002; Takahashi et al. 1986). Because of this reporting deficiency, and because formaldehyde solutions are very unstable (due to formaldehyde's high reactivity and volatility), the reader should be aware that there is uncertainty associated with oral dose levels reported in this addendum. Another issue of uncertainty is the impurity of commercially available aqueous solutions of formaldehyde (often called formalin), which

normally contain approximately 10–15% methanol to prevent polymerization. Attempts have been made, however, to note when formalin was the source of the ingested formaldehyde, so that the reader will be aware of possible confounding effects from methanol.

Case reports of human exposure are summarized in Table 2-3.

Table 2-3. Human Case Reports—Ingestion of Formalin

Reference	Patient	Ingested dose (mg/kg/day)	Effects
Baccioglu and Kalpaklioglu 2007	54-year-old male	233	Bronchospasm, respiratory crackles, bilateral lung infiltrates, fever, esophagitis, gastritis
Yanagawa et al. 2007	28-year-old male	258	Acute respiratory distress, tachypnea and low blood pressure, esophageal erosion, gastric ulcers, gastric outlet obstruction, metabolic acidosis

2.2.2.2 Systemic Effects

Respiratory Effects. Baccioglu and Kalpaklioglu (2007) described the case of a 54-year-old man who accidentally ingested 200 mL of a 10% solution of formaldehyde (233 mg/kg). Inhalation occurred while the patient was vomiting and the patient developed cough, wheezing, dyspnea, and expectoration of blood 2 days later. Bronchospasm and decreased FEV were observed, and bilateral infiltrates were seen on chest x-ray. Endoscopy showed low-grade esophagitis and gastritis. These pulmonary symptoms responded well to treatment with systemic corticosteroids and salbutamol. Two weeks after the accident, the patient experienced fever, increased white blood cells, massive expectoration of blood, bronchospasm, respiratory crackles, and new infiltrates on chest x-ray. The patient recovered following treatment with

antibiotics and steroids. Total and formaldehyde-specific IgE levels were normal, suggesting that observed pulmonary symptoms were not related to an allergic hypersensitivity response.

Yanagawa et al. (2007) described the case of a 28-year-old man who ingested 150 mL of a 40% solution of formalin (258 mg formaldehyde/kg) in an attempted suicide. He was alert when admitted to the hospital 2 hours following ingestion. Physical examination findings included erosions of the oropharyngeal mucosa, respiratory stridor, epigastric tenderness, and hypoactive bowel sounds. The patient was given sodium bicarbonate to treat metabolic acidosis and esophageal lesions. Acute respiratory distress developed, requiring mechanical ventilation, and bilateral pleural effusions noted on chest X-ray were drained by chest tubes. Tachycardia, low blood pressure, and oligouria developed and were treated with intravenous fluids and dobutamine. Mechanical ventilation ended on day 43, and the patient was discharged on day 73 following treatment for severe gastrointestinal effects.

Cardiovascular Effects. As previously discussed, Yanagawa et al. (2007) described the case of a 28-year-old man who ingested 150 mL of a 40% solution of formalin (258 mg formaldehyde/kg) in an attempted suicide. The patient developed tachycardia, low blood pressure, and oligouria, which were treated with intravenous fluids and dobutamine. The patient eventually recovered and was released from the hospital following treatment for respiratory and gastrointestinal effects (see Respiratory Effects and Gastrointestinal Effects sections).

Soffritti et al. (2002) did not observe treatment-related histopathological changes in the heart of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks.

Gastrointestinal Effects. In the case described by Yanagawa et al. (2007) of a 28-year-old man who ingested 150 mL of a 40% solution of formalin (258 mg formaldehyde/kg) in an attempted suicide, the man was alert when admitted to the hospital 2 hours following ingestion. Physical examination findings

included erosions of the oropharyngeal mucosa, respiratory stridor, epigastric tenderness, and hypoactive bowel sounds. The patient was given sodium bicarbonate to treat metabolic acidosis and esophageal lesions. Acute respiratory distress developed, requiring mechanical ventilation, and bilateral pleural effusions noted on chest X-ray were drained by chest tubes. Tachycardia, low blood pressure, and oligouria developed and were treated with intravenous fluids and dobutamine. Mechanical ventilation ended on day 43 and the patient was discharged on day 73 following treatment for severe gastrointestinal effects.

Baccioglu and Kalpaklioglu (2007) described the case of a 54-year-old man who accidentally ingested 200 mL of a 10% solution of formaldehyde (233 mg/kg). Endoscopy showed low-grade esophagitis and gastritis, which were treated with proton pump inhibitors and parenteral hydration. The patient recovered and was released from the hospital following treatment for respiratory effects related to formaldehyde aspiration during vomiting. Soffritti et al. (2002) did not observe non-neoplasic treatment-related lesions in the oral cavity, esophagus, stomach, or intestines of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks. Tumors of the stomach and small intestine were observed in this study.

Hepatic Effects. Soffritti et al. (2002) did not observe treatment-related histopathological changes in the liver of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks.

Renal Effects. Soffritti et al. (2002) did not observe treatment-related histopathological changes in the kidneys of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks.

Endocrine Effects. Soffritti et al. (2002) did not observe treatment-related histopathological changes in the adrenal, pituitary, thyroid, or pancreas of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks.

Dermal Effects. No adverse histopathology was noted in skin samples from male and female Wistar rats receiving ≤109 mg/kg/day formaldehyde in drinking water after 2 years of exposure (Til et al. 1989) or from male and female Sprague-Dawley rats receiving ≤188 mg/kg/day formaldehyde in drinking water after 2 years of exposure (Soffritti et al. 2002).

Ocular Effects. Soffritti et al. (2002) did not observe treatment-related histopathological changes in the Harderian gland of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks.

Body Weight Effects. The daily food consumption and body weights of Sprague-Dawley rats (50/sex/group) administered formaldehyde for 104 weeks in the drinking water at concentrations of 10, 50, 100, 500, 1,000, or 1,500 mg/L (1, 6, 13, 63, 125, or 188 mg/kg/day, respectively) were similar to those of controls (100/sex/group) (Soffritti et al. 2002).

Metabolic Effects. Yanagawa et al. (2007) described the case of a 28-year-old man who ingested 150 mL of a 40% solution of formalin (258 mg formaldehyde/kg) in an attempted suicide. The patient was given sodium bicarbonate to treat metabolic acidosis and eventually recovered following treatment for respiratory and gastrointestinal effects.

2.2.2.3 Immunological and Lymphoreticular Effects

Charpin et al. (2000) reported an allergic hypersensitivity reaction in an adult female following ingestion of formaldehyde in pharmaceutical preparations and toothpaste. A patch test was positive for formaldehyde, and oral challenge with a formaldehyde preparation resulted in recurrence of reported symptoms (headache, pharyngitis, dysphonia, and colitis), which lasted for approximately 24 hours.

Soffritti et al. (2002) did not observe treatment-related non-neoplastic lesions in the spleen, thymus, or subcutaneous, pancreatic, or mesenteric lymph nodes of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks. An increase in the incidence of rats with hemolymphoreticular tumors was observed in this study (see Section 2.2.2.8).

2.2.2.4 Neurological Effects

Soffritti et al. (2002) did not observe treatment-related histopathological changes in the brain or peripheral nervous system of male and female Sprague-Dawley rats given up to 188 mg/kg/day formaldehyde in drinking water for 104 weeks.

2.2.2.8 Cancer

Soffritti et al. (2002) presented further analysis of the tumor data from rats treated with formaldehyde from 7 weeks of age, as described in the Soffritti et al. (1989) study. Statistical analysis of the tumor multiplicity data for malignancies (i.e., number of malignant tumors per 100 animals) indicated that a higher number of malignant tumors were found in males and females exposed to 1,000 or 1,500 ppm, in males exposed to 500 ppm, and in females exposed to 100 ppm compared to untreated controls. The incidence of animals with malignant tumors (i.e., number of tumor-bearing rats) was significantly

increased ($p<0.05$) only in males exposed to the highest formaldehyde concentration (1,500 ppm). An analysis of total hemolymphoreticular neoplasms was performed, and the analysis combined the incidence of leukemias and lymphomas and included the thymus, spleen, and subcutaneous, pancreatic, and mesenteric lymph nodes. The incidence of hemolymphoreticular neoplasms was significantly increased ($p<0.05$) in male rats exposed to 100, 500, 1,000, and 1,500 ppm and in female rats exposed to 1,000 and 1,500 ppm. Additionally, Soffritti et al. (2002) suggested that formaldehyde ingestion increased the number of malignant mammary tumors in female rats and testicular interstitial cell adenomas in formaldehyde-exposed male rats (i.e., increased tumor multiplicity).

Environment Canada/Health Canada (2001) and WHO (2002) concluded that although there is no definitive evidence to indicate that formaldehyde is carcinogenic when administered orally to laboratory animals, the potential carcinogenic hazard associated with the ingestion of formaldehyde cannot be eliminated due to concerns about the known reactivity of this substance with biological macromolecules at the portal of entry and observations of histopathological and cytogenetic changes within the aerodigestive tract in rats administered formaldehyde orally. IARC (2006) summarized inconsistencies in the tumor findings across four drinking water studies in rats, but it did not provide an overall conclusion regarding the relevance of these data for assessing the potential for formaldehyde ingestion to induce cancer in humans.

2.2.3 Dermal Exposure

Takahashi et al. (2007) conducted a prospective study of clinical symptoms and skin test reactions in 143 medical students exposed to 2.4 ±0.49 ppm formaldehyde, 15 hours/week for 2 months. Skin irritation was reported in more than 25% of the students after repeated exposure to formaldehyde. Students with a history of atopic dermatitis (22 of 143 students) complained of skin irritation and redness more often than students without a history of atopic dermatitis. Positive patch testing was reported for only 2 of 60 students (3.3%) (one male with allergic hand dermatitis due to direct contact with a cadaver

and one female with an atopic background and symptoms). Negative patch test findings were also reported for 58 students similarly exposed to formaldehyde 2–4 years previously.

2.2.3.3 Immunological and Lymphoreticular Effects

Xu et al. (2002) further evaluated contact hypersensitivity to formaldehyde and the cytokine response in mouse skin, spleen, and lymph nodes. Mice received three topical applications (1/day) of 100 µL of 17.5% formaldehyde to the shaved abdominal skin. To induce contact hypersensitivity to formaldehyde, both ears were painted with 2% formaldehyde on day 3 following the last abdominal application. Mouse ear thickness was measured immediately before ear challenge and 24 hours later. Mice were sacrificed 3, 5, 7, 9, and 12 days after the last abdominal application, and ear skin, spleen, and draining lymph nodes were removed for evaluation of cytokine expression. Formaldehyde challenge induced a weak contact hypersensitivity response (i.e., ear swelling) and increased expression of IL-4 and IFN-γ in mouse ear skin. Abdominal application of formaldehyde produced a lasting expression of IL-4 and IFN-γ and a transient increase in IL-13 in spleen and draining lymph nodes. Additional cytokines (IL-2, IL-15, IL-12p40) were expressed only in the spleen following dermal exposure to formaldehyde.

2.3 TOXICOKINETICS

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

The ability of respiratory and olfactory tissues to oxidize formaldehyde was examined in male F-344 rats. To determine the effects of repeated formaldehyde exposure on enzyme activities, rats were exposed to 15 ppm formaldehyde 6 hours/day for 10 days. At the completion of formaldehyde exposure, rats were sacrificed, and respiratory and olfactory mucosal tissues were harvested. The enzymatic capacity of the tissues was determined in the presence and absence of glutathione. Tissue homogenates from both the respiratory and olfactory mucosa demonstrated the ability to oxidize formaldehyde. The oxidation of formaldehyde occurred at similar rates in the respiratory and olfactory mucosal homogenates. Human bronchial epithelial cells were shown to bio-transform formaldehyde to formic acid at a relatively fast rate (i.e., similar to rat hepatocytes) for concentrations up to 3 mM (Ovrebo et al. 2002).

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Computational Fluid Dynamics (CFD) models of airflow in the nasal passages of rats, monkeys, and humans have been developed to determine the degree to which interspecies and interregional differences in uptake patterns along airway passages may account for differing distributions of formaldehyde-induced upper respiratory tract lesions in rats and primates. These models enable extrapolation of exposures associated with upper respiratory tract tissue damage in rats or monkeys to human exposures (Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell and Subramaniam 2001; Kimbell et al. 1997a, 1997b, 2001a, 2001b; Morgan 1997; Subramaniam et al. 1998). Airflow pattern is expected to be one of three important determinants of upper respiratory tract tissue uptake, along with interactions at the airway/

tissue interface, such as off-gassing and tissue properties influencing absorption rates (e.g., mucociliary clearance or rate of biotransformation).

Kimbell et al. (2001b) described a flux binning approach where the nasal surface of the rat, monkey, and human were partitioned by flux into smaller regions characterized by surface area and average flux rate. There was a decreasing gradient of flux observed from proximal to distal nasal sites in all three species; however, the gradient was predicted to be less steep in humans than for rats or monkeys. Human nasal flux patterns shifted distally, and uptake percentage decreased as the inspiratory flow rate increased.

Overton et al. (2001) described an anatomical model of formaldehyde dosimetry for the entire respiratory tract that applied one-dimensional mass transport equation. This model was made consistent with CFD nasal models by using similar values for air flow rate and uptake during inspiration in the nasal passages. Tracheo-bronchial flux was predicted to be larger than flux in the first pulmonary region, and there was essentially no predicted flux in the alveolar sacs. This model also suggested that >95% of inhaled formaldehyde is predicted to be retained in the respiratory tract. Franks (2005) also provided a mathematical model demonstrating that insignificant amounts of formaldehyde enter the systemic circulation following absorption and metabolism in nasal tissues. Schlosser (1999) suggested that as much as 2% to 22 of inhaled formaldehyde may be removed by nasal mucus flow (Overton et al. 2001).

Conolly et al. (2000) extended the rat model developed by Hubal et al. (1997) to the Rhesus monkey and humans. Essential inputs to the tissue model were site-specific flux predictions provided by anatomically realistic CFD models for the nasal airways and site-specific mucosal epithelial thickness estimates measured in rats and Rhesus monkeys. Regional DNA-protein cross link data were obtained for the rat (Casanova et al. 1991) and Rhesus monkey (Casanova et al. 1994). The thickness of the nasal mucosa was measured at high and low tumor sites in the rat nose and at several locations in the nasal cavity of the Rhesus monkey (anterior lateral walls and septum, the nasopharynx, and the middle turbinates). The

human model was developed on the basis of allometric scaling from the rat and monkey data. The empirical strength of an allometric relationship derived from regressing two data points (rat and monkey) has, however, been characterized as extremely weak by Subramaniam et al. (2008). As described for Hubal et al. (1997), each model describes three disposition processes for formaldehyde: a saturable pathway representing enzymatic bio-transformation of formaldehyde, a separate first-order pathway representing the intrinsic reactivity of formaldehyde with tissue constituents, and pseudo first-order binding to DNA. The rat model accurately predicted the concentration of DNA-protein cross links in the high and low tumor regions of the rat nasal cavity. The Rhesus monkey model also provided good fit to the data for DNA-protein cross links in different regions of the nose. In the human model, differences in the predictions of DNA-protein cross links between regions are accounted for by site-specific tissue thickness and flux estimates. Georgieva et al. (2003) further refined the rat model described by Conolly et al. (2000) by including measurements of nasal tissue thickness and DNA distribution maps for respiratory and transitional nasal epithelium. Sensitivity analysis of this model indicated that model fit was sensitive to V_{max} and predictions were sensitive to changes in tissue thickness.

Two approaches have been proposed for using the CFD and pharmacokinetic models to extrapolate dose-response relationships for formaldehyde-induced rat nasal tumors and related end points, such as rates of cellular proliferation in specific regions of the nasal epithelium to derive estimates of cancer risks in humans. One approach makes predictions for respiratory tract cancer risks in humans by using an approximation to a two-stage clonal growth cancer model incorporating data on cell division rates, number of cells at risk, tumor incidence, DNA-protein cross link measurements, and site-specific flux of formaldehyde (see also CIIT 1999; Conolly et al. 2000, 2003, 2004; Kimbell et al. 2001a; Overton et al 2001). Conolly et al. (2002) and Gaylor et al. (2004) described the analysis of dose-response data for nasal regenerative cell proliferation, which is characterized by a non-monotonic or J-shaped dose-response curve. However, Subramaniam et al. (2008) analyzed the large uncertainty and variability in the labeling index data (from which cell replication rates were derived) and concluded that, given these

qualitative and quantitative uncertainties and in their interpretation, a variety of cell replication dose-response models that included both non-monotonic and monotonically-increasing shapes are plausible as reasonable characterization of the data. Conolly et al. (2002) and Gaylor et al. (2004) described the analysis of dose-response data for nasal regenerative cell proliferation, which is characterized by a non-monotonic or J-shaped dose-response curve.

The two-stage clonal expansion model was developed to link DNA-protein cross links and regenerative cell proliferation. A novel contribution of the CIIT model is that cell replication rates and DNA-protein cross links concentrations are driven by local formaldehyde dose, a feature that is important in the case of a highly reactive gas like formaldehyde for which uptake patterns are spatially localized and significantly different across species (Kimbell et al. 2001). DNA-protein cross links concentration levels were incorporated into the two-stage clonal expansion model as a dose surrogate for the putative directly mutagenic action of formaldehyde. The modeling in Conolly et al. (2003, 2004) concluded that cancer risks at environmental exposures were negligible and that the directly mutagenic action of formaldehyde does not play a significant role in tumor formation by the use of nasal dosimetry predicted by using CFD models (Conolly et al. 2003, 2004).

The CIIT modeling and available data have been evaluated in a series of peer-reviewed papers (Crump et al. 2008; Subramaniam et al. 2007, 2008) and debated further in the literature (Conolly et al. 2009; Crump et al. 2009). Subramaniam et al. (2007) and Crump et al. (2008) considered several alternative formulations of the modeling in Conolly et al. (2000, 2003, 2004). These authors claimed that their alternate implementations were consistent with the available mechanistic and nasal tumor incidence data, yet yielded estimates of low-dose risk that varied by many orders of magnitude, even when only maximum likelihood estimates of risk were considered. Modeling results were extremely sensitive to assumptions on the kinetics of initiated cells for which there were no data and to the use of data from historical control animals (Crump et al. 2008, 2009; Subramaniam et al. 2008). Furthermore,

Subramaniam et al. (2007) concluded that a substantial contribution from formaldehyde's mutagenic potential could be needed in the model to explain formaldehyde tumorigenicity.

A second approach (a benchmark dose approach) makes predictions of nasal cancer risk in humans by using curve fitting of relevant rat exposure-response data (e.g., nasal tumors or precursor lesions such as pre-neoplastic foci or squamous papillomas, rates of cellular proliferation, or rates of DNA-protein cross link formation) and CFD modeling and/or pharmacokinetic modeling for extrapolation purposes (CIIT 1998; Schlosser et al. 2003). Benchmark concentrations were lower for cell proliferation than for tumors. Two extrapolation methods were employed, including a CFD model used to determine the rate of delivery of formaldehyde to the nasal lining and a CFD method combined with a pharmacokinetic model to predict formaldehyde dose by using DNA-protein cross links as a dose metric. Both extrapolation methods gave similar results (Schlosser et al. 2003).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Several studies have suggested that distant site effects of formaldehyde are associated with the production of reactive oxygen species in blood, liver, kidneys, and testes (Kum et al. 2007; Petushok 2000; Sogut et al. 2004; Zararsiz et al. 2006; Zhou et al. 2006). Studies in isolated cell systems suggest that oxidative stress may play a role in formaldehyde-induced cytoxicity (Ayaki et al. 2005; Saito et al. 2005; Teng et al. 2001). Administration of Vitamin E was shown to protect against oxidative damage by formaldehyde in the plasma, liver, and brain of rats. Formaldehyde was administered by intraperitoneal injection in these studies, so that the significance of these findings is unclear (Gulec et al. 2006a; Gurel et al. 2005). Zhou et al. (2006) showed that pretreatment of rats with Vitamin E prevented the testicular toxicity observed after inhalation of 8 ppm formaldehyde 12 hours/day for 2 weeks.

An example of a local effect of formaldehyde vapor was demonstrated in the rat nasal epithelium. The mechanisms responsible for formaldehyde deposition in the nasal cavity are well understood. The patterns of air flow are related to the anatomical structure of the nasal passages (Kimbell 2006). Formaldehyde dissolves in the nasal mucosal tissue upon contact due to its high water solubility. The reactivity of formaldehyde leads to interaction with proteins and other macromolecules at the site of contact in the nose (Medinsky and Bond 2001). In rat studies where cell turnover was measured (a measure of formaldehyde cytotoxicity), the no-effect level is approximately 2 ppm (Monticello et al. 1991) for 6 hours/day exposures for $\leq$9 days. At higher concentrations (6, 10, or 15 ppm), higher rates of cell turnover were seen (Monticello et al. 1991) and a dose-response was observed. The increase in cell proliferation (as measured by thymidine incorporation) was more sensitive to formaldehyde exposure than histopathological changes. Similar results were seen in a 6-week experiment at these same doses in which the rats were exposed 5 days/week. Monticello et al. (1996) also determined that the nasal cell target population size, increased cell proliferation of specific target cells (due to differences in regional airflow with the rat nasal cavity), and the nonlinear kinetics of formaldehyde binding to DNA explain why specific regions of the rat nose are more prone to develop formaldehyde-induced nasal squamous cell carcinomas than other sites in the nasal cavity.

McGregor et al. (2006) proposed a cancer mode of action for formaldehyde based on the induction of sustained cytotoxicity and regenerative cell proliferation. Dose-response and temporal relationships were consistent with key events for this mode of action, although genotoxicity could not be conclusively ruled out as possibly contributing to carcinogenicity. The proposed mode of action was considered to be potentially relevant to humans, although human data for key events are limited. Environment Canada/Health Canada (2001) and WHO (2002) have evaluated the mode of carcinogenic action for inhaled formaldehyde. The sustained increase in epithelial cell regenerative proliferation resulting from cytotoxicity is considered a requisite precursor in the mode of induction of nasal tumors in rats.

Mutation, for which the formation of DNA-protein crosslinks serves as a marker of potential, may also contribute to the carcinogenicity of the compound in the nasal cavity of rats. The hypothesized mode of induction of formaldehyde-induced tumors was determined to satisfy several criteria for weight of evidence (i.e., consistency, concordance of exposure-response relationships across intermediate endpoints, and biological plausibility and coherence of the database) and was considered likely relevant to humans, at least qualitatively.

Several recent studies have described changes in gene expression that are associated with formaldehyde-induced toxicity in the respiratory tract (Feick et al. 2006; Hester et al. 2003, 2005; Lee et al. 2008; Thomas et al. 2007; Yang et al. 2005). Formaldehyde exposure produced changes in the expression of genes related to cell proliferation and differentiation, immunity and inflammation, xenobiotic metabolism, cytoskeletal integrity, cell cycle, apoptosis, and DNA repair.

It has been suggested that formaldehyde inhalation may produce or exacerbate allergic effects or asthma in children or adults (Mendell 2007; Sakamoto et al. 1999). Individuals with allergic conditions or respiratory disease may be more sensitive to the effects of irritants (Mendell 2007; Sakamoto et al. 1999). The possible mechanisms for these effects have not been fully determined; however, it has been suggested that formaldehyde may facilitate an IgE sensitization to other antigens or may produce an IgE-mediated response to itself (Sakamoto et al. 1999). There are only a few available case reports of bronchial asthma suggestive of respiratory tract sensitization to formaldehyde gas (Kim et al. 2001; Lemiere et al. 1995), and the mechanism of sensitization in these subjects is uncertain. Several studies have examined serum for formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed humans (Doi et al. 2003; Dykewicz et al. 1991; Grammer et al. 1990; Kim et al. 1999; Wantke et al. 1996a, 1996b). In general, the studies do not provide consistent evidence for a formaldehyde-induced allergic respiratory syndrome, but they provide suggestive evidence that children may have an increased tendency to develop specific antibodies after exposure to low levels of formaldehyde in indoor air (Wantke et al. 1996a). Some animal

experiments suggest that exposure to formaldehyde may enhance allergic responses of the respiratory tract to other respiratory allergens (Riedel et al. 1996; Tarkowski and Gorski 1995). Casset et al. (2006) indicated that acute formaldehyde exposure (by mouth-breathing only) could affect the bronchial response to mite allergen in human subjects with mild asthma and allergic sensitization to house dust mites. However, a similar study did not demonstrate an effect of formaldehyde exposure on allergenic responses in human subjects with intermittent asthma and allergy to grass pollen (Ezratty et al. 2007). These investigators suggested that further research is necessary to confirm the hypothesis of formaldehyde facilitation of other respiratory allergens and to determine if this is relevant to humans exposed to formaldehyde (Ezratty et al. 2007). The dermal sensitization response in experimental animals involves an increase in the production of proinflammatory cytokines (Dearman et al. 1999; Hilton et al. 1996; Ushio et al. 1999; Xu et al. 2002); however, this mechanism has not been clearly demonstrated in the respiratory tract (Fujimaki et al. 2004, 2005; Jung et al. 2007).

2.4.3 Animal-to-Human Extrapolations

As described in a draft document by EPA (1991), the formaldehyde rat study by Kerns et al. (1983) was the best animal study for cancer risk extrapolation for human cancer risks at low exposure concentrations; it used rates of DNA-protein cross links in target tissue as a measure of delivered dose (Hernandez et al. 1994). Adjustments to continuous exposure were used to calculate lifetime human cancer unit risk estimates of 3.3×10^{-4} ppm formaldehyde based on monkey data and of 2.8×10^{-3} ppm formaldehyde based on rat data (Hernandez 1994).

As discussed in Section 2.3.5, two approaches have been proposed for using the CFD and pharmacokinetic models to extrapolate exposure-response relationships for formaldehyde-induced rat nasal tumors and related end points, such as rates of cellular proliferation in specific regions of the nasal epithelium, to derive estimates of cancer risk in humans exposed to inhaled formaldehyde. One approach

makes predictions for respiratory tract cancer risk in humans exposed to inhaled formaldehyde by using two-stage clonal-growth cancer models incorporating data on cell division rates, numbers of cell at risk, tumor incidence, and site-specific flux of formaldehyde (see also CIIT 1998; Conolly and Andersen 1993; Conolly et al. 1992, 2003, 2004; Morgan 1997). A second approach (a benchmark dose approach) makes predictions of nasal cancer risk in humans by using curve fitting of relevant rat exposure-response data (e.g., nasal tumors or precursor lesions such as preneoplastic foci or squamous papillomas, rates of cellular proliferation, or rates of DNA-protein cross link formation) and CFD modeling and/or pharmacokinetic modeling for extrapolation purposes (CIIT 1998; Schlosser et al. 2003).

2.5 Relevance to Public Health

As presented in the 1999 Toxicological Profile for Formaldehyde, the following MRLs were derived for formaldehyde:

Inhalation MRLs

- An MRL of 0.04 ppm has been derived for acute-duration exposure.
- An MRL of 0.03 ppm has been derived for intermediate-duration exposure.
- An MRL of 0.008 ppm has been derived for chronic-duration exposure.

Oral MRLs

- An MRL of 0.3 mg/kg/day has been derived for intermediate-duration exposure.
- An MRL of 0.2 mg/kg/day has been derived for chronic-duration exposure.

For details on these MRLs, refer to the 1999 formaldehyde profile available at: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=220&tid=39.

ATSDR is currently in the process of re-evaluating the MRLs for formaldehyde. The evaluation is pending review of US EPA toxicological review of formaldehyde by a committee of the National Research Council (NRC) (IRIS 2010).

2.6 CHILDREN'S SUSCEPTIBILITY

A recent review by Mendell (2007) suggested that indoor residential exposure to formaldehyde may be associated with risk of asthma, allergies, and pulmonary infections in children. Several epidemiology studies have examined the relationship between residential formaldehyde exposure and asthma and/or allergies. However, inconsistent findings were reported. Krzyzanowski et al. (1990) reported that children who lived in households with formaldehyde air concentrations >0.06 ppm had greater prevalence rates of physician-diagnosed bronchitis or asthma than children who lived in households with concentrations <0.06 ppm. Franklin et al. (2000) reported that residential formaldehyde concentrations of >0.05 ppm did not affect pulmonary function variables (FVC or FEV_1) in 224 healthy children (6 to 13 years old). This study did not provide a concentration range for the children exposed to >0.05 ppm. Rumchev et al. (2002) suggested that young children 6 months to 3 years old with exposure to formaldehyde concentrations >0.06 mg/m^3 (0.049 ppm) are at a 39% increased risk of asthma than children not exposed to such levels. Venn et al. (2003) performed a case-control study of 193 children (9 to 11 years old) with persistent wheezing and 223 healthy controls. There were no significant differences in formaldehyde concentrations in the homes between the cases and controls. However, there was an association between increased frequency of symptoms (i.e.,wheezing) and formaldehyde in the homes of the cases. The adjusted OR for increased symptoms was 1.4 (95% CI 1.0–1.9). Smedje et al. (1997) reported an association between formaldehyde concentration in the classroom and the prevalence of current asthma (OR 1.1, 95% CI 1.01–1.2) in Swedish school children. Current asthma was defined as physician-diagnosed asthma with current symptoms and/or current asthma treatment. Delfino et al. (2003) reported an association between ambient formaldehyde concentration and the severity of

symptoms reported by 22 asthmatic children (10–16 years old) living in a Los Angeles community with high traffic density. The adjusted OR for bothersome or more severe asthma with an IQR increase (0.003 ppm) in formaldehyde was 1.37 (95% CI 1.04–1.8) with a 1-day lag. There was no relationship between formaldehyde concentration and PEFR. Garrett et al. (1999) observed a trend between the residential formaldehyde concentration and the proportion of atopic children, using a cross-sectional survey of 80 homes in Australia (148 children, 53 of whom were asthmatic). The number of positive skin prick tests and the average size of the allergen wheal were increased in the highest formaldehyde exposure category (>0.05 mg/m^3, >0.04 ppm) compared to the lowest formaldehyde exposure group (<0.02 mg/m^3 or <0.02 ppm). No relationship between formaldehyde exposure and asthma was observed in this study. In a cross-sectional, case-control study, Tavernier et al. (2006) investigated the home environment of 105 asthmatic children (4–17 years old) and 95 healthy controls. There were no differences in indoor air concentrations of formaldehyde in the homes of the cases and controls. The results of these studies indicated that low residential indoor air levels of formaldehyde may predispose young children to asthma or allergies. However, the dose-response relationship has not been clearly established and further research is necessary.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

2.7.1 Biomarkers Used to Identify or Quantify Exposures to Formaldehyde

Formaldehyde that is not rapidly metabolized to formate can react with a variety of cellular components, including nucleotides, proteins, and glutathione, to form adducts, such as N6-hydroxymethyl-deoxyadenosine and N2-hydroxymethyldeoxyguanosine, and DNA-protein cross links. Several of these formaldehyde-induced products have been examined as potential biomarkers of exposure for repeated exposure to formaldehyde. A method for detecting biomarkers such as N^6-hydroxymethyldeoxy-adenosine and N^2-hydroxymethyldeoxyguanosine (the major adducts formed by formaldehyde *in vitro*)

had experimental complications and does not appear to provide useful biomarkers of formaldehyde exposures (Fennell 1994). Zhong and Que Hee (2004) described a high performance liquid chromatography (HPLC) method to identify and quantify formaldehyde DNA adducts isolated from human nasal epithelial cells. Analysis of formaldehyde-modified deoxynucleosides may serve as a useful biomarker for samples obtained from nasal lavage or biopsy. N-Methylvaline is a molecular adduct that is formed by the reaction of formaldehyde with hemoglobin. Bono et al. (2006) demonstrated an association between formaldehyde exposure in plywood and laminate factory workers (n=21) and the occurrence of N-methylvaline in blood. However, this assay could not distinguish between subjects exposed to formaldehyde through tobacco smoke, on the one hand, and nonsmokers, on the other.

Many studies conducted earlier (e.g., Casanova and Heck 1987; Casanova et al. 1989a, 1989b, 1991, 1994; Casanova-Schmitz et al. 1984a) used radiolabeled compounds tagged with ^{14}C and/or ^{3}H to facilitate detection of DNA-protein cross links. However, this approach would not work to detect past exposures in humans. The formation of DNA-protein cross links in isolated rat nasal epithelial cells (respiratory and olfactory epithelial cells) incubated with formaldehyde has also been reported (Kuykendall et al. 1995). Using a sensitive technique to detect total DNA-protein cross links, Shaham et al. (1996, 2003) reported 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. Although DNA-protein cross links are known to be formed by other agents such as ionizing radiation and alkylating agents, Shaham et al. (1996, 2003) concluded that their results suggested that levels of DNA-protein cross links in white blood cells may provide an indicator of formaldehyde-induced tissue damage and a biomarker of occupational exposure to formaldehyde.

2.7.2 Biomarkers Used to Characterize Effects Caused by Formaldehyde

Increased eosinophil concentration and increased levels of albumin and total protein have been found in nasal lavage fluid taken from subjects exposed to 0.4 ppm formaldehyde for 2 hours (Krakowiak et al. 1998). Although these variables are not expected to be influenced only by formaldehyde exposure, they appear to be promising biomarkers of acute respiratory irritation from airborne formaldehyde.

Franklin et al. (2000) reported that exhaled nitric oxide levels were elevated in children living in homes with formaldehyde concentrations of >0.05 ppm compared to children living in homes with formaldehyde concentrations of <0.05 ppm. This was considered to represent a subclinical inflammatory response in the airways of healthy children, because there was no effect on pulmonary function in children in this study. Although exhaled nitric oxide is a potential marker of eosinophilic airway inflammation in atopic airways, it has limited use as a biomarker because it is not specific to formaldehyde and may be affected by a number of factors, including allergic disease, atopic sensitization, age, and gender.

Iarmarcovai et al. (2007) suggested that evaluation of the number of centromeric signals in a micronucleus assay can provide information about the mechanism of genotoxicity and can serve as a biomarker of genotoxic effects. Peripheral blood lymphocytes obtained from pathologists and anatomists exposed to formaldehyde (n=18) showed an increase in centromere-positive micronuclei with a single centromere. These data suggest that impaired chromosome migration may contribute to aneuploidy following prolonged exposure to formaldehyde (Iarmarcovai et al. 2007).

Several studies have evaluated gene expression profiling following formaldehyde exposure and have suggested that genes and/or proteins that are up- or- down-regulated may eventually be used as biomarkers for the effects of formaldehyde (Im et al. 2006; Lee et al. 2008; Li et al. 2007; Sul et al. 2007).

2.8 INTERACTIONS WITH OTHER CHEMICALS

Mautz (2003) examined the potential interaction between ozone and formaldehyde on respiratory tract toxicity in exercising animal models. Rats were exposed to 10 ppm formaldehyde and 0.6 ppm ozone, alone or in combination, at rest and during exercise. Combined exposure to ozone and formaldehyde resulted in greater nasal epithelial injury than formaldehyde exposure alone. The injury to lung parenchyma produced by ozone was not enhanced by formaldehyde, suggesting that formaldehyde does not effectively penetrate to the distal portions of the respiratory tract, even during exercise. The respiratory toxicity of formaldehyde and ozone, alone or in combination, was increased by exposure, compared to resting exposure conditions.

Kum et al. (2007) evaluated the effects of xylene and formaldehyde inhalation on hepatic oxidative stress in the adult and developing rat. Rats were exposed to technical xylene (300 ppm), formaldehyde (6 ppm), or both 8 hours/day for 6 weeks. No effects were seen in the livers of adult rats. However, biomarkers of oxidative stress (i.e., catalase and superoxide dismutase activity, glutathione content) were altered in the developing rat liver after exposure to formaldehyde and xylene. The effects of combined exposure did not differ from the effects seen following exposure to the individual chemicals.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

The following texts provide specific information about treatment following exposures to formaldehyde:

Caraccio TR, McGuigan MA. 2004. Formaldehyde and glutaraldehyde. In: Dart RC, ed. Medical toxicology. Philadelphia, PA: Lippincott Williams & Wilkins, 1246–1250.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 2002. Formaldehyde. In: Goldfrank's toxicologic emergencies. New York, NY: McGraw-Hill, 1284.

Leikin JB, Paloucek JB. 2002. Formaldehyde. In: Leikin and Paloucek's poisoning and toxicology handbook. Hudson, OH: Lexi-Comp, Inc., 600–602.

Viccellio P, Bania T, Brent J, et al., eds. 1998. Formaldehyde. In: Emergency toxicology. Philadelphia, PA: Lippincott-Raven Publishers, 519–522.

The primary concern after oral intoxication with formaldehyde is correcting the severe acidosis and decreased blood pressure that this chemical induces. Treatment should be aimed at increasing the blood pressure to a somewhat normal state (sympathomimetic drugs may be used) as well as treating the acidosis with bicarbonate (Caraccio and McGuigan 2004; Goldfrank et al. 2002; Leikin and Paloucek 2002; Viccellio et al. 1998). Dialysis may also be used to remove excess formate (as formic acid) in the blood in order to correct the acidosis (Caraccio and McGuigan 2004; Goldfrank et al. 2002; Leikin and Paloucek 2002).

2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to formaldehyde may occur by inhalation, ingestion, or dermal contact. There are no known antidotes to formaldehyde poisoning in humans, particularly after oral exposure. General recommendations for reducing absorption of formaldehyde include removing the exposed individual from the contaminated area and removing contaminated clothing, if applicable. If the eyes and skin were exposed, they should be flushed with copious amounts of water. Since formaldehyde is highly corrosive, vomiting after oral ingestion should not be induced. The stomach contents can be diluted with milk or water by mouth if the patient is alert and responsive; otherwise, gastric lavage may be indicated. A bolus of charcoal and isotonic saline cathartic may also be useful (Goldfrank et al. 2002; Leikin and Paloucek 2002).

2.10.2 Reducing Body Burden

Despite a relatively fast clearance of formaldehyde from the body, toxic effects may develop in exposed individuals, particularly in cases of acute oral poisonings that quickly overwhelm the body's natural mechanisms to metabolize formaldehyde (particularly via formaldehyde dehydrogenase). With the exception of sodium bicarbonate administration and hemodialysis to remove excess formate from the blood, there is no standard method or practice to enhance the elimination of the absorbed dose of formaldehyde (Caraccio and McGuigan 2004; Goldfrank et al. 2002; Leikin and Paloucek 2002).

2.11 ADEQUACY OF THE DATABASE

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Results from human and animal studies indicate that portal-of-entry tissues are the critical targets of acute-duration exposures to formaldehyde: the nose and eyes with inhalation exposure; the gastrointestinal tract with oral exposure; and the skin with dermal exposure.

Studies of humans under controlled conditions clearly indicate that acute exposures to air concentrations of formaldehyde gas range from 0.4 to 3 ppm (Bender et al. 1983;Day et al. 1984; Gorski et al. 1992; Krwakowiak et al. 1998; Kulle 1993; and Lang et al. 2008).

Intermediate-Duration Exposure. Intermediate-duration exposure to formaldehyde is expected to affect the same critical targets as acute exposure: the upper respiratory tract with inhalation exposure; the gastrointestinal tract with oral exposure; and the skin with dermal exposure.

Although there are numerous human studies of acute inhalation toxicity from formaldehyde (controlled-exposure and occupational exposure studies) and numerous investigations of toxic effects from chronic occupational exposures, only a few studies of humans exposed for intermediate durations were located. Eye, nose, and throat irritation were observed in medical students exposed to formaldehyde for 2–3 months during gross anatomy class (Kim et al. 1999; Kriebel et al. 2001; Takahashi et al. 2007; Takigawa et al. 2005; Wei et al. 2007). Formaldehyde exposure concentrations were highly variable during the exposure period (0.1–10 ppm formaldehyde), and symptom reporting by study participants was used as the primary effect measure. Objective measures of formaldehyde irritation (i.e., clinical examination, nasal lavage, nasal biopsy) were not examined in these studies.

Children's Susceptibility.

There is some evidence to suggest that formaldehyde may contribute to or worsen the symptoms of asthma in children (Delfino et al. 2003; Rumchev et al. 2002; Smedje et al. 1997; Venn et al. 2003); however, inconsistent findings have been reported (Franklin et al. 2000; Garrett et al. 1999; Tavernier et al. 2006). Studies that evaluate the effect of early life exposure (<2 years) to formaldehyde on the subsequent development of respiratory disease are needed.

There is a need to further study the effects of formaldehyde-bound particles from acute, intermediate, and chronic exposures. There is also a need to study the effects of formaldehyde in the presence of other chemicals and the potential for resulting interactive effects.

2.11.3 Ongoing Studies

Barbara A. Sorg of the Washington State University is researching an animal model for chemical intolerance, sponsored by the National Institute for Environmental Health Sciences (NIEHS) (CRISP 2008).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated information.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Production volume of formaldehyde (37% by weight basis) in the United States in 1990, 1995, and 2000 were reported to be 7.5, 8.7, and 10.3 billion pounds, respectively (IARC 2006). From 1995 to 2000, formaldehyde production averaged an annual growth rate of 1.8% per year and was predicted to grow at a rate of 1.0% per year through 2004 (CMR 2001). The estimated total annual formaldehyde capacities in 1998 and 2001 were 11.3 and 12.5 billion pounds, respectively (C&EN 1998; CMR 2001). The annual growth rate of formaldehyde production from 2001 to 2006 was 0.9% per year, and was predicted to grow at a rate of 1.0% per year through 2010 (CMR 2007). The total annual capacity of formaldehyde production (37% solution basis) in the United States in 2007 was 11.9 billion pounds (SRI 2007). Table 4-1 shows capacity and production volumes for selected years between 1960 and 2007.

As of 2007, three manufacturers of formaldehyde were responsible for over 50% of the annual capacity for the United States: Georgia-Pacific Chemicals LLC. (Albany, Oregon; Columbus, Ohio; Conway, North Carolina; Crossett, Arkansas; Grayling, Michigan; Louisville, Mississippi; Lufkin, Texas; Russellville, South Carolina; Taylorsville, Mississippi; and Vienna, Georgia); Celanese Ltd. (Bishop, Texas); and Hexion Specialty Chemicals, Inc. (Baytown, Texas; Demopolis, Alabama; Diboll, Texas; Fayetteville, North Carolina; Fremont, California; Geismar, Louisiana; Hope, Arkansas; La Grande,

Oregon; Louisville, Kentucky; Missoula, Montana; Riegelwood, North Carolina; Sheboygan, Wisconsin; South Glens Falls, New York; and Springfield, Oregon) (SRI 2007). In addition to the above facilities, the following companies contributed to the overall U.S. capacity: Capital Resin Corporation (Columbus, Ohio); D.B. Western, Inc. (La Porte, Texas); DuPont (Parkersburg, West Virginia); Dynea USA, Inc. (Andalusia, Alabama; Moncure, North Carolina; Springfield, Oregon; Toledo, Ohio; and Winnfield, Louisiana); GEO Specialty Chemicals, Inc. (Allentown, Pennsylvania); Hercules Inc. (Louisiana, Missouri); Perstorp Polyols, Inc. (Toledo, Ohio); Praxair, Inc. (Geismar, Louisiana); and Solutia Inc. (Alvin, Texas) (SRI 2007).

Table 4-1. U.S. Formaldehyde Capacity and Production

	Million pounds/year	
Year	Capacity	Production volume
1960	2,449	1,870
1965	3,556	3,106
1970	Not available	4,427
1975	8,384	4,557
1977	8,830	6,045
1978	9,008	6,499
1982	Not available	4,817
1986	Not available	5,549
1990	9,700	7,500
1992	10,080	8,280
1995	Not available	8,699
1998	11,300	Not available
2000	Not available	10,251
2001	12,500	Not available
2007	11,900	Not available

Sources: C&EN 1994, 1998; CMR 2001; Gerberich et al. 1980; IARC 1995, 2006; SRI 1992, 2007

Table 4-2 lists the facilities in each state that manufacture or process formaldehyde, the intended use, and the range of amounts of formaldehyde that are stored on site. The data listed in Table 4-2 are derived

from the Toxics Release Inventory (TRI06 2008). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Table 4-2. Facilities that Produce, Process, or Use Formaldehyde

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	5	100,000	9,999,999	1, 2, 3, 4, 5, 7, 9
AL	116	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	65	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
AZ	17	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12
CA	95	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	11	0	9,999	1, 2, 5, 6, 7, 10, 11
CT	42	0	99,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 14
DE	11	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12
FL	34	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	117	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	1	10,000	99,999	7
IA	32	0	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14
ID	16	0	99,999	1, 2, 3, 5, 6, 8, 10, 11, 13
IL	90	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	69	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
KS	31	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
KY	46	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	106	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	44	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Table 4-2. Facilities that Produce, Process, or Use Formaldehyde

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MD	24	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
ME	40	0	999,999	1, 2, 3, 5, 6, 7, 8, 11, 12, 13, 14
MI	104	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	91	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	50	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	49	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MT	24	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 12, 13
NC	136	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	5	1,000	99,999	2, 3, 10, 11
NE	9	0	999,999	1, 5, 6, 7, 12, 13
NH	25	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12
NJ	75	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
NM	6	100	9,999,999	1, 3, 4, 6, 7, 8
NV	2	1,000	99,999	6, 7
NY	72	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	134	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	39	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	99	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	98	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 4-2. Facilities that Produce, Process, or Use Formaldehyde

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	24	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
RI	18	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13
SC	112	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	9	0	9,999	1, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14
TN	43	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
TX	160	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	16	0	999,999	1, 3, 5, 6, 7, 8, 10, 11, 12
VA	78	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	6	100	99,999	2, 3, 6, 7, 8, 10
WA	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	96	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	47	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	3	0	99,999	1, 2, 3, 5, 7

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses: numbers are defined as follows

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI06 2008 (Data are from 2006.)

Formaldehyde has been manufactured primarily from methanol since the beginning of the 21st century (Gerberich and Seaman 2004). Because methanol is manufactured from synthesis gas, usually produced from methane, there have been extensive efforts to develop a one-step process that makes formaldehyde directly from methanol by partial oxidation. Although a successful commercial process has not been developed, a wide range of catalysts and oxidation conditions have been studied (Gerberich and Seaman 2004). Following World War II, approximately 20% of the production volume in the United States was manufactured by vapor phase, non-catalytic oxidation of propane and butanes. This nonselective oxidation process produces a variety of coproducts that require a costly and complex separation system, and therefore, the methanol process is preferred (Gerberich and Seaman 2004).

Formaldehyde is also produced in solid form as its cyclic trimer, trioxane, and as its polymer, paraformaldehyde. As a readily available source of formaldehyde for certain applications, paraformaldehyde is prepared commercially by the concentration of aqueous formaldehyde solutions under vacuum in the presence of small amounts of formic acid and metal formates. Trioxane is prepared commercially by strong acid-catalyzed condensation of formaldehyde in a continuous process (IARC 2006). Available information indicates that paraformaldehyde is produced in the United States by three companies and trioxane is produced by two companies (IARC 2006).

4.2 IMPORT/EXPORT

In 1999, the import and export volumes were 82 and 21 million pounds, respectively, and in 2000 they were 62 and 18 million pounds, respectively (CMR 2001). In 2005, the import and export volumes were 21 and 27 million pounds, respectively, and in 2006 they were 22 and 31 million pounds, respectively (CMR 2007).

4.3 USE

The most extensive use of formaldehyde is in the manufacture of urea-formaldehyde, phenol-formaldehyde, melamine-formaldehyde resins, and polyacetal resins (IARC 2006). Formaldehyde-based resins are used as adhesives and as impregnating resins in the manufacture of particle board, fiber board, plywood, furniture, and other wood products. Plywood is the largest market for phenol-formaldehyde resins, and particle board is the largest for urea-formaldehyde resins (Gerberich and Seaman 2004). These resins are also used for the production of curable moulding materials (appliances, electric controls, telephones, wiring services) and as raw materials for surface coatings and controlled release nitrogen fertilizers. Additionally, they are used in the textile, leather, rubber, and cement industries. Further uses are as binders for foundry sand, stonewool, and glasswool mats in insulating materials, abrasive paper, and brake linings (IARC 2006).

Polyacetal plastics produced by polymerization of formaldehyde are incorporated into automobiles to reduce weight and fuel consumption. They are also used in the manufacture of functional components of audio and video electronics equipment (IARC 2006).

Formaldehyde consumption in the United States in 2005 and 2006 was reported as 10.24 and 10.50 billion pounds, respectively, and it is projected to be 10.93 billion pounds in 2010 (CMR 2007). Formaldehyde consumption in 1999 and 2000 was reported as 9.6 and 9.8 billion pounds, respectively (CMR 2001; IARC 2006). This was a slight decrease from the 11.3 and 11.6 billion pounds demand reported for formaldehyde in 1994 and 1995 (C&EN 1995). The decrease was due to the softening of the housing and construction market, a softening that depressed the demand for formaldehyde in urea- and phenol-formaldehyde resins used in particle board and plywood, respectively (CMR 2007). Since these two classes of thermosetting resins account for more than one-third of formaldehyde consumption, the demand for formaldehyde will continue to track the demand in the housing and construction industry

(CMR 2001). In 2001, it was reported that the fastest growing formaldehyde market, at about 5% per year, in the United States is in the production of acetylenic chemicals (butanediol), MDI, and acetal resins (CMR 2001). Table 4-3 shows the distribution of formaldehyde use for select periods between 1963 and 2007.

Table 4-3. Distribution of Formaldehyde Production According to Uses in the United States

	Percentage of consumption							
	1963	1969	1972	1977	1989	1998	2001	2007
Phenol-formaldehyde resins	22	22	26	25	22	19	16.5	17
Urea-formaldehyde resins	21	25	26	25	25	23	24	22
Acetal resins	4	6	7	9	9	11	13	13
Acetylenics (butanediol)	NA	2	4	6	11	12	11	9
Melamine resins	6	7	6	5	4	4	3	3
Methylene diisocyanate	NA	NA	NA	NA	5	6	7	10
Pentaerythritol	9	7	7	5	7	5	5	5
Hexamethylenetetramine	6	9	6	5	6	4	3	3
Fertilizer	3	3	4	NA	6	4	3.5	3
Trimethylolpropane	NA	1.1	1.5	NA	NA	NA	NA	NA
Ethylene glycol	12	4	0	0	NA	NA	NA	NA
Miscellaneous	17	14	12	20	5	12	14	15

NA = not available

Sources: C&EN 1989, 1998; CMR 2001, 2007; Gerberich and Seaman 1994; Gerberich et al. 1980.

4.4 DISPOSAL

Formaldehyde has been treated by use of biofilters, polymer-coated zeolites, and polymeric membrane, but these procedures can be capital- and space-intensive (Cowan et al. 2005). It has been reported that formaldehyde generated in the engineered wood industry can potentially be stripped from an air stream in a fluidized bed containing boiler ash, which can be returned to a boiler to incinerate the formaldehyde.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Formaldehyde has been identified in at least 29 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for formaldehyde is not known.

In December 2007 and January 2008, the Centers for Disease Control and Prevention (CDC) tested travel trailers, park models, and mobile homes provided by the Federal Emergency Management Agency (FEMA) as temporary housing to Gulf Coast residents in Louisiana and Mississippi who were displaced by Hurricanes Katrina and Rita. The results showed an average indoor air concentration of 77 ppb, with measured levels ranging from 3 to 590 ppb; the range is higher than typical background indoor air concentrations of 10-30 ppb (CDC 2008). Formaldehyde levels are generally lower in cooler temperatures and lower humidity; therefore, levels measured in this study are likely to underestimate those that would occur in the summer months (CDC 2008).

5.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report their releases (EPA 2005). TRI is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except

1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.2.1 Air

Estimated releases of 8.88 million pounds (~4,028 metric tons) of formaldehyde to the atmosphere from 725 domestic manufacturing and processing facilities in 2006 accounted for about 41% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Table 5-1.

Table 5-1. Releases to the Environment from Facilities that Produce, Process, or Use Formaldehyde[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	3,871	0	0	250	0	3,871	250	4,121
AL	37	417,877	37,125	0	2,125	0	455,597	1,530	457,127
AR	15	292,714	19,719	0	1,012	0	312,483	963	313,446
AZ	4	9,813	No data	0	167	0	9,813	167	9,980
CA	26	196,556	10	0	3,267	750	197,263	3,320	200,583
CO	1	0	No data	0	0	0	0	0	0
CT	5	21,647	1,078	0	2,230	1,096	22,725	3,326	26,051
DE	1	1,965	0	0	0	0	1,965	0	1,965
FL	15	295,914	19,431	89,497	423	0	405,265	0	405,265
GA	35	795,077	19,572	0	1,317	805	814,677	2,094	816,771
IA	16	156,218	4,554	10,868	5	0	160,772	10,873	171,645
ID	1	25,410	5,600	0	0	0	31,010	0	31,010
IL	32	59,702	2,818	0	5,662	518	62,520	6,180	68,700
IN	13	74,451	No data	0	19,402	1,550	74,451	20,952	95,403
KS	11	112,150	0	0	201	0	112,150	201	112,351
KY	14	40,966	6,018	0	0	0	46,984	0	46,984
LA	32	394,829	28,805	10,818,233	19,874	0	11,257,892	3,849	11,261,741
MA	10	53,737	6,490	0	1,336	377	60,227	1,713	61,940

Table 5-1. Releases to the Environment from Facilities that Produce, Process, or Use Formaldehyde[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
MD	4	22,113	No data	0	0	0	22,113	0	22,113
ME	8	236,773	5,693	0	766	0	242,481	751	243,232
MI	26	144,342	1,837	9	65,194	9	146,182	65,209	211,391
MN	12	121,667	0	0	8	0	121,675	0	121,675
MO	12	34,045	311	0	9,541	0	34,361	9,536	43,897
MS	11	311,085	2,539	0	239	0	313,624	239	313,863
MT	4	591,312	60	0	45	0	591,414	3	591,417
NC	42	503,529	31,057	0	16,581	776	536,450	15,493	551,943
NE	7	49,763	0	0	5	0	49,768	0	49,768
NH	2	2,808	128	0	1	0	2,936	1	2,937
NJ	10	2,564	0	0	32	0	2,596	0	2,596
NV	1	0	No data	0	0	0	0	0	0
NY	19	80,795	27,272	0	480	5,105	108,179	5,473	113,652
OH	39	397,719	1,160	235,776	98,696	0	466,416	266,935	733,351
OK	8	184,179	1,837	0	5	0	186,021	0	186,021
OR	27	873,071	10,970	0	1,511	0	884,047	1,505	885,552
PA	26	371,071	3,875	0	5,263	43	374,959	5,293	380,252
PR	2	1,161	No data	0	0	2,617	1,161	2,617	3,777

Table 5-1. Releases to the Environment from Facilities that Produce, Process, or Use Formaldehyde[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
RI	3	15	No data	0	0	0	15	0	15
SC	33	682,966	31,124	0	23,447	0	719,275	18,262	737,537
SD	2	42,541	No data	0	0	0	42,541	0	42,541
TN	12	88,806	13,563	0	562	161	102,369	723	103,092
TX	68	561,366	6,079	808,681	14,573	2,216	1,371,887	21,028	1,392,915
UT	3	8,081	No data	0	28	48	8,081	76	8,157
VA	15	166,330	971	0	2,672	0	168,611	1,362	169,974
VT	1	253	No data	0	20	0	253	20	273
WA	13	147,481	32,723	0	973	90	180,204	1,063	181,267
WI	32	140,158	7,721	0	5,394	5	152,839	439	153,278
WV	12	84,897	555	0	229	0	85,456	225	85,681
WY	2	75,715	No data	0	0	0	75,715	0	75,715
Total	725	8,879,500	330,696	11,963,064	303,537	16,166	21,021,291	471,671	21,492,962

Table 5-1. Releases to the Environment from Facilities that Produce, Process, or Use Formaldehyde[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site

[a]The TRI data should be used with caution, since only certain types of facilities are required to report. TRI is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

"Clean" fuels such as natural gas can also produce significant levels of formaldehyde (Dasgupta et al. 2005). In large-bore gas turbine engine exhaust, the ratio of formaldehyde to total hydrocarbons in the exhaust is about 1–2.5%. Exhaust from internal combustion engines powered by sludge digester gas contains formaldehyde levels of 50-200 ppm. Formaldehyde generation is also an issue with the clean power generation technologies of the future. Methanol-based fuel cells, which many regard as ultimately more practical than hydrogen fuel cells, can produce substantial amounts of formaldehyde (Dasgupta et al. 2005).

There is a potential for release of formaldehyde to air from hazardous waste sites. Formaldehyde has been detected in air samples collected at 6 of the 29 hazardous waste sites where formaldehyde has been detected in some environmental media (HazDat 2008).

Some materials used to construct and finish the interiors of new houses emit formaldehyde. The emissions of formaldehyde from these materials can result in substantial contamination of indoor air. In the past, elevated concentrations of formaldehyde in newly manufactured homes were a result of emissions from engineered wood products. An understanding of the problem led to the development of test methods and the establishment of guidelines for the emissions of formaldehyde from wood products by the U.S. Department of Housing and Urban Development. Today, the emissions of formaldehyde from wood products are substantially lower (Hodgson et al. 1999). Specific emission rates of formaldehyde measured in 1997 and 1998 in four newly manufactured homes in Plant City, Florida, several of which had incorporated interior finish materials with lower volatile organic compound (VOC) emissions and one of which had a modified ventilation system, had a median value of 41 $\mu g/m^2$/hour, and all the emission rates measured were <70 $\mu g/m^2$/hour (Hodgson et al. 1999). These emission rates are generally consistent with the formaldehyde emission rates measured for various engineered wood products (Hodgson et al. 1999). Formaldehyde emission rates reported in a study of four new manufactured houses sampled over 2-9.5 months after installation and seven new site built houses sampled 1–2 months after completion in 1997 and 1998 were 29–68 and 10–58 $\mu g/m^2$/hour, respectively (Hodgson et al. 2000). Construction materials that were identified as major sources of formaldehyde included plywood flooring, latex paint, and sheet vinyl flooring. A plywood specimen used in the construction of these houses had an emission rate of 29 $\mu g/m^2$/hour after 72 hours of exposure (Hodgson et al. 2000). In a study measuring emission rates in a new, unoccupied manufactured house in Gaithersburg, Maryland over the course of 1 year (August 2002–September 2003), formaldehyde emission rates ranged from 34 to 121 $\mu g/m^2$/hour (DOE 2004).

Newly manufactured structural insulated panels obtained in March 2003 from two separate manufacturers and measured at 1 and 4 months had formaldehyde emission rates of 4.8 and <3 μg/m^2/hour, respectively (DOE 2003).

Measured formaldehyde emission rates from low nitrogen oxide-emitting, unflued gas heaters ranged from <0.1 to 2.5 ng/Joule (Brown et al. 2004).

5.2.2 Water

Estimated releases of 0.33 million pounds (~150 metric tons) of formaldehyde to surface water and to publicly owned treatment works (POTWs) from 725 domestic manufacturing and processing facilities in 2006 accounted for about 1.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Table 5-1.

There is a potential for release of formaldehyde to water from hazardous waste sites. Formaldehyde has been detected in surface water samples collected at 6 of the 29 hazardous waste sites and in groundwater samples collected at 4 of the 29 hazardous waste sites where formaldehyde has been detected in some environmental media (HazDat 2008).

5.2.3 Soil

Estimated releases of 0.30 million pounds (~138 metric tons) of formaldehyde to soils from 725 domestic manufacturing and processing facilities in 2006 accounted for about 1.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 11.96 million pounds (~5,426 metric tons), constituting about 56% of the total environmental emissions, were released via underground injection (TRI06 2008). These releases are summarized in Table 5-1.

Formaldehyde may be directly released to soil during agricultural application as a fumigant fungicide or a bactericide (Tomlin 2003).

There is a potential for the release of formaldehyde to soil from hazardous waste sites. Formaldehyde has been detected in soil samples collected at 1 of the 29 hazardous waste sites and in sediment samples collected at 1 of the 29 hazardous waste sites where formaldehyde has been detected in some environmental media (HazDat 2008).

5.3 ENVIRONMENTAL FATE

5.3.2.1 Air

Formaldehyde reacts with the NO_3 radical by H-atom extraction with a lifetime of 83 days, assuming a 12-hour average nighttime NO_3 radical concentration of $5x10^8$ molecules per cm^3 (Atkinson and Arey 2003).

5.3.2.3 Sediment and Soil

The fate of formaldehyde in soil is not fully understood, but it is biodegradable to carbon dioxide and water or formic acid under both aerobic and anaerobic conditions. It is also biologically active, reacting readily with phenol, amine, amide, sulfide, purine, and pyrimidine functional groups, each of which can be found in soil humic substances. Further, formaldehyde is subject to spontaneous polymerization, forming units of paraformaldehyde (Cooke et al. 2003).

In a study investigating chemical interactions with soil humic substances by use of co-elution of radiolabelled compounds with gel filtration chromatography-separated humic substance fractions, results suggested a direct association of free formaldehyde with low molecular weight humic substances (Cooke et al. 2003). This study also suggested that the degree of binding of formaldehyde to the humic substances became more stable over time (Cooke et al. 2003).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The main source of formaldehyde in the atmosphere is believed to be photochemical oxidation of hydrocarbon combustion products. As much as 88% of formaldehyde in urban air is thought to be photochemically derived (Austin 2003).

Dasgupta et al. (2005) measured summertime ambient formaldehyde levels in a study of five major U.S. cities: Nashville, Tennessee (June–July 1999); Atlanta, Georgia (August 1999); Houston, Texas (August–September 2000); Philadelphia, Pennsylvania (June–July 2001); and Sydney, Florida (April–June 2002). Reported concentration ranges were 1.43–12.67 ppb (mean 5.05 ppb) in Nashville, 0.42–18.25 ppb (mean 7.96 ppb) in Atlanta, 0.15–47.13 ppb (mean 4.49 ppb) in Houston, 0.33–9.53 ppb (mean 3.12 ppb) in Philadelphia, and 0.37–9.38 ppb (mean 2.63 ppb) in Sydney. It was shown that land-sea breeze circulations played an important role in observed concentrations in coastal cities, and clear diurnal patterns were observed at all the sites (Dasgupta et al. 2005).

Multimedia sampling at a subset of Arizona homes participating in EPA's National Human Exposure Assessment Survey was conducted in order to assess residential environmental exposure to volatile organic compounds (Gordon et al. 1999). Formaldehyde was found in 69% of the indoor air samples

collected, with a median concentration of 17 ppb (21 μg/m^3) and 21% of the outdoor air samples collected had a median concentration of 5.1 ppb (6.3 μg/m^3).

The median formaldehyde concentration measured in 1997 and 1998 in four newly manufactured homes in Plant City, Florida, several of which had incorporated interior finish materials with lower VOC emissions and one of which had a modified ventilation system, was reported as 37 ppb, and all the concentrations were <50 ppb (DOE 1999). A mean indoor air formaldehyde concentration of 40 ppb was reported in a study of four new manufactured houses sampled over 2-9.5 months after those houses were installed and of seven new site-built houses sampled 1-2 months after completion in 1997 and 1998 (Hodgson et al. 2000). Formaldehyde concentrations ranged from 21 ppb - 47 ppb in the manufactured houses and from 14 -58 ppb in the site-built houses. Major identified sources of formaldehyde included plywood flooring, latex paint, and sheet vinyl flooring. In a study measuring indoor air in a new, unoccupied manufactured house in Gaithersburg, Maryland over the course of 1 year (August 2002–September 2003), formaldehyde concentrations exhibited temporal variability ranging from 20 ppb -104 ppb (25 - 128 μg/m^3) with the lowest concentrations occurring in winter months when indoor relative humidity was low (DOE 2004).

In December 2007 and January 2008, CDC tested travel trailers, park models, and mobile homes provided by FEMA as temporary housing to Gulf Coast residents in Louisiana and Mississippi, residents who were displaced by Hurricanes Katrina and Rita. The results showed an average indoor air concentration of 77 ppb, with measured levels ranging from 3 to 590 ppb, a range higher than typical background indoor air concentrations of 10–30 ppb. Formaldehyde levels are generally lower in cooler temperatures and lower humidity; therefore, levels measured in this study are likely to underestimate those that would occur in the summer months (CDC 2008).

Levels of formaldehyde in conventional homes and workplaces housing nonsmokers ranged from 0.03 to 0.06 mg/m^3 (0.02–0.05 ppm), while it ranged from 0.05 to 0.35 mg/m^3 (0.04–0.28 ppm) in homes and workplaces containing environmental tobacco smoke (WHO 2000).

5.4.2 Water

Synthetic resin-producing industries generate waste water with high levels of organic matter, including formaldehyde as a major component. Formaldehyde has been measured in these waste waters at concentrations ranging from 7 to 2,711 mg/L (Eiroa et al. 2005).

5.4.4 Other Environmental Media

Formaldehyde was detected in commercial 2% and fresh whole milk of cows fed on a typical North American dairy diet, with average concentrations of 0.164 and 0.027 mg/kg, respectively (Kaminski et al. 1993). Available data suggest that the highest concentrations of formaldehyde naturally occurring in foods (up to 60 mg/kg) are in some fruits and marine fish (Environment Canada/Health Canada 2001). Maple syrup collected from maple trees that had been implanted with paraformaldehyde to deter bacterial growth in tap holes contained a maximum formaldehyde concentration of 14 mg/kg, whereas syrup from untreated trees had a concentration of <1 mg/kg (Environment Canada/Health Canada 2001). Formaldehyde concentrations of 3.4 and 4.5 mg/kg in brewed coffee and 10 and 16 mg/kg in instant coffee have been reported (Hayashi et al. 1986).

Mansfield et al. (1977) used liquid chromatography to measure formaldehyde as a combustion product in tobacco smoke from six different brands of American filter tip cigarettes. The average amount of formaldehyde by brand ranged from 45.2 to 73.1 μg/ per cigarette and from 5.1 to 8.9 μg/ per puff. Triebig and Zober report that the level of formaldehyde in side stream cigarette smoke is 50 times higher

than main stream smoke (Triebig and Zober 1984), while the National Research Council put the value at 5–8 times more formaldehyde in side stream smoke (NRC 1986).

Formaldehyde is sometimes used as a biocide in finger-paints, and it has been detected in finger-paints at concentrations of 441–793 ppm (mg/kg) (Garrigos et al. 2001).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The contribution of various atmospheric environments to the average exposure to formaldehyde is given in Table 5-2 (WHO 2000).

Table 5-2. The Contribution of Various Atmospheric Environments to the Average Exposure to Formaldehyde

Source	mg/day
Air	
Outdoor air (10% of time)	0.002–0.04
Indoor air	
Home (65% of time)	
Conventional	0.3–0.6
Mobile home	1.0
Environmental tobacco smoke	0.5–3.5
Workplace (25% of time)	
Without occupational exposure	0.2–0.5
With occupational exposure	8.0
Environmental tobacco smoke	0.4–2.8
Smoking (20 cigarettes/day)	0.9–2.0

Source: WHO 2000

In 13 healthy adult volunteers aged 24–50 years old, formaldehyde was detected in all urine samples collected from 9 men and 4 women at background concentrations of 56.85–70.57 and 60.84–144.57 µg/L, respectively (Takeuchi et al. 2007). The median observed formaldehyde levels in the urine of the men and women were 62.10 and 79.30 µg/L, respectively. Formaldehyde was detected at concentrations ranging from 1,230 to 72,729 ppb in exhaled breath samples collected from 344 adult volunteers having a mean age of 61.6 years. The median observed formaldehyde level detected in exhaled breath samples was 4.263 ppb (Moser et al. 2005).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Formaldehyde concentrations in mobile homes may be up to 14 times higher than in conventional homes (Gammage and Hawthorne 1985; Hawthorne et al. 1986). Gulf Coast residents in Louisiana and Mississippi who were displaced by Hurricanes Katrina and Rita and were provided travel trailers and mobile homes as temporary housing by FEMA have been exposed to higher-than-normal formaldehyde levels. The average indoor air concentration measured in the study of this housing was 77 ppb (CDC 2008).

Smokers and persons who live in a home with a cigarette smoker also may be exposed to higher levels of formaldehyde. Environmental tobacco smoke, which is a combination of diluted sidestream smoke released from a cigarette's burning end and mainstream smoke exhaled by an active smoker, can contribute 10–25% (0.1–1 mg/day) of the total average indoor exposure to formaldehyde (WHO 1986).

5.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies. These studies may fill in some of the data needs identified in Section 6.8.1. The studies are summarized in Table 5-3.

Table 5-3. Ongoing Studies on Formaldehyde

Investigator	Affiliation	Research description	Sponsor
Faloona, Ian C	University of California, Davis	Researchers are conducting a study of gas phase formaldehyde in a forested environment and the photochemical oxidation of hydrocarbons. The goals of this study are to better understand the atmospheric processing of VOCs and their concurrent formaldehyde production.	National Science Foundation
Kretzschmar, Ilona	CUNY City College	This study describes a method for the generation of porous, cylindrical polymer membranes with a uniform catalyst coating that will lead to the development of new material for the separation and decomposition of formaldehyde in indoor air streams.	National Science Foundation
Marotta, Christopher L	Eltron Research, Inc.	Researchers are conducting a study to develop a small, inexpensive sensor for measuring the concentration of formaldehyde in real-time in order to protect workers who encounter formaldehyde in the chemical industry. The aim is also to create a sensor platform that can be readily adapted for indoor air quality or environmental monitoring applications.	NIOSH

CUNY = City University of New York; NIOSH = National Institute for Occupational Safety and Health; VOC = volatile organic compound

Source: FEDRIP 2008

As previously discussed, in the aftermath of Hurricanes Katrina and Rita, the Federal Emergency Management Agency (FEMA) provided travel trailers, park models, and mobile homes to displaced Gulf Coast residents who had lost their homes. Residents of these trailers and mobile homes have raised concerns about air quality in the trailers and the occurrence of respiratory and other symptoms resulting

from exposure to formaldehyde. The Centers for Disease Control and Prevention's (CDC's) National Center for Environmental Health (NCEH) has been working with FEMA to investigate the health concerns of those living in the trailers and mobile homes and to take action to protect residents' health. In December 2007 and January 2008, CDC tested travel trailers, park models, and mobile homes provided by FEMA as temporary housing to Gulf Coast residents in Louisiana and Mississippi who were displaced by hurricanes Katrina and Rita (CDC 2008). The study aimed to determine formaldehyde levels in occupied trailers, determine trailer characteristics that could affect formaldehyde levels, and provide information to assist FEMA in deciding whether to relocate residents from FEMA-supplied trailers in the Gulf Coast area. The findings of this study have been addressed in an official CDC Press Release found on the CDC/NCEH Website at http://www.cdc.gov/nceh/ehhe/trailerstudy/residents.htm#final.

A new survey, NHANES IV, is in the process of being conducted by CDC.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

Takeuchi et al. (2007) developed a technique for quantifying formaldehyde in urine by derivatization with O-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine (PFBHA) to the PFBHA-formaldoxime, using a headspace sampler coupled to a gas chromatograph equipped with an electron capture detector (ECD) (see Table 6-1).

Table 6-1. Analytical Methods for Determining Formaldehyde in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Derivatization with O-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine.	GC/EC	1.08 μg/L	99	Takeuchi et al. 2007

GC/EC = gas chromatography/electron capture

6.2 ENVIRONMENTAL SAMPLES

The most widely used methods for the determination of the concentration of formaldehyde in air are based on ultraviolet/visible (UV/VIS) spectrophotometry measurements of the absorption band at 580 nm following derivitization with chromotropic and sulfuric acid. Sensitivities of 0.01–0.03 mg/m^3 can be achieved by use of these methods. Other methods include colorimetry, fluorimetry, high-performance liquid chromatography (HPLC), polarography, gas chromatography (GC), infrared detection, and gas

detector tubes. Most methods require the formation of a formaldehyde derivative for separation and detection (IARC 2006). Formaldehyde determination by use of HPLC can achieve a limit of detection of ≤2 μg/m^3, and HPLC is the most sensitive method. Gas detection tubes that have sensitivities of about 0.05–0.12 μg/m^3 (0.04–0.1 ppm) and infrared analyzers that have sensitivities of about 1.2–230 μg/m^3 (1–110 ppb) are often used to monitor workplace atmospheres (IARC 2006).

One type of passive sampler uses a glass fiber filter or a tape impregnated with 2,4-dinitrophenylhydrazine (DNPH) and phosphoric acid mounted in a polystyrene cassette (see Table 6-2). SKC Inc. and GMD Systems use this passive sampling method for commercially available badges (Levin and Lindahl 1994; Levin et al. 1989).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Preparation of passive monitor, formaldehyde in air adsorbs onto DNPH and sulfuric acid impregnated glass fiber filter or tape	UV/VIS absorbance at 365 nm	6 μg/m^3 (5 ppb) (8 hours) 1.2 μg/m^3 (1 ppb) (24 hours)	100% (5% RSD)	Levin and Lindahl 1994; Levin et al. 1989
Air	Drawing of air through a sampling tube containing silica gel coated with DNPH. Elution of derivative with acetonitrile.	GC/NPD	0.12 μg/sample	>95	Jeong and Paik 2005

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Atmospheric water	Reaction of formaldehyde in water with ammonium acetate and 2,4-pentanedione in FIA system to form 3,5-diacetyl-1,4-dihydro-lutidine.	FIA/fluor-escence	3 μg/L (3 ppb)	No data	Dong and Dasgupta 1987

DNPH = 2,4-dinitrophenylhydrazine; FIA = flow injection analysis; GC = gas chromatography; NPD =nitrogen-phosphorus detector; RSD = relative standard deviation; UV/VIS = ultraviolet/visible absorbance detection

Jeong and Paik (2005) have reported a method in which the DNPH formaldehyde derivatives are analyzed by use of GC equipped with a nitrogen-phosphorus detector (GC-NPD) in order to measure personal exposure in the workplace. In laboratory tests, this new method, referred to as the GC-NPD method, is as sensitive as the NIOSH analytical method, which uses HPLC equipped with an ultraviolet detector (Jeong and Paik 2005).

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.

6.3 ADEQUACY OF THE DATABASE

6.3.2 Ongoing Studies

The information in Table 6-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2008).

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 give detection limits in the low parts per trillion (ppt) range.

Table 6-3. Ongoing Studies on Formaldehyde

Investigator	Affiliation	Research description	Sponsor
Kretzschmar, Ilona	CUNY City College	This study describes a method for the generation of porous, cylindrical polymer membranes with a uniform catalyst coating that will lead to the development of new material for the separation and decomposition of formaldehyde in indoor air streams.	National Science Foundation
Marotta, Christopher L	Eltron Research, Inc.	Researchers are conducting a study to develop a small, inexpensive sensor for measuring the concentration of formaldehyde in real-time in order to protect workers who encounter formaldehyde in the chemical industry. The aim is also to create a sensor platform that can be readily adapted for indoor air quality or environmental monitoring applications.	NIOSH

CUNY = City University of New York; NIOSH = National Institute for Occupational Safety and Health

Source: FEDRIP 2008

7. REGULATIONS, ADVISORIES, AND GUIDELINES

The EPA oral reference dose (RfD) for formaldehyde is 0.2 mg/kg/day for causing gastrointestinal damage (IRIS 2010). EPA began a reassessment of the inhalation reference concentration (RfC) in January 1998, and a draft assessment was released for public comment in June 2010. A committee of the NRC is conducting an independent scientific review of this EPA draft human health assessment of formaldehyde for IRIS (IRIS 2010). The committee will provide a brief report that comments on EPA's identification of potential adverse non-cancer health effects, assessment of carcinogenic potential, exposure-response analysis for identified end points, quantitative risk assessment methods, and evaluation of sources of uncertainty in the health assessment.

The international and national regulations, advisories, and guidelines regarding formaldehyde in air, water, and other media are summarized in Table 7-1.

The National Toxicology Program (NTP) (2005) noted that formaldehyde is reasonably anticipated to be a human carcinogen. NTP has included formaldehyde as an item under consideration for the Twelfth Report on Carcinogens (NTP 2008, 2010). In 2006, the International Agency for Research on Cancer (IARC) has reclassified formaldehyde from Group 2A to Group 1 (IARC 2008). The EPA has classified formaldehyde as a B1 compound, probable human carcinogen, on the basis of limited evidence in humans and sufficient evidence in animals (IRIS 2010).

Formaldehyde is on the list of chemicals subject to the requirements of The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) (EPA 2008c). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the

chemicals on this list to report annually their release of those chemicals to any environmental media (EPA 2008c).

OSHA requires employers of workers who are occupationally exposed to formaldehyde to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use controls and practices, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 0.75 ppm. The 15-minute, short-term exposure limit (STEL) for formaldehyde is 2 ppm (OSHA 2007b).

The EPA regulates formaldehyde under the Clean Air Act (CAA) and has designated formaldehyde as a hazardous air pollutant (HAP) (EPA 2008c); formaldehyde is listed among the urban HAPs for the Integrated Urban Air Toxics Strategy (EPA 1999). The major source category for which formaldehyde emissions are controlled is the Synthetic Organic Chemicals Manufacturing Industry (SOCMI) (EPA 2008e, 2008i).

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), owners of vessels or facilities are required to immediately report release of formaldehyde equal to or greater than the reportable quantity of 100 pounds (45.4 kg) (EPA 2008c).

The Food and Drug Administration (FDA) identifies formaldehyde as an indirect food additive for use only as a component of adhesives (FDA 2007b). When used in accordance with specified conditions, the food additive, formaldehyde, is permitted in feed and drinking water of animals (FDA 2007a).

Table 7-1. Regulations, Advisories, and Guidelines Applicable to Formaldehyde

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 1[a]	IARC 2008
WHO	Air quality guidelines[b]	0.1 mg/m^3	WHO 2000
	Drinking water quality guidelines	0.9 mg/L	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (ceiling limit)	0.3 ppm	ACGIH 2007
	TLV basis (critical effects)[c]	Upper respiratory tract and eye irritation	
AIHA	ERPG-1[d]	1 ppm	AIHA 1988
	ERPG-2[d]	10 ppm	
	ERPG-3[d]	25 ppm	
EPA	AEGL-1[e]		EPA 2007a
	10 minutes	0.90 mg/m^3	
	30 minutes	0.90 mg/m^3	
	60 minutes	0.90 mg/m^3	
	4 hours	0.90 mg/m^3	
	8 hours	0.90 mg/m^3	
	AEGL-2[e]		
	10 minutes	14 mg/m^3	
	30 minutes	14 mg/m^3	
	60 minutes	14 mg/m^3	
	4 hours	14 mg/m^3	
	8 hours	14 mg/m^3	
	AEGL-3[e]		
	10 minutes	100 mg/m^3	
	30 minutes	70 mg/m^3	
	60 minutes	56 mg/m^3	
	4 hours	35 mg/m^3	
	8 hours	35 mg/m^3	
	Second list of AEGL priority chemicals	Yes	EPA 2008a

Table 7-1. Regulations, Advisories, and Guidelines Applicable to Formaldehyde

Agency	Description	Information	Reference
	for guideline development		
	Hazardous air pollutant (HAP)	Yes	EPA 2007b 42 USC 7412
	Listed on the Urban HAPs for the Integrated Urban Air Toxics Strategy	Yes	EPA 1999 64 FR 38706
NATIONAL *(cont.)*			
	National emission standards for organic hazardous air pollutants from the SOCMI	Yes	EPA 2008i 40 CFR 68.107, Table 2
EPA	Regulated toxic substances and threshold quantities for accidental release prevention under Section 112(r) of the Clean Air Act	15,000 pounds	EPA 2008g 40 CFR 68.130
	Standards of performance for equipment leaks of VOC in SOCMI	Yes	EPA 2008e 40 CFR 68.489
NIOSH	REL (10-hour TWA)	0.016 ppm	NIOSH 2005
	Ceiling limit (15-minute)	0.1 ppm	
	IDLH	20 ppm	
	Target organs	Eyes and respiratory system	
	Potential occupational carcinogen	Yes	
	Category of pesticides	Group 1 pesticide[f]	NIOSH 1992
OSHA	PEL (8-hour TWA) for general, shipyard, and construction industry (ceiling limit)	0.75 ppm	OSHA 2007b 29 CFR 1910.1048
	STEL (15-minute)	2 ppm	
	Highly hazardous chemical which present a potential for a catastrophic event or above the threshold quantity	Yes	OSHA 2007a 29 CFR 1910.119
	Threshold quantity	1,000 pounds	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2008b 40 CFR 116.4
	Drinking water standards and health		EPA 2006a

Table 7-1. Regulations, Advisories, and Guidelines Applicable to Formaldehyde

Agency	Description	Information	Reference
	advisories		
	1-day health advisory for a 10-kg child	10 mg/L	
	10-day health advisory for a 10-kg child	5 mg/L	
	DWEL	7 mg/L	
	Lifetime	1 mg/L	
	National primary drinking water standards	No data	EPA 2003
	National recommended water quality criteria	No data	EPA 2006b
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	100 pounds	EPA 2008d 40 CFR 117.3
NATIONAL *(cont.)*			
c. Food			
FDA	EAFUS[g]	Yes	FDA 2008
	Indirect food additives: adhesives and components of coatings	Yes	FDA 2007b 21 CFR 175.105
	Food additive permitted in feed and drinking water of animals	Yes	FDA 2007a 21 CFR 573.460
d. Other			
ACGIH	Carcinogenicity classification	A2[h]	ACGIH 2007
EPA	Carcinogenicity classification	Group B1[i]	IRIS 2010
	RfC	Under review	
	RfD	0.2 mg/kg/day	
	Master Testing List	Yes[j]	EPA 2008h
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[k]	EPA 2008c 40 CFR 302.4
	Reportable quantity	100 pounds	
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2008j 40 CFR 372.65
	Extremely Hazardous Substances		EPA 2008f 40 CFR 355,
	Reportable quantity	100 pounds	

Table 7-1. Regulations, Advisories, and Guidelines Applicable to Formaldehyde

Agency	Description	Information	Reference
	Threshold planning quantity	500 pounds	Appendix A
	Identification and listing of hazardous waste		EPA 2008l 40 CFR 261, Appendix VIII
	Hazardous waste number	U122	
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2005
	Twelfth report on carcinogens; items under consideration	Yes	NTP 2008

[a]Group 1: The agent is carcinogenic to humans.
[b]TWA based on effects other than cancer or odor/annoyance using an averaging time of 30 minutes.
[c]Sensitization designation refers to the potential for an agent to produces sensitization, as confirmed by human or animal data.
[d]ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing other than mild, transient health effects; ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing irreversible or other serious adverse effects; and ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without life-threatening health effects (AIHA 1988).
[e]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects; however, the effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; and AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2007a).
[f]Group 1 pesticide: contains the pesticides that pose a significant risk of adverse acute heatlh effects at low concentrations.
[g]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[h]A2: Suspected human carcinogen.
[i]Group B1: Probable human carcinogen, based on limited evidence in humans, and sufficient evidence in animals.
[j]Formaldehyde was recommended to the MTL by Office of Pollution Prevention and Toxics in 1992 and the chemical testing program is currently underway under a voluntary testing agreement for emissions testing.
[k]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of the Resource Conservation and Recovery Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = Emergency Response Planning Guidelines; FDA = Food and Drug Administration; FR = Federal Register;

Table 7-1. Regulations, Advisories, and Guidelines Applicable to Formaldehyde

Agency	Description	Information	Reference

GRAS = Generally Recognized As Safe; HAP = hazardous air pollutant; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; SOCMI = Synthetic Organic Chemicals Manufacturing Industry; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; VOC = volatile organic compounds; WHO = World Health Organization

8. REFERENCES

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