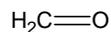


Formaldehyde Reference Exposure Levels DRAFT

(Methanal, oxomethane, methylene oxide)

CAS 50-00-0



1. Summary

The non-cancer adverse health effects of formaldehyde are largely a manifestation of its ability to irritate mucous membranes. As a result of its solubility in water and high reactivity, formaldehyde is efficiently absorbed into the mucus layers protecting the eyes and respiratory tract where it rapidly reacts, leading primarily to localized irritation. Acute high exposure may lead to eye, nose and throat irritation, and in the respiratory tract, nasal obstruction, pulmonary edema and dyspnea. Prolonged or repeated exposures have been associated with allergic sensitization, respiratory symptoms (coughing, wheezing, shortness of breath), histopathological changes in respiratory epithelium, and decrements in lung function. Children, especially those with diagnosed asthma, may be more likely to show impaired pulmonary function and symptoms than are adults following chronic exposure to formaldehyde. The studies reviewed for this document include those published through the Spring of 2008.

1.1 Formaldehyde Acute REL

<i>Reference Exposure Level</i>	55 µg/m³ (44 ppb)
<i>Critical effect(s)</i>	Mild and moderate eye irritation
<i>Hazard Index target(s)</i>	Eye irritation

1.2 Formaldehyde 8-Hour REL

<i>Reference Exposure Level</i>	9 µg/m³ (7 ppb)
<i>Critical effect(s)</i>	Nasal obstruction and discomfort, lower airway discomfort, and eye irritation
<i>Hazard Index target(s)</i>	Respiratory

1.3 Formaldehyde Chronic REL

<i>Reference Exposure Level</i>	9 µg/m³ (7 ppb)
<i>Critical effect(s)</i>	Nasal obstruction and discomfort, lower airway discomfort, and eye irritation
<i>Hazard Index target(s)</i>	Respiratory

2. Physical & Chemical Properties (ATSDR, 1999)

<i>Description</i>	Colorless gas
<i>Molecular formula</i>	CH ₂ O
<i>Molecular weight</i>	30.03 g/mol
<i>Density</i>	0.815 g/L @ -20° C
<i>Boiling point</i>	-19.5° C
<i>Melting point</i>	-92° C
<i>Vapor pressure</i>	3883 mm Hg @ 25° C
<i>Flashpoint</i>	300° C
<i>Explosive limits</i>	7% - 73%
<i>Solubility</i>	soluble in water, alcohol, ether and other polar solvents
<i>Odor threshold</i>	0.05-0.5 ppm
<i>Metabolites</i>	formic acid
<i>Conversion factor</i>	1 ppm in air = 1.24 mg/m ³ @ 25° C

3. Occurrence and Major Uses

Formaldehyde has four major applications: as an intermediate in the manufacture of melamine, polyacetal, and phenolic resins; as an intermediate in the production of industrial chemicals; as a bactericide or fungicide; and as a component in the manufacture of end-use consumer products. Phenol-formaldehyde resins are used in the production of plywood, particleboard, foam insulation, and a wide variety of molded or extruded plastic items. Formaldehyde is also used as a preservative, a hardening and reducing agent, a corrosion inhibitor, a sterilizing agent, and in embalming fluids. Indoor sources include upholstery, permanent press fabrics, carpets, pesticide formulations, urea-formaldehyde foam insulation, and cardboard and paper products. Outdoor sources include emissions from fuel combustion (motor vehicles), industrial fuel combustion (power generators), oil refining processes, and other uses (copper plating, incinerators, etc.). The largest portion of outdoor ambient formaldehyde results from photochemical oxidation of a number of reactive organic gases in the atmosphere (CARB, 2006). According to the California Toxics Inventory (CARB, 2005a), the mean statewide ambient level of formaldehyde in 2004 was 2.69 ppb, with the highest levels (3.76 ppb) reported for the South Coast Air Basin. The California Air Resources Board (CARB) reported statewide emissions of 20,251 tons from stationary and mobile sources (CARB, 2005b).

4. Metabolism

Inhaled formaldehyde reacts rapidly at the site of contact and is efficiently absorbed in the respiratory tract. A portion of the formaldehyde entering the fluid layer covering the respiratory epithelium, the respiratory tract lining fluid (RTLFL), is reversibly hydrated to methylene glycol. Among other components, the RTLFL is rich in antioxidants including glutathione (Cross et al., 1994) with which formaldehyde may reversibly react to form S-hydroxymethylglutathione. Both the hydrated and unreacted formaldehyde may be absorbed into the epithelial layer where there is further opportunity for formaldehyde to bind to glutathione. This glutathione conjugate in turn is oxidized to S-formylglutathione by formaldehyde dehydrogenase. Hydrolysis of S-

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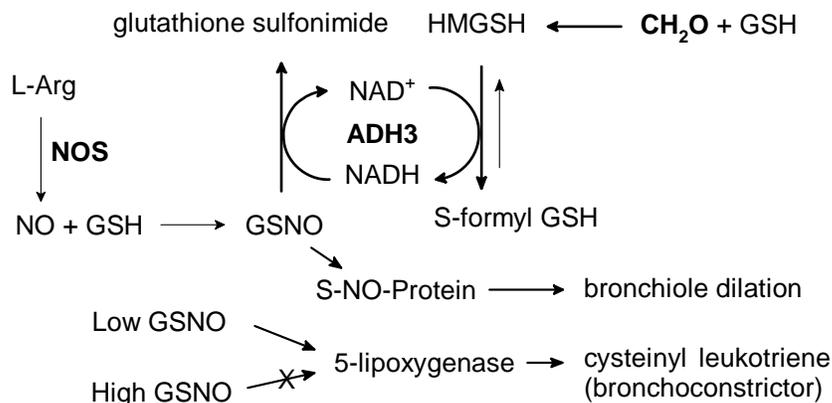
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formylglutathione yields formate and glutathione. Formic acid may be eliminated in urine and feces, or dehydrogenated to CO₂ and exhaled. The presence of glutathione and formaldehyde dehydrogenase in epithelial cells of the respiratory tract varies with location and influences the amount of formaldehyde reaching the blood. While glutathione-bound formaldehyde is rapidly metabolized, free formaldehyde in cells can form DNA-protein cross-links (Franks, 2005).

Formaldehyde dehydrogenase (ADH3), although central to the metabolism of formaldehyde, has a broad specificity that includes the structurally related compound, S-nitrosoglutathione (GSNO), an endogenous bronchodilator and reservoir of nitric oxide (NO) activity (Jensen et al., 1998). In cultured cells, formaldehyde appears to trigger ADH3-mediated GSNO reduction by enzyme-bound cofactor recycling (Staab et al., 2008). As shown in Figure 1, the S-hydroxymethylglutathione (HMGS) formed spontaneously from formaldehyde and glutathione is oxidized by ADH3 with the formation of NADH that may then participate in the ADH3-mediated reduction of GSNO (Thompson and Grafstrom, 2008). (Because of its participation in this reaction, ADH3 is also known as GSNO reductase.) This reductive pathway results in low levels of GSNO that in turn stimulate the production and activity of 5-lipoxygenase, the rate-limiting enzyme in the synthesis of powerful bronchoconstrictors, the cysteinyl leukotrienes. On the other hand, high levels of GSNO inhibit this enzyme and thus the synthesis of the bronchoconstrictors (Zaman et al., 2006). Up-regulation of the degradation of GSNO has been demonstrated in mouse lung following inhalation of formaldehyde (Yi et al., 2007), while low levels of GSNO in the lungs have been associated with severe asthma attacks in children (Gaston et al., 1998) and airway hyperactivity in mice (Que et al., 2005). These results suggest that the potential association of formaldehyde exposure with asthma-like respiratory symptoms is in part due to its effects on NO via the enhanced degradation of GSNO. Nitric oxide has multiple functions in the lungs, from its participation in the regulation of airway and vascular tone to mucin secretion and mucociliary clearance (Reynaert et al., 2005). The dysregulation of NO by formaldehyde helps to explain the variety and variability in the toxic manifestations following formaldehyde inhalation.

Figure 1 Formaldehyde Driven Reduction of GSNO

Oxidation of the glutathione conjugate of formaldehyde, HMGSH, by ADH3 generates NADH that drives the reduction of GSNO, also by ADH3, thereby reducing the nitric oxide available for bronchiole dilation. Low GSNO levels stimulate, but high GSNO levels inhibit 5-lipoxygenase production of cysteinyl leukotriene.

5. Acute Toxicity of Formaldehyde

The acute effects of formaldehyde exposure appear to be largely a result of its irritant properties. However, some individuals experience symptoms following acute exposures that are a result of previous sensitization following acute high formaldehyde exposure, or long term low level exposures. For this reason, some of the studies included in this section describe manifestations of toxicity in which acute exposure was the precipitating event but in which the contribution of previous exposures or sensitization is unknown. Sensitization [manifests as heightened responsiveness and](#) may be of an immunological nature with the development of formaldehyde-specific IgE or IgG (e.g. Thrasher et al. 1987). [Alternatively, heightened responsiveness](#) may be neurologically mediated with involvement of the hypothalamic/pituitary/adrenal axis (Sorg et al., 2001a,b). In addition, genetic variation among individuals in the alcohol dehydrogenases mentioned above affects individual responses to formaldehyde. This is especially germane to studies in which the effects include symptoms such as bronchoconstriction and airway hyperreactivity, and in which there is unexpected individual variation.

Many of the studies described in this document have evaluated the relationship between formaldehyde inhalation and clinically-diagnosed asthma or asthma-like symptoms. Asthma is a chronic disease of airway obstruction resulting in variable airflow that has classically been considered to involve both airway inflammation and airway hyperresponsiveness. [Asthma](#) manifests as a characteristic cough, wheeze, and shortness of breath due to spasmodic contractions of the bronchi and mucus hypersecretion. These symptoms may or may not reflect an underlying allergic response. As shown in the study by Que et al. (2005), the hyperresponsiveness and the inflammation are not necessarily coupled. Although the RELs presented in this document are not based on studies that used asthma as the critical endpoint, uncertainty factors were applied in the REL estimates to explicitly consider the potential of formaldehyde to cause or exacerbate asthma-like wheeze and cough symptoms, especially in

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asthmatic children. We have therefore included discussion of recent work that provides a biochemical mechanism by which formaldehyde exposure is linked to at least one symptom of asthma, bronchoconstriction. The bronchoconstrictive effects of formaldehyde exposure may be partially responsible for the lower airway discomfort reported in the study upon which the 8-hour and chronic RELs are based.

5.1 Acute Toxicity to Adult Humans

In small human studies, exposure to formaldehyde (1-3 ppm) has resulted in eye and upper respiratory tract irritation (Weber-Tschopp et al., 1977; Kulle et al., 1987). Most people cannot tolerate exposures to more than 5 ppm formaldehyde in air; above 10-20 ppm symptoms become severe and shortness of breath occurs (Feinman, 1988). High concentrations of formaldehyde may result in nasal obstruction, pulmonary edema, choking, dyspnea, and chest tightness (Porter, 1975; Solomons and Cochrane, 1984).

A few human case studies report severe pulmonary symptoms. A medical intern with known atopy and exposure to reportedly high (but unspecified) levels of formaldehyde over a period of 1 week developed dyspnea, chest tightness, and edema, following a subsequent 2 hour exposure to formaldehyde (Porter, 1975). Five workers exposed to formaldehyde from newly installed urea-formaldehyde chipboard in a poorly ventilated basement experienced intolerable eye and upper respiratory tract irritation, choking, marked dyspnea, and nasal obstruction (Solomons and Cochrane, 1984). However, the concentration of formaldehyde and the contribution of other airborne chemicals were unknown in both reports.

Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritative and pulmonary effects (Frigas et al., 1984; Sheppard et al., 1984; Sauder et al., 1986; Schachter et al., 1986; Kulle et al., 1987; Sauder et al., 1987; Schachter et al., 1987; Witek et al., 1987; Uba et al., 1989; Harving et al., 1990; Akbar-Khanzadeh et al., 1994). Short exercise sessions during exposure on a bicycle ergometer were included in some of the studies. Concentrations of formaldehyde in the human exposure studies ranged as high as 3 ppm for up to 3 hours. The major findings in these studies were mild to moderate eye and upper respiratory tract irritation typical of mild discomfort from formaldehyde exposure.

Chemosensory irritation and subjective symptoms following exposure to formaldehyde at concentrations relevant to the workplace were examined by Lang et al. (2008) in 11 male and 10 female volunteers. Each subject was exposed for 4 hours to a randomized sequence of ten exposure conditions. These included exposures at concentrations of 0, 0.15, 0.3 and 0.5 ppm, exposures at 0.3 and 0.5 ppm that included four transient peak exposures at 0.6 and 1.0 ppm, respectively, and exposures in the presence of 10 ppm ethyl acetate of 0, 0.3, 0.5, and 0.5 ppm with 1.0 ppm peaks. Objective measures of irritation included conjunctival redness, blinking frequency, nasal flow resistance, pulmonary function, and reaction times. The participant's subjective evaluation of physical and mental wellbeing was assessed by questionnaire before, during and after each day's exposure. To assess the potential influence of personality traits on subjective responses, each subject's positive or negative affectivity was evaluated [with PANAS \(Positive and Negative Affectivity Schedule\) that consists of 10 positive affects \(interested,](#)

[excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active](#)) and 10 negative affects ([distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid](#)). Participants are asked to rate items on a scale from 1 to 5, based on the strength of emotion where 1 = "very slightly or not at all," and 5 = "extremely". [Subjective ratings of eye irritation and olfactory symptoms were significantly higher than control at 0.3 ppm. However, when negative affectivity \(anxiety\) was included as a covariate, eye and olfactory irritation at this exposure level were no longer significant.](#) Conjunctival irritation and blinking frequency, [objective measures of irritation](#), were significantly elevated only with exposure to 0.5 ppm with peaks of 1.0 ppm ($p < 0.05$). The authors considered this level to be a LOAEL. [However, at 0.5 ppm without 1.0 ppm peaks, conjunctival irritation and blinking were not significantly increased so this was considered a NOAEL for these effects.](#) There were no statistically significant changes in nasal resistance, pulmonary function or reaction time. While there were large inter-individual differences in complaints or reports of wellbeing, there were no significant treatment effects. This study identified eye irritation as the most sensitive endpoint, with personality traits, such as negative affectivity, as a modifying factor.

In a human irritation study by Weber-Tschopp et al. (1977), 33 subjects were exposed to formaldehyde at concentrations ranging from 0.03-3.2 ppm (0.04-4.0 mg/m³) for 35 minutes. Thresholds were 1.2 ppm (1.5 mg/m³) for eye and nose irritation, 1.7 ppm (2.1 mg/m³) for eye blinking, and 2.1 ppm (2.6 mg/m³) for throat irritation.

Kulle et al. (1987) exposed nonasthmatic humans to up to 3.0 ppm (3.7 mg/m³) formaldehyde in a controlled environmental chamber for 3 hours. Significant dose-response relationships were seen with odor and eye irritation (Table 5.1) as ranked on symptom questionnaires as none, mild, moderate or severe. Irritation was assessed in this manner prior to exposure, at the end of exposure, and again 24 hour after exposure.

Table 5.1 Mean Symptom Difference ($t_{180}-t_0$) \pm SE with Formaldehyde*
(from Kulle et al., 1987)

	Formaldehyde conc. (ppm)				P value
	0.0	1.0	2.0	3.0	
Odor sensation	0.00 \pm 0.00	0.22 \pm 0.15	0.44 \pm 0.18	1.00 \pm 0.29	<0.0001
Nose/throat irritation	0.00 \pm 0.00	0.11 \pm 0.11	0.33 \pm 0.17	0.22 \pm 0.15	0.054
Eye irritation	0.00 \pm 0.00	0.44 \pm 0.24	0.89 \pm 0.26	1.44 \pm 0.18	<0.0001
Chest discomfort	0.00 \pm 0.00	0.00 \pm 0.00	0.11 \pm 0.11	0.00 \pm 0.00	0.62
Cough	0.00 \pm 0.00	0.11 \pm 0.11	0.00 \pm 0.00	0.00 \pm 0.00	0.11
Headache	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00	0.11 \pm 0.11	0.33

*Presence and severity of symptoms scored as: 0 = none; 1 = mild (present but not annoying); 2 = moderate (annoying); 3 = severe (debilitating). Data from Table II.

At 0.5 ppm for 3 hours, none of 9 subjects had eye irritation. At 1.0 ppm, 3 of 19 subjects reported mild eye irritation and one experienced moderate irritation. At 2.0 ppm, 6 subjects reported mild and 4 reported moderate eye irritation. Measured nasal flow resistance was increased at 3.0 ppm but not at 2.0 ppm (2.5 mg/m³). With respect to the lower respiratory tract, there were no significant decrements in pulmonary function nor increases in methacholine

induced bronchial reactivity as a result of 3-hour exposures to 0.5-3.0 ppm (0.6-3.7 mg/m³) formaldehyde at rest or during exercise, including 24 hours post exposure.

Eleven healthy subjects and nine patients with formalin skin sensitization were exposed to 0.5 mg/m³ (0.4 ppm) formaldehyde for 2 hours (Pazdrak et al., 1993). Nasal lavage was performed prior to and 5 to 10 minutes, 4 hours, and 18 hours after exposure. Rhinitis was reported and increases in the number and proportion of eosinophils, elevated albumin and increased protein levels were noted in nasal lavage fluid 4 and 18 hours after exposure. No differences were found between patients with skin sensitization and healthy subjects.

In a study by Green et al. (1987), volunteer asthmatic and normal subjects exposed to formaldehyde displayed decrements in pulmonary function. Exposure to 3 ppm formaldehyde for 1 hour resulted in clinically significant reductions of forced expiratory volume in one second (FEV₁) (defined as > 20% or more) and FEV₁/forced vital capacity (FVC) (ratio 70% or less) in 5 individuals in the study (2 of 16 asthmatics, 2 of 22 normal subjects, and one clinically normal subject with hyperactive airways). Of these individuals, 3 had reductions of FEV₁ of 20% or more during exposure. One of 22 asthmatics had a greater than 20% reduction in FEV₁ (-25.8%) at 17 minutes into exposure following a 15 minute moderate exercise session (minute ventilation [V_E] = 30-40 l/min), which, according to the authors, was low enough to prevent exercise-induced bronchospasm. One of 22 normal subjects also exhibited a greater than 20% clinically significant reduction in FEV₁ (-24.4%) and in FEV₁/FVC, which occurred at 47 minutes into exposure to 3 ppm formaldehyde. These reductions occurred following a second 15-minute heavy-exercise session (V_E = 60-70 l/min) near the end of the 1 hour exposure period. A third asymptomatic "normal" subject with hyperactive airways had a clinically significant reduction of FEV₁ (-20.5%) at 17 minutes, following the first heavy exercise session. This subject exhibited occult airway hyperactivity and was excluded from analysis with the other exposure groups due to his respiratory condition. Subjects exhibiting reductions in FEV₁ of greater than 20% following exposure also exhibited FEV₁/FVC ratios of less than 70%. However, none of the subjects in the study exhibited a clinically significant reduction of 50% or greater in airway conductance (SG_{aw}) during exposure to 3 ppm formaldehyde.

Kriebel et al. (2001) conducted a subchronic epidemiological study of 38 anatomy class students who, on average, were exposed to a geometric mean of 0.70 ± 2.13 ppm for 2 hours per week over 14 weeks. After class, eye, nose and throat irritation was significantly elevated compared with pre-laboratory session exposures, with a one unit increase in symptom intensity/ppm of formaldehyde. Peak expiratory flow (PEF) was found to decrease by 1%/ppm formaldehyde during the most recent exposure. Changes in PEF and symptom intensity following formaldehyde exposure were most pronounced during the first weeks of the semester but attenuated with time, suggesting partial acclimatization.

Rhinitis and a wide range of respiratory symptoms can result from exposure to formaldehyde. Some studies have reported that workers exposed to low concentrations may develop severe prolonged asthma attacks after prior exposure; this suggests that they may have become sensitized (Feinman, 1988). However, in adults, an association between formaldehyde exposure and allergic sensitization through IgE- and IgG-mediated mechanisms has been observed only

inconsistently (Thrasher et al., 1987; Krakowiak et al., 1998; Wantke et al., 2000; Kim et al., 2001).

Formaldehyde provocation of human subjects, occupationally exposed to formaldehyde and suffering from respiratory symptoms such as wheezing, shortness of breath, or rhinitis, occasionally resulted in pulmonary function decrements (2 to 33% response rate) consistent with immediate, delayed, or both immediate and delayed bronchoconstriction (Hendrick and Lane, 1977; Wallenstein et al., 1978; Burge et al., 1985; Nordman et al., 1985). While some of the concentrations of formaldehyde that elicited a positive response following provocation tests (6 to 20.7 ppm) were quite high, the authors of these studies suggested that formaldehyde-induced bronchial hyperreactivity is due to specific sensitization to the gas. However, none of these studies was able to detect antibodies to formaldehyde which would support that sensitization to formaldehyde occurs through an immunologic pathway. Alternatively, the wheezing and shortness of breath may be related to the formaldehyde-stimulated depletion of the bronchodilator, GSNO, in the airways.

In controlled studies with asthmatics from urea-formaldehyde insulated homes, formaldehyde concentrations equal to or greater than those found in indoor environments have not resulted in hematologic or immunologic abnormalities. These tests include: blood count and differential, erythrocyte sedimentation rate; lymphocyte subpopulations (E-rosetting, T3, T4, T8, B73.1, Fc receptor positive lymphocytes and large granular lymphocytes); lymphocyte response to phytohemagglutinin and formalin-treated red blood cells; serum antibody against the Thomsen-Friedenrich RBC antigen and against formalin-RBC; and natural killer, interferon-boosted natural killer, and antibody-dependent cell-mediated cytotoxicity (Pross et al., 1987). While six of the studies cited above reported decrements in lung function associated with short-term formaldehyde exposure among at least some of the asthmatic subjects, a number of other exposure studies of patients with asthma have failed to demonstrate that exposure to formaldehyde results in onset or aggravation of the patients' asthmatic symptoms (Sheppard et al., 1984; Sauder et al., 1987; Harving et al., 1990; Krakowiak et al., 1998).

The effects of formaldehyde on asthmatics may be dependent on previous, repeated exposure to formaldehyde. Burge et al. (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief durations exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV₁) were observed in 12 occupationally-exposed workers challenged with 2.0 ppm (2.5 mg/m³) formaldehyde (Nordman et al., 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard et al. (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume.

Gorski et al. (1992) evaluated the production of active oxygen species by neutrophils in 18 persons exposed to 0.5 mg/m³ formaldehyde for 2 hours. All 13 subjects who had allergic contact dermatitis (tested positive to formaldehyde in skin patch) exhibited significantly higher

chemiluminescence of granulocytes isolated from whole blood 30 minutes and 24 hours post-exposure than the individuals who were not formaldehyde sensitive. Thus, the immune cellular response of skin-sensitized individuals to an inhalation exposure to formaldehyde indicates increased production of active oxygen species. This is consistent with increasing evidence that endogenous or exogenous reactive oxygen and reactive nitrogen species are responsible for the airway inflammation of asthma (Sugiura and Ichinose, 2008).

In addition to its effects on the respiratory tract, the irritant properties of formaldehyde also manifest as ocular irritation. In an anatomy dissecting laboratory, formaldehyde levels were found to peak at 0.62 ppm, with a gradual decrease to 0.11 ppm. Formaldehyde-related irritation of the eyes, nose, throat, airways and skin was reported by 59% of the students. These effects were significantly ($p < 0.001$) higher among wearers of contact lenses compared with students without glasses or wearing glasses (Tanaka et al., 2003). The ability of contact lenses to trap and concentrate volatile compounds, and to extend the exposure time by limiting the eye's normal self-cleansing, may make contact lens wearers more susceptible to ocular exposure and irritation by formaldehyde.

5.2 Acute Toxicity to Infants and Children

No studies of the effects of acute exposure to formaldehyde in children or young experimental animals were located. However, as noted above for adults, there is evidence that following acute exposure to formaldehyde, asthmatics and others previously sensitized to formaldehyde may be more likely to show respiratory symptoms such as wheezing, shortness of breath, rhinitis, and/or decrements in pulmonary function consistent with immediate and/or delayed bronchoconstriction (Nordman et al., 1985; Burge et al., 1985; Hendrick and Lane, 1977; Wallenstein et al., 1978). Furthermore, some asthmatics may respond with significant reductions in lung function due to the irritant effects on asthma, sensitized or not. Additionally, the depletion of the endogenous bronchodilator, GSNO, following formaldehyde exposure may be particularly important in children. Gaston et al. (1998) compared concentrations of tracheal S-nitrosothiol concentrations in eight asthmatic children in respiratory failure with those of 21 non-asthmatic children undergoing elective surgery. In asthmatic children, the metabolism of GSNO was accelerated and the mean S-nitrosothiol concentrations significantly lower compared to normal children (65 ± 45 vs 502 ± 429 nmol/l). Thus asthmatic children, with low levels of GSNO, are expected to be unusually vulnerable to any further depletion of GSNO caused by formaldehyde.

The potential association between formaldehyde exposure and asthma is of special concern for children since, as noted in OEHHA (2001): "*OEHHA considers asthma to impact children more than adults. Children have higher prevalence rates of asthma than do adults (Mannino et al., 1998). In addition, asthma episodes can be more severe due to the smaller airways of children, and result in more hospitalizations in children, particularly from the ages of 0 to 4 years, than in adults (Mannino et al., 1998).*" Thus children, particularly asthmatic children, may be at greater risk from acute exposure to formaldehyde.

5.3 Acute Toxicity to Experimental Animals

Acute exposures of experimental animals to formaldehyde are associated with changes in pulmonary function (decreased respiratory rate, increased airway reactivity and resistance) at low concentrations, while pulmonary edema and death have been reported at high concentrations. Neurochemical and neurobehavioral changes have also been observed.

In 72 rats exposed to approximately 600-1,700 mg/m³ (500-1,400 ppm) formaldehyde vapor for 30 minutes, the LC₅₀ was found to be 1,000 mg/m³ (800 ppm) (Skog, 1950). The first deaths did not occur until 6 hours after cessation of exposure. Respiratory difficulty lasted several days after exposure and the last of 49 rats died after 15 days of purulent bronchitis and diffuse bronchopneumonia. Three weeks following exposure, histological examinations of the 23 surviving animals revealed bronchitis, pulmonary microhemorrhages, and edema. No changes were seen in other organs.

A multispecies study by Salem and Cullumbine (1960) showed that a 10-hour exposure to 15.4 ppm (19 mg/m³) formaldehyde vapor killed 3 out of 5 rabbits, 8 of 20 guinea pigs, and 17 of 50 mice. The report stated that formaldehyde exposure resulted in delayed lethality.

Alarie (1981) determined the 10 minute LC₅₀ for formaldehyde in mice to be 2,162 ppm (95% confidence interval, 1,687-2,770 ppm). The post-exposure observation period was 3 hours. From the concentration mortality graph provided in the report, an MLE₀₅ and BC₀₅ of 1,440 ppm and 778 ppm, respectively, could be estimated for a 10-minute formaldehyde exposure. However, as indicated in the previous reports, delayed deaths occur with formaldehyde which suggests that the 3-hour post-exposure observation period used in this study may not have been long enough.

In other lethality studies, Nagorny et al. (1979) determined a 4-hour formaldehyde LC₅₀ in rats and mice to be 588 mg/m³ (474 ppm) and 505 mg/m³ (407 ppm), respectively. However, the raw data for this study were not included in the report. Horton et al. (1963) observed that a 2-hour exposure of mice to 0.9 mg/l (900 mg/m³) formaldehyde resulted in deaths from massive pulmonary hemorrhage and edema, but a 2 hour exposure to 0.14 mg/l (140 mg/m³) did not produce signs of "substantial distress."

Swiecichowski et al., (1993) exposed groups of five to seven guinea pigs to 0.86, 3.4, 9.4, 31.1 ppm (1.1, 4.2, 11.6, 38.6 mg/m³) formaldehyde for 2 hours, or to 0.11, 0.31, 0.59, 1.05 ppm (0.14, 0.38, 0.73, 1.30 mg/m³) formaldehyde for 8 hours. An 8-hour exposure to levels greater than or equal to 0.3 ppm (≥ 0.4 mg/m³) formaldehyde was sufficient to produce a significant increase in airway reactivity. Similar effects occurred after greater than 9 ppm (> 11 mg/m³) formaldehyde for the 2-hour exposure group. Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine (or carbachol) *ex vivo*. No inflammation or epithelial damage was seen up to 4 days after exposure. The researchers suggest that duration of exposure is important to the induction of airway hyperreactivity and that prolonged (8-hour), low-level exposures may generate abnormal physiologic responses in the airways not detectable after acute (2-hour) exposures.

Male F-344 rats, 7-9 weeks old, were exposed to 0.5, 2, 6 or 15 ppm formaldehyde for 6 hours per day for 1 to 4 days (Monteiro-Riviere and Popp, 1986). Effects noted in the rat nasal respiratory epithelium with 0.5 or 2 ppm were limited to altered cilia with occasional wing-like projections on the ends of the ciliary shafts. Effects noted at 6 ppm for 1 day were autophagic vacuoles in some basal cells, neutrophils in the basal and suprabasal layers, and hypertrophy of goblet and ciliated cells. Loss of microvilli in ciliated cells was noted at all exposure concentrations.

Rats were exposed to 0, 5, 10 or 20 ppm formaldehyde for 3 hours per day on 2 consecutive days (Boja et al., 1985). Decreased motor activity and neurochemical changes in dopamine and 5-hydroxytryptamine neurons were reported.

The effects of formaldehyde inhalation on open-field behavior in mice were examined by Malek et al. (2004) 2 and 24 hours after a single 2-hour exposure to 0, 1.1, 2.3 or 5.2 ppm. Two hours after exposure there were significant decreases in rearing and in several measures of exploratory behavior, with evidence of dose-dependence in all dose groups compared with controls. At 24 hours, there were still significant differences between dosed and control mice but the dose-dependence was no longer evident.

Nielson et al. (1999) analyzed the breathing patterns of Balb/c mice exposed to 0.2-13 ppm formaldehyde and found a concentration-dependent decrease in respiratory rate of 32.9%/log concentration. In the range of 0.3-4.0 ppm, the decrease in respiratory rates was attributable to sensory irritation. Above 4.0 ppm, bronchoconstriction also contributed to the decreased breathing rate. The authors suggest a NOEL of 0.3 ppm for these effects in mice.

Amdur (1960) exposed groups of 4 to 18 guinea pigs to formaldehyde at 0.05, 0.31, 0.58, 1.22, 3.6, 11.0, or 49 ppm formaldehyde for one hour. Resistance to flow and lung compliance were calculated from measures of intrapleural pressure, tidal volume, and rate of flow to the lungs at the end of exposure and one hour later. Resistance and compliance were significantly different from the control level for the 0.31 ppm exposure ($p < 0.05$) and increasingly significant at higher concentrations. One hour later, only the 49 ppm exposure remained significant ($p < 0.01$). In addition, the tracheas of groups of 6 to 10 guinea pigs were cannulated and exposed for one hour to 0.90, 5.2, 20, or 50 ppm formaldehyde, and 1.14 or 3.6 ppm formaldehyde with 10 mg/m³ sodium chloride. With the protective effect of the trachea bypassed, the resistance and compliance changed substantially. The addition of sodium chloride further enhanced the effect, including a significant effect after one hour for the 1.14 ppm formaldehyde exposure. These results show that formaldehyde that reaches the lungs has a marked effect on airways resistance and compliance in addition to an effect on the upper airways.

Riedel et al. (1996) studied the influence of formaldehyde exposure on allergic sensitization in guinea pigs. Three groups of guinea pigs (12/group) were exposed to clean air or two different formaldehyde concentrations (0.13 and 0.25 ppm) over five consecutive days. Following exposure, the animals were sensitized to allergen by inhalation of 0.5% ovalbumin (OA). Three weeks later the animals were subjected to bronchial provocation with OA and specific anti-OA-IgG1 (reaginic) antibodies in serum were measured. In another group of six animals, the respiratory tract was examined histologically for signs of inflammation directly after the end of

formaldehyde or clean air exposure. In the group exposed to 0.25 ppm formaldehyde, 10/12 animals were found to be sensitized to OA (positive reaction on specific provocation) vs. 3/12 animals in the control group ($P < 0.01$). Furthermore, compressed air measurements of specific bronchial provocation and serum anti-OA-antibodies were significantly higher in the 0.25 ppm formaldehyde group than in controls. The median for compressed air measurement was 0.35 ml for the formaldehyde-exposed group vs. 0.09 ml for the controls ($p < 0.01$), indicating increased bronchial obstruction. The median for the anti-OA-IgG1 measured in the formaldehyde-exposed group was 13 vs. less than 10 EU in the controls, ($p < 0.05$), indicating enhanced sensitization. In the group exposed to 0.13 ppm formaldehyde, no significant difference was found compared to the control group. Histological examination found edema of the bronchial mucosa, but there was no sign of inflammation of the lower airways in formaldehyde-exposed guinea pigs. The investigators concluded that short-term exposure to a low concentration of formaldehyde (0.25 ppm) can significantly enhance sensitization to inhaled allergens in the guinea pig.

As described in Section 5, the main formaldehyde-metabolizing enzyme, ADH3, also reduces the endogenous bronchodilator GSNO. To examine the role of GSNO and ADH3 (known in this study as GSNO reductase, GSNOR) in airway tone and asthma, Que et al. (2005) used wild type mice and mice with a targeted deletion of GSNOR (GSNOR^{-/-}). Following a challenge with allergen (ovalbumin), GSNOR activity in bronchoalveolar lavage fluid from wild type mice increased significantly ($p < 0.05$) compared to buffer (PBS) controls, while as expected, no GSNOR activity was detected in the GSNOR^{-/-} mice with either treatment. Levels of S-nitrosothiols (SNO) were assayed in homogenates of lung tissues from both types of mouse and found to be barely detectable with PBS treatment. However, after ovalbumin challenge, SNO levels were significantly higher ($p < 0.02$) in GSNOR^{-/-} mice compared to wild type, indicating metabolism of SNOs by GSNOR under “asthmatic-like” conditions in wild type mice. Metabolism of GSNO results in a loss of bronchodilation capacity. Deletion of GSNOR had no effect on NO generation by NO synthase as there were no differences between wild type and GSNOR^{-/-} mice in nitrate or nitrite levels regardless of treatment. To investigate the effects of deletion of GSNOR on airway hyper-responsiveness, pulmonary resistance was measured at baseline (PBS) and after methacholine challenge, with and without ovalbumin treatment. At baseline, there was no difference among mouse types and treatments, while at higher methacholine levels (100-1000 $\mu\text{g}/\text{kg}$), pulmonary resistance was found to be significantly lower ($p < 0.001$) in GSNOR^{-/-} mice than in wild type, presumably due to higher GSNO levels that enhance bronchodilation. Importantly, ovalbumin caused a marked increase in airway responsiveness in wild type mice but had little effect in GSNOR^{-/-} mice. This indicates that GSNOR regulates basal airway tone as well as hyper-responsiveness to both allergen challenge and bronchoconstrictor agonists. It is also noteworthy that the total number and composition of leukocytes, levels of interleukin-13 and total serum IgE were comparable between wild type and GSNOR^{-/-} mice. This indicates that protection from asthma in the GSNOR^{-/-} mice is not a result of a suppressed response to allergen, and that SNOs, especially GSNO, can preserve airway patency in the presence of inflammation. Thus the inflammatory response is not linked to hyper-responsiveness as long as adequate levels of GSNO are maintained.

A connection between formaldehyde and the activity of GSNOR described in the study above by Que et al., was outlined by Thompson and Grafstrom (2008) and supported by Yi et al. (2007) and Staab et al. (2008). In the study by Yi and associates, groups of 6 mice were exposed to

formaldehyde at 0, 1, or 3 mg/m³ continuously for 72 hours. Following exposure, lungs were isolated to allow measurement of GSNOR mRNA levels by RT-PCR, and enzymatic activity with GSNO. Formaldehyde at 3 mg/m³ significantly increased the numbers of GSNOR transcripts compared to control (0.58 vs 0.4 GSNOR/ β actin; $p < 0.05$), while GSNO reduction of GSNO showed a significant dose-dependent increase with formaldehyde concentration ($p < 0.01$). The stimulation of GSNO reduction by formaldehyde was also observed by Staab et al. (2008) in an in vitro study using recombinant human GSNOR. In this study, GSNO levels in buccal carcinoma cells were reduced in a dose-dependent fashion following a 1 hour exposure to formaldehyde in the 1-5 mM range with significance at 5 mM ($p < 0.05$). The results from this study support a model in which formaldehyde (as the glutathione conjugate, HMGS) is oxidized by GSNOR (ADH3) in the presence of high levels of NAD⁺, producing NADH. This process was found to be accelerated by high levels of GSNO. GSNO is in turn reduced with the oxidation of NADH to form glutathione sulfonamide. Formaldehyde thus depletes cellular SNO (in the form of GSNO) which results in dysregulation of NO signaling pathways.

6. Chronic Toxicity of Formaldehyde

6.1 Chronic Toxicity to Adult Humans

Formaldehyde primarily affects the mucous membranes of the upper airways and eyes. Exposed populations that have been studied include embalmers, residents in houses insulated with urea-formaldehyde foam, anatomy class students, histology technicians, wood and pulpmill workers, and asthmatics. A number of studies describing these effects have been briefly summarized below. For the sake of brevity, only the studies that best represent the given effects are presented. Formaldehyde is also a recognized carcinogen (IARC, 2006), however, this document will address only its non-carcinogenic properties.

In the study chosen for determination of the 8-hour and chronic RELs, nasal obstruction and discharge, and frequency of cough, wheezing, and symptoms of bronchitis were reported in 66 workers in a formaldehyde production plant exposed for 1-36 years (mean = 10 years) to a mean concentration of 0.21 ppm (0.26 mg/m³) formaldehyde (Wilhelmsson and Holmstrom, 1992). All workers were exposed almost exclusively to formaldehyde, the concentrations of which were measured in the ambient air of the worksite with personal sampling equipment. Referents consisted of 36 office workers in a government office with exposure to a mean concentration of 0.07 ppm (0.09 mg/m³) formaldehyde, and no industrial solvent or dust exposure. Symptom data, collected by questionnaire, were separated into general and work-related, and allowed identification of individuals with atopy and mucosal hyperreactivity. The critical effects from chronic exposure to formaldehyde in this study included nasal obstruction, lower airway discomfort, and eczema or itching. The frequency of reported lower airway discomfort (intermittent cough, wheezing, or symptoms of chronic bronchitis) was significantly higher among formaldehyde-exposed vs non-exposed workers (44 vs 14%; $p < 0.01$) (Table 6.1). Work-related nasal discomfort also was significantly higher in the formaldehyde group (53%) compared with the referent group (3%; $p < 0.001$). Similarly, work-related eye discomfort was 20% in the formaldehyde group but nonexistent among referents. The significant increase in symptoms of nasal discomfort in exposed workers did not correlate with total serum IgE antibody levels. However, two exposed workers, who complained of nasal discomfort, had

elevated IgE levels. The investigators concluded that formaldehyde can induce nonspecific nasal hypersensitivity.

Table 6.1.1 Symptoms of Formaldehyde Exposure vs Reference Group
(from Wilhelmsson and Holmstrom, 1992)

	Formaldehyde	Reference	Rate difference	
	% (n=66)	% (n=36)	%	95% CI
General nasal discomfort	67	25	42	24-60
Workplace nasal discomfort	53	3	50	37-63
General lower airway discomfort	44	14	30	14-47
Workplace lower airway discomfort	33	3	28	15-40
General eye discomfort	24	6	18	6-36
General skin discomfort	36	11	25	10-41

In a cross-sectional study supportive of these results, Edling et al. (1988) reported histopathological changes in nasal mucosa of workers (n=75) occupationally exposed to formaldehyde (one wood laminating plant) or formaldehyde plus wood dust (two particle board plants). Ambient formaldehyde measurements in these three composite wood processing plants between 1975 and 1983 gave a time-weighted average (TWA) of 0.1-1.1 mg/m³ (0.08- 0.89 ppm) with peaks of up to 5 mg/m³ (4 ppm). The exposed workers were compared on the basis of medical and work histories, clinical examinations and nasal biopsies to 25 workers selected with regard to age and smoking habits but without occupational formaldehyde exposure.

Based on the histories, there was a high frequency of eye and upper airway symptoms among workers. Nasal symptoms (running nose and crusting) associated with formaldehyde exposure were reported in 60% of the workers, while 75% complained of lacrimation. Clinical examinations revealed grossly normal nasal mucosa in 75% of the cases while 25% had swollen or dry changes, or both, to the nasal mucosa. Histological examination (Table 6.2) revealed that only 3 of the 75 formaldehyde-exposed workers had normal, ciliated pseudostratified epithelium. Squamous metaplasia was reportedly observed in 59, while 6 showed mild dysplasia, and in 8 there was loss of ciliated cells and goblet cell hyperplasia. The histological grading showed a significantly higher score for nasal lesions among workers with formaldehyde exposure when compared with the referents (2.9 versus 1.8; p < 0.05). Exposed smokers had a higher, but non-significant, score than ex-smokers and non-smokers.

While the mean exposure time was 10.5 years (range 1-39 yr), there was no discernable difference among histology scores as a function of years of employment. The histology scores were also not different between workers in the particle board plants, exposed to both formaldehyde and wood dust, and workers in the laminate plant with exposure only to formaldehyde. The authors thus attribute the pathological changes in the nasal mucosa and the other adverse effects to formaldehyde alone in the 0.1-1.1 mg/m³ range.

Table 6.1.2 Distribution of Histological Characteristics Associated with Formaldehyde Exposure (from Edling et al., 1988)

Histological characteristic	Grading score	Point score	Workers	%
Normal respiratory epithelium	0	0	3	4
Loss of ciliated cells	1	1	8	11
Mixed cuboidal/squamous epithelium, metaplasia	2	2	24	32
Stratified squamous epithelium	3	3	18	24
Keratosis	4	4	16	21
Budding of epithelium	add 1	5	0	0
Mild or moderate dysplasia	6	6	6	8
Severe dysplasia	7	7	0	0
Carcinoma	8	8	0	0

Histological changes in the nasal mucosa of formaldehyde-exposed workers were also reported by Boysen et al. (1990). In this study, nasal biopses were collected from 37 workers with 5 or more years of occupational formaldehyde exposure (0.5 - > 2 ppm) and compared with age-matched, unexposed controls who otherwise had similar environmental exposures and smoking habits. Histological changes in the nasal epithelium were scored as indicated in Table 6.1.3.

Table 6.1.3 Types of Nasal Epithelia and Scoring (from Boysen et al., 1990)

Types of epithelia	Histological score
Pseudostratified columnar	0
Stratified cuboidal	1
Mixed stratified cuboidal/stratified squamous	2
Stratified squamous, non-keratinizing	3
Stratified squamous, keratinizing	4
Dysplasia	5

As shown by the histological scoring in Table 6.1.4 below, metaplastic changes in the nasal epithelium were more pronounced in the formaldehyde-exposed workers although this difference did not reach statistical significance.

Table 6.1.4 Histological Scores of Nasal Epithelia

	No	Histological score						Mean
		0	1	2	3	4	5	
Exposed	37	3	16	5	9	1	3	1.9
Controls	37	5	17	10	5	0	0	1.4

Rhinoscopic examination revealed hyperplastic nasal mucosa in 9 of 37 formaldehyde-exposed workers but in only 4 of the controls. In addition, the incidence of subjective nasal complaints

was significantly ($p < 0.01$) higher in the exposed group. While the small size of this study, and the small amount of the nasal mucosa accessible to biopsy limited its ability to detect formaldehyde-related histopathology, the results are consistent with the histopathologies reported by Edling et al. above.

In another occupational health study (Grammer et al., 1990), 37 workers, who were exposed for an unspecified duration to formaldehyde concentrations in the range of 0.003 to 0.073 ppm, reported ocular irritation. However, no significant serum levels of IgE or IgG antibodies to formaldehyde-human serum albumin were detected.

Kerfoot and Mooney (1975) reported that estimated formaldehyde exposures of 0.25-1.39 ppm evoked numerous complaints of upper respiratory tract and eye irritation among seven embalmers at six different funeral homes. Three of the seven embalmers in this study reportedly had asthma. Levine et al. (1984) examined the death certificates of 1477 Ontario undertakers. Exposure measurements taken from a group of West Virginia embalmers were used as exposure estimates for the embalming process, ranging from 0.3-0.9 ppm (average 1-hour exposure) and 0.4-2.1 ppm (peak 30-minute exposure). Mortality due to non-malignant diseases was significantly elevated due to a two-fold excess of deaths related to the digestive system. The authors suggest increased alcoholism could have contributed to this increase.

Ritchie and Lehnen (1987) reported a dose-dependent increase in health complaints (eye and throat irritation, and headaches) in 2000 residents living in 397 mobile and 494 conventional homes. Complaints of symptoms of irritation were noted at concentrations of 0.1 ppm formaldehyde or above. Similarly, Liu et al. (1991) found that exposure to 0.09 ppm (0.135 mg/m³) formaldehyde exacerbated chronic respiratory and allergy problems in residents living in mobile homes.

Employees of mobile day-care centers (66 subjects) reported increased incidence of eye, nose and throat irritation, unnatural thirst, headaches, abnormal tiredness, menstrual disorders, and increased use of analgesics as compared to control workers (Olsen and Dossing, 1982). The mean formaldehyde concentration in these mobile units was 0.29 ppm (0.43 mg/m³) (range = 0.24 - 0.55 mg/m³). The exposed workers were exposed in these units for a minimum of 3 months. A control group of 26 subjects in different institutions was exposed to a mean concentration of 0.05 ppm (0.08 mg/m³) formaldehyde.

Occupants of houses insulated with urea-formaldehyde foam insulation (UFFI) (1726 subjects) were compared with control subjects (720 subjects) for subjective measures of irritation, measures of pulmonary function (FVC, FEV₁, FEF₂₅₋₇₅, FEF₅₀), nasal airway resistance, odor threshold for pyridine, nasal cytology, and hypersensitivity skin-patch testing (Broder et al., 1988). The mean length of time of exposure to UFFI was 4.6 years. The mean concentration of formaldehyde in the UFFI-exposed group was 0.043 ppm, compared with 0.035 ppm for the controls. A significant increase in symptoms of eye, nose and throat irritation was observed in subjects from UFFI homes, compared with controls. No other differences from control measurements were observed.

Alexandersson and Hedenstierna (1989) evaluated symptoms of irritation, spirometry, and immunoglobulin levels in 34 wood workers exposed to formaldehyde over a four-year period. Exposure to 0.4 - 0.5 ppm formaldehyde resulted in significant decreases in FVC, FEV₁, and FEF₂₅₋₇₅. Removal from exposure for four weeks allowed for normalization of lung function in the non-smokers.

Kriebel et al. (2001) conducted a subchronic epidemiological study of 38 anatomy class students who, on average, were exposed to a geometric mean of 0.70 ± 2.13 ppm formaldehyde for two hours per week over fourteen weeks. After class, eye, nose and throat irritation was significantly elevated compared with pre-laboratory session exposures, with a one unit increase in symptom intensity/ppm formaldehyde. Peak respiratory flow (PEF) was found to decrease by 1%/ppm formaldehyde during the most recent exposure. Changes in PEF and symptom intensity following formaldehyde exposure were most pronounced during the first week of the semester but attenuated with time, suggesting partial acclimatization.

Histology technicians (280 subjects) were shown to have reduced pulmonary function, as measured by FVC, FEV₁, FEF₂₅₋₇₅, and FEF₇₅₋₈₅, compared with 486 controls (Kilburn et al., 1989). The range of formaldehyde concentrations was 0.2 - 1.9 ppm, volatilized from formalin preservative solution.

Malaka and Kodama (1990) investigated the effects of formaldehyde exposure in plywood workers (93 exposed, 93 controls) exposed for 26.6 years, on average, to 1.13 ppm (range = 0.28 - 3.48 ppm). Fifty-three smokers were present in both exposed and control groups. Exposure assessment was divided into three categories: high (> 5 ppm), low (< 5 ppm), and none (reference group). Subjective irritation and pulmonary function tests were performed on each subject, and chest x-rays were taken of ten randomly selected volunteers from each group. Respiratory symptoms of irritation were found to be significantly increased in exposed individuals, compared with controls. In addition, exposed individuals exhibited significantly reduced FEV₁, FEV₁/FVC, and forced expiratory flow rate at 25% through 75% of FVC (FEF₂₅₋₇₅), compared with controls. Forced vital capacity was not significantly reduced. Pulmonary function was not found to be different after a work shift, compared to the same measurement taken before the shift. No differences in chest x-rays were observed between exposed and control workers.

Occupational exposure to formaldehyde concentrations estimated to be 0.025 ppm (0.038 mg/m³) for greater than six years resulted in complaints by 22 exposed workers of respiratory, gastrointestinal, musculoskeletal, and cardiovascular problems, and in elevated formic acid excretion in the urine (Srivastava et al., 1992). A control group of twenty seven workers unexposed to formaldehyde was used for comparison. A significantly higher incidence of abnormal chest x-rays was also observed in formaldehyde-exposed workers compared with controls.

Chemical plant workers (70 subjects) were exposed to a mean of 0.17 ppm (0.26 mg/m³) formaldehyde for an unspecified duration (Holmstrom and Wilhelmsson, 1988). Compared with 36 control workers not exposed to formaldehyde, the exposed subjects exhibited a higher

frequency of eye, nose, and deep airway discomfort. In addition, the exposed subjects had diminished olfactory ability, delayed mucociliary clearance, and decreased FVC.

Alexandersson et al. (1982) compared the irritant symptoms and pulmonary function of 47 carpentry workers exposed to a mean concentration of formaldehyde of 0.36 ppm (range = 0.04 - 1.25 ppm) with 20 unexposed controls. The average length of employment for the exposed workers was 5.9 years. Symptoms of eye and throat irritation as well as airway obstruction were more common in exposed workers. In addition, a significant reduction in FEV₁, FEV₁/FVC, and MMF was observed in exposed workers compared with controls.

Horvath et al. (1988) compared subjective irritation and pulmonary function in 109 workers exposed to formaldehyde with similar measures in a control group of 254 subjects. The formaldehyde concentrations for the exposed and control groups were 0.69 ppm (1.04 mg/m³) and 0.05 ppm (0.08 mg/m³), respectively. Mean formaldehyde concentration in the pre-shift testing facility and the state (Wisconsin) ambient outdoor - formaldehyde level were both 0.04 ppm (0.06 mg/m³). Duration of formaldehyde exposure was not stated. Subjects were evaluated pre- and post work-shift and compared with control subjects. Significant differences in symptoms of irritation, FEV₁, FEV₁/FVC ratio, FEF₅₀, FEF₂₅, and FEF₇₅ were found when comparing exposed subjects' pre- and post work-shift values. However, the pre-workshift values were not different from controls.

The binding of formaldehyde to endogenous proteins creates haptens that can elicit an immune response. Chronic exposure to formaldehyde has been associated with immunological hypersensitivity as measured by elevated circulating IgG and IgE autoantibodies to human serum albumin (Thrasher et al., 1987). In addition, a decrease in the proportion of T-cells was observed, indicating altered immunity. Thrasher et al. (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts in patients occupationally exposed, or residents of mobile homes or of homes containing particleboard sub-flooring. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

An epidemiological study of the effects of formaldehyde on 367 textile and shoe manufacturing workers employed for a mean duration of 12 years showed no significant association between formaldehyde exposure, pulmonary function (FVC, FEV₁, and PEF) in normal or asthmatic workers, and occurrence of specific IgE antibodies to formaldehyde (Gorski and Krakowiak, 1991). The concentrations of formaldehyde did not exceed 0.5 ppm (0.75 mg/m³).

Workers (38 total) exposed for a mean duration of 7.8 years to 0.11 - 2.12 ppm (mean = 0.33 ppm) formaldehyde were studied for their symptomatology, lung function, and total IgG and IgE levels in the serum (Alexandersson and Hedenstierna, 1988). The control group consisted of 18 unexposed individuals. Significant decrements in pulmonary function, FVC ($p < 0.01$) and FEV₁ ($p < 0.05$) were observed, compared with the controls. Eye, nose, and throat irritation was also reported more frequently by the exposed group. No correlation was found between duration of exposure, or formaldehyde concentration, and the presence of IgE and IgG antibodies.

As described in section 5.1, chronic or repeated exposure to formaldehyde may influence the response of asthmatics to acute or short-term challenges. In the study by Burge et al. (1985) late asthmatic reactions were noted in 3 out of 15 occupationally exposed workers after short-duration exposure to 1.5 – 20.6 ppm formaldehyde. Similarly, among workers with occupational exposure to formaldehyde, asthmatic responses (decreased PEF, FVC, and FEV₁) were reported in 12 workers challenged with 1.67 ppm (2.5 mg/m³) formaldehyde (Nordman et al., 1985) and in 5 of 28 hemodialysis workers following challenge with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In contrast, Sheppard et al. (1984) found that in asthmatics not occupationally exposed to formaldehyde, a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume. Thus individuals with chronic formaldehyde exposure may be at greater risk for adverse responses to acute exposures. These individuals may have been sensitized immunologically, as in the cases of elevated circulating antibodies, or [rendered](#) neurologically [hyperresponsive](#), following repeated or chronic exposures to formaldehyde (Sorg et al., 2001a,b).

6.2 Chronic Toxicity to Infants and Children

There are few studies that compare the effects of chronic formaldehyde exposure on children versus adults. Among those that do there is evidence that children are more susceptible to the adverse effects of chronic exposure. Krzyzanowski et al. (1990) assessed chronic pulmonary symptoms and function in 298 children (6-15 years of age) and 613 adults (> 15 years of age) in relation to measured formaldehyde levels in their homes. Information on pulmonary symptoms and doctor-diagnosed asthma and chronic bronchitis was collected by questionnaire. Pulmonary function was assessed as peak expiratory flow rates (PEFR) measured up to four times a day. The prevalence of chronic respiratory symptoms in children was not related to formaldehyde levels measured in tertiles (< 40, 41-60, > 60 ppb). However, doctor-diagnosed asthma and chronic bronchitis were more prevalent in houses with elevated formaldehyde (p for trend < 0.02). This effect was driven by the high disease prevalence observed in homes with kitchen formaldehyde levels >60 ppb, and was especially pronounced among children with concomitant exposure to environmental tobacco smoke (Table 6.2.1). By comparison, in adults, while the prevalence rates of chronic cough and wheeze were somewhat higher in houses with higher formaldehyde, none of the respiratory symptoms or diseases was significantly related to formaldehyde levels.

Table 6.2.1 Prevalence Rate (per 100) of Diagnosed Bronchitis and Asthma in Children with Formaldehyde (from Krzyzanowski et al., 1990)

Bronchitis	Formaldehyde (ppb)			P value X^2 trend
	≤ 40 (N)	41-60 (N)	>60 (N)	
Household mean	3.5 (258)	17.2 (29)	9.1 (11)	<0.02
Main room mean	3.2 (253)	15.6 (32)	9.1 (11)	<0.01
Bedroom mean	3.8 (262)	16.0 (25)	9.1 (11)	<0.04
Subject's bedroom	4.7 (256)	6.7 (30)	11.1 (9)	>0.35
Kitchen	3.5 (255)	0 (22)	28.6 (21)	<0.001
No ETS	4.3 (141)	0 (12)	10.0 (10)	>0.40
ETS	1.9 (106)	0 (10)	45.5 (11)	<0.001
Asthma				
All children	11.7 (256)	4.2 (24)	23.8 (21)	<0.03
No ETS	8.5 (142)	8.3 (12)	0 (10)	>0.50
ETS	15.1 (106)	0 (12)	45.5 (11)	<0.05

In a random effects model, Krzyzanowski et al. (1990) reported that lung function (PEFR) in children, but not adults, was significantly decreased by formaldehyde (coefficient ± SE: -1.28 ± 0.46 vs 0.09 ± 0.27). Measurements of PEFR in the morning suggested that children with asthma ($n = 4$) were more severely affected than healthy children (coefficient ± SE: -1.45 ± 0.53 vs 0.09 ± 0.15) (Table 6.2.2). Compared to children, the effects of formaldehyde on pulmonary function in adults were smaller, transient, limited to morning measurements, and generally most pronounced among smokers exposed to the higher levels of formaldehyde. These studies suggest that children may be more susceptible to the effects of chronic formaldehyde exposure on lung function than are adults.

Table 6.2.2 Relation of PEFR (L/min) to Indoor Formaldehyde (from Krzyzanowski et al., 1990)

Factor	Child coefficient ± SE	Adult coefficient ± SE
HCHO house mean	-1.28 ± 0.46	0.09 ± 0.27
Morning vs bedtime	-6.10 ± 3.0	-5.90 ± 1.10
HCHO bdrm mean/morning	0.09 ± 0.15	-0.07 ± 0.04
HCHO bdrm mean/morning/asthma	-1.45 ± 0.53	

Among studies of children only, a case-control study by Rumchev et al. (2002) examined risk factors for asthma among young children (6 mo- 3 yr). Cases included children with clinically-diagnosed asthma, and controls were children of the same age group without such a diagnosis. Formaldehyde levels were measured in the homes, once in summer and once in winter. Questionnaires were used to assess potential risk factors for asthma and to collect parental reports of respiratory symptoms characteristic of asthma (cough, shortness of breath, wheeze, runny nose, trouble breathing, and hay fever) in their children. Formaldehyde levels were higher in the homes of children exhibiting respiratory symptoms. Estimates of the relative risk for clinically-diagnosed asthma (odds ratios) were adjusted for measured indoor air pollutants,

relative humidity, temperature, atopy, family history of asthma, age, gender, socioeconomic status, pets, smoke exposure, air conditioning, and gas appliances. Compared with children exposed to < 8 ppb, children in homes with formaldehyde levels > 49 ppb had a 39% higher risk of asthma ($p < 0.05$) after adjusting for common asthma risk factors.

Franklin et al. (2000) measured exhaled nitric oxide (eNO) levels in 224 children 6-13 years of age as an indicator of inflammation of the lower airways following chronic low-level formaldehyde exposure in the home. While there was no effect of formaldehyde on lung function measured by spirometry, eNO was significantly higher in children from homes with average formaldehyde levels ≥ 50 ppb compared with those from homes with levels ≤ 50 ppb (15.5 ppb eNO vs 8.7; $p = 0.02$).

Garrett et al. (1999) examined the association between formaldehyde levels at home (median $15.8 \mu\text{g}/\text{m}^3$; maximum $139 \mu\text{g}/\text{m}^3$) and atopy and allergic sensitization in 148 children, 7-14 years of age. The risk of atopy increased by 40% with each $10 \mu\text{g}/\text{m}^3$ increase in bedroom formaldehyde. Two measures of allergic sensitization to twelve common environmental allergens, the number of positive skin prick tests and maximum wheal size, both showed linear associations with increasing maximum formaldehyde exposure levels. After adjusting for parental asthma and allergy, there was no evidence of an association between asthma in the children and formaldehyde levels. However, these data do suggest that formaldehyde levels commonly found in homes can enhance sensitization of children to common aeroallergens.

Of the numerous, primarily occupational, studies in adults, the NOAEL and LOAEL are $17 \mu\text{g}/\text{m}^3$ (14 ppb) and $101 \mu\text{g}/\text{m}^3$ (81 ppb), respectively, after adjustment for exposure continuity. These values are based on data on nasal and eye irritation as observed in Wilhelmsson and Holstrom (1992), and histological lesions in the nasal cavity as documented in Edling et al. (1988). However, studies in children, including the Krzyzanowski study above, indicate adverse health impacts in children at concentrations as low as 30 ppb. Wantke et al. (1996) reported that formaldehyde-specific IgE and respiratory symptoms were reduced when children transferred from schools with formaldehyde concentrations of 43 to 75 ppb to schools with concentrations of 23 to 29 ppb. While these human studies are not entirely consistent with each other, and there is potential for confounding in each, nevertheless, taken together, they suggest that children may be more sensitive to formaldehyde toxicity than adults.

A potential role for formaldehyde, GSNO and its metabolizing enzyme, GSNOR, in asthma is described in Section 5 above. The activity of GSNOR tends to be higher, and the levels of GSNO lower, in the lungs of asthmatics compared to non-asthmatics. This connection prompted Wu et al. (2007) to investigate whether genetic variation in GSNOR is associated with childhood asthma and atopy. The study group included 532 children, aged 4 to 17 with clinically diagnosed asthma, and their parents. Seven single nucleotide polymorphisms (SNPs) in GSNOR were genotyped in DNA extracted from lymphocytes to examine the relationship between common haplotypes and asthma. Atopy was determined with skin prick tests using a collection of 25 aeroallergens. Two of the GSNOR SNPs were associated with increased risk of asthma, but none was associated with atopy. Whereas a lower risk for asthma was associated with one (RR 0.77; 95% CI 0.61-0.97) or two (RR 0.66; 95% CI 0.44-0.99) copies of the minor A allele of SNP rs1154404, homozygosity for the major T allele of this SNP carried an increased risk of

asthma. Homozygosity for the minor allele of SNP re28730619 also carried an increased risk of asthma (RR 1.60; 95% CI 1.13-2.26; $p = 0.0077$). In the haplotype analysis, children with the most common GSNOR haplotype (GTCGG), that contained the major T allele of rs1154404 and the minor G allele of rs28730619, were at increased risk of childhood asthma. These results thus suggest that variants in GSNOR genotype influence childhood asthma susceptibility.

It should be noted that while term neonates have high levels of reduced glutathione in the fluid lining the lungs, these levels drop rapidly after birth. However, among premature infants, glutathione levels are typically substantially below those of term infants (Grigg et al., 1993) and adults (Reise et al., 1997). As a result of low levels of a critical component of formaldehyde metabolism, glutathione, these infants may be at increased risk from formaldehyde exposure.

6.3 Chronic Toxicity to Experimental Animals

Studies of the effects of chronic formaldehyde exposure in experimental animals tend to focus on lesions in the upper respiratory tract and the hyperplastic or metaplastic changes observed in the respiratory epithelium. Systemic effects, such as changes in body or organ weight, or blood chemistry, appear to be secondary to the effects of the olfactory irritation on feeding behavior. There is also evidence that repeated or long-term exposure to formaldehyde may cause neurologically-based [hyperresponsiveness to formaldehyde](#) (Sorg et al., 2001a) and altered expression of stress hormones (Sorg et al., 2001b).

Deleted: sensitization

In studies examining respiratory effects, Fischer-344 rats and B6C3F1 mice (120 animals/sex) were exposed to concentrations of 0, 2.0, 5.6, or 14.3 ppm formaldehyde vapor for 6 hours/day, 5 days/week for 24 months (Kerns et al., 1983). The exposure period was followed by up to six months of non-exposure. Interim sacrifices were conducted at 6, 12, 18, 24, 27, and 30 months. Both male and female rats in the 5.6 and 14.3 ppm groups demonstrated decreased body weights over the two-year period. At the 6 month sacrifice, the rats exposed to 14.3 ppm formaldehyde had non-neoplastic lesions of epithelial dysplasia in the nasal septum and turbinates. As the study progressed, epithelial dysplasia, squamous dysplasia, and mucopurulent rhinitis increased in severity and distribution in all exposure groups. In mice, cumulative survival decreased in males from 6 months to the end of the study. Serous rhinitis was detected at 6 months in the 14.3 ppm group of mice. Metaplastic and dysplastic changes were noted at 18 months in most rats in the 14.3 ppm group and in a few mice in the 5.6 ppm exposure group. By 24 months, the majority of mice in the 14.3 ppm group had metaplastic and dysplastic changes associated with serous rhinitis, in contrast to a few mice in the 5.6 ppm group and a few in the 2 ppm group (exact number not given).

Woutersen et al. (1989) exposed male Wistar rats (60 animals/group) 6 hours/day for 5 days/week to 0, 0.1, 1.0 and 10 ppm formaldehyde vapor for 28 months. Compound-related nasal lesions of the respiratory and olfactory epithelium were observed only in the 10 ppm group. In the respiratory epithelium, the lesions consisted of rhinitis, squamous metaplasia and basal cell/pseudoepithelial hyperplasia. In the olfactory region, the lesions included epithelial degeneration and rhinitis. No differences in behavior or mortality were noted among the various groups. However, growth retardation was observed in the 10 ppm group from day 14 onwards. In a parallel study, male Wistar rats were exposed to 0, 0.1, 1.0 and 10 ppm formaldehyde for 3

months followed by a 25-month observation period. Compound-related histopathological changes were found only in the noses of the 10 ppm group and comprised increased incidence of squamous metaplasia of the respiratory epithelium, and rhinitis.

In a chronic exposure study that primarily investigated aspects of nasal tumor development, Monticello et al. (1996) examined nasal cavities of male F-344 rats (0-10 ppm, 90 animals/group; 15 ppm, 147 animals) following exposure to 0, 0.7, 2, 6, 10, and 15 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months. Treatment-related decreases in survival were apparent only in the 15 ppm group. Nasal lesions at the two highest doses included epithelial hypertrophy and hyperplasia, squamous metaplasia, and a mixed inflammatory cell infiltrate. Lesions in the 6 ppm group were minimal to absent and limited to focal squamous metaplasia in the anterior regions of the nasal cavity. No formaldehyde-induced lesions were observed in the 0.7 or 2 ppm groups.

Kamata et al. (1997) exposed 32 male F-344 rats/group to gaseous formaldehyde at 0, 0.3, 2, and 15 ppm 6 hours/day, 5 days/week for up to 28 weeks. A room control, non-exposed group was also included in the study. Five animals per group were randomly selected at the end of the 12, 18, and 24 months, and surviving animals at 28 months were sacrificed for full pathological evaluation. Behavioral effects related to sensory irritation were evident in the 15 ppm group. Significant decreases in food consumption, body weight and survival were also evident in this group. No exposure-related hematological findings were observed. Biochemical and organ weight examination revealed decreased triglyceride levels and absolute liver weights at the highest exposure, but was likely related to reduced food consumption. Abnormal histopathological findings were confined to the nasal cavity. Inflammatory cell infiltration, erosion or edema of the nasal cavity was evident in all groups, including controls. Significantly increased incidence of non-proliferative (squamous cell metaplasia without epithelial cell hyperplasia) and proliferative lesions (epithelial cell hyperplasia with squamous cell metaplasia) were observed in the nasal cavities beginning at 2 ppm. In the 0.3 ppm group, a non-significant increase in proliferative nasal lesions (4/20 animals) were observed in rats that were either sacrificed or died following the 18th month of exposure.

Rusch et al. (1983) exposed groups of 6 male cynomolgus monkeys, 20 male or female rats, and 10 male or female hamsters to 0, 0.2, 1.0, or 3.0 ppm (0, 0.24, 1.2, or 3.7 mg/m³) formaldehyde vapor for 22 hours/day, 7 days/week for 26 weeks. There was no treatment-related mortality during the study. In monkeys, the most significant findings were hoarseness, congestion and squamous metaplasia of the nasal turbinates in 6/6 monkeys exposed to 2.95 ppm. There were no signs of toxicity in the lower exposure groups. In the rat, squamous metaplasia and basal cell hyperplasia of the nasal epithelia were significantly increased in rats exposed to 2.95 ppm. The same group exhibited decreased body weights and decreased liver weights. In contrast to monkeys and rats, hamsters did not show any signs of response to exposure, even at 2.95 ppm.

Kimbell et al. (1997) exposed male F-344 rats (≤ 6 /group) to 0, 0.7, 2, 6, 10, and 15 ppm 6 hr/day, 5 days/week for 6 months. Squamous metaplasia was not observed in any regions of the nasal cavity in any of the control, 0.7, or 2 ppm groups. However, the extent and incidence of squamous metaplasia in the nasal cavity increased with increasing dose beginning at 6 ppm.

In subchronic studies, Wilmer et al. (1989) found that intermittent (8 hours/day, 5 days/week) exposures of rats to 4 ppm formaldehyde for 13 weeks resulted in significant histological changes in the nasal septum and turbinates. In contrast, continuous exposure of rats for 13 weeks to 2 ppm formaldehyde did not produce significant lesions. This study revealed the concentration dependent nature of the nasal lesions caused by formaldehyde exposure. Zwart et al. (1988) exposed male and female Wistar rats (50 animals/group/sex) to 0, 0.3, 1, and 3 ppm formaldehyde vapor for 6 hr/day, 5 days/week for 13 weeks. Compound related histopathological nasal changes varying from epithelial disarrangement to epithelial hyperplasia and squamous metaplasia were found in the 3 ppm group, and were restricted to a small area of the anterior respiratory epithelium. These changes were confirmed by electron microscopy and were not observed in other groups.

Woutersen et al. (1989) exposed rats (20 per group) to 0, 1, 10, or 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. Rats exposed to 20 ppm displayed retarded growth, yellowing of the fur, and significant histological lesions in the respiratory epithelium. Exposure to 10 ppm did not affect growth, but resulted in significant histological lesions in the respiratory tract. No effects on specific organ weights, blood chemistries, liver glutathione levels, or urinalysis were detected at any level. No significant adverse effects were seen at the 1.0 ppm exposure level.

Appelman et al. (1988) found significant nasal lesions in rats (20 per group; 0, 0.1, 1.0, or 10.0 ppm) exposed to 10 ppm formaldehyde 6 hours/day, 5 days/week for 52 weeks, but exposure to 1.0 ppm or less for this period did not result in nasal histological lesions. However, the rats exposed to formaldehyde displayed decreased body weight in all groups compared with controls.

Apfelbach and Weiler (1991) determined that rats (5 exposed, 10 controls) exposed to 0.25 ppm (0.38 mg/m³) formaldehyde for 130 days lost the olfactory ability to detect ethyl acetate odor.

Maronpot et al. (1986) exposed groups of 20 mice to 0, 2, 4, 10, 20, or 40 ppm formaldehyde 6 hours/day, 5 days/week, for 13 weeks. Histological lesions in the upper respiratory epithelium were seen in animals exposed to 10 ppm or greater. Exposure to 40 ppm was lethal to the mice.

A six-month exposure of rats to 0, 0.5, 3, and 15 ppm formaldehyde (3 rats per group) resulted in significantly elevated total lung cytochrome P450 in all formaldehyde-exposed groups (Dallas et al., 1989). The degree of P450 induction was highest after 4 days exposure and decreased slightly over the course of the experiment.

A series of studies have addressed the effects of long-term repeated exposures to formaldehyde on altered functioning of the hypothalamic-pituitary-adrenal (HPA) axis (Sorg et al., 2001b) and on neurobehavioral changes in rats (Sorg et al., 2001a). To study formaldehyde's effects on the HPA, Sorg et al. (2001b) measured corticosterone levels in the trunk blood of male Sprague-Dawley rats 20 or 60 min following acute chamber exposures to air or formaldehyde (0.7 or 2.4 ppm). All groups showed increased corticosterone levels above naive basal levels at 20 min followed by a return to baseline by 60 min, with no differences between treatment groups. A second experiment assessed the effects of repeated formaldehyde exposure (1 h/day, 5 days/week for 2 or 4 weeks) on basal corticosterone levels and those after a final challenge. Basal

corticosterone levels were increased above naive values after 2 week exposure to air or 0.7 ppm formaldehyde. By 4 weeks, corticosterone levels in the air group returned to naive values, but remained elevated in the 0.7 ppm formaldehyde group. There were no differences in basal corticosterone levels among either 2.4 ppm exposed groups. After a final air or formaldehyde challenge, the 2 and 4 week air and 0.7 ppm formaldehyde groups had elevated corticosterone levels similar to their acute response, while in the 2 and 4 week 2.4 ppm formaldehyde groups, corticosterone levels were higher than their acute response levels, indicating enhanced reactivity of the HPA axis to subsequent formaldehyde. It thus appears that repeated low-level formaldehyde exposure alters HPA axis functioning and the release of stress hormones. Since glucocorticoids may stimulate or inhibit the synthesis of surfactant-associated proteins in the lung (Liley et al., 1988), the alteration of HPA function may represent another pathway by which formaldehyde affects pulmonary function. For example, the pulmonary surfactants that regulate surface tension in the lungs are in turn regulated by surfactant-associated proteins. Reports of lower airway discomfort associated with chronic formaldehyde exposure may be related to the altered release or activity of these surfactant-associated proteins in the lung.

In another study of the effects of formaldehyde and the hypothalamus-pituitary-adrenal (HPA) axis, Sari et al. (2004) exposed female C3H/He mice to formaldehyde (0, 80, 400, 2000 ppb) by inhalation for 16 h/day, 5 days/week, for 12 weeks. Immunocytochemistry was used to examine corticotropin releasing hormone (CRH)-immunoreactive (ir) neurons in the hypothalamus, and adrenocorticotropin hormone (ACTH)-ir cells in the pituitary. RT-PCR was used to quantify ACTH mRNA in the pituitary. Two groups of female mice were exposed, one of which comprised control mice with no allergen exposure. The other group was made allergic by injection of ovalbumin and alum prior to exposure to formaldehyde. Animals in the second group were further exposed to aerosolized ovalbumin as a booster four times during the exposure period. In the non-allergic group, formaldehyde caused a dose-dependent increase in the number of CRH-ir neurons with a similar pattern of increases in ACTHir cells and ACTH mRNA. The allergic mice showed an increase in basal levels of all these markers of HPA activity, and were responsive to the lowest concentration of formaldehyde. Thus at low levels of exposure, allergen and formaldehyde exposure exacerbate each other's effects on the stress response of the HPA.

7. Developmental and Reproductive Toxicity

In humans there are few data on the association of teratogenicity or adverse reproductive effects with formaldehyde exposure. Existing data do not suggest that formaldehyde, by inhalation or oral routes, produces significant teratogenic or reproductive effects (ATSDR, 1999).

A developmental toxicity study on formaldehyde was conducted by Martin (1990). Pregnant rats (25 per group) were exposed to 0, 2, 5, or 10 ppm formaldehyde for 6 hours/day, during days 6-15 of gestation. Although exposure to 10 ppm formaldehyde resulted in reduced food consumption and body weight gain in the maternal rats, no effects on the number, viability or normal development of the fetuses were seen. In addition, Saillenfait et al. (1989) exposed pregnant rats (25 per group) to 0, 5, 10, 20, or 40 ppm formaldehyde from days 6 - 20 of gestation. Maternal weight gain and fetal weight were significantly reduced in the 40 ppm exposure group. No significant fetotoxicity or teratogenic defects were observed at formaldehyde levels that were not also maternally toxic.

Evidence of embryotoxicity was reported by Kitaeva et al. (1990) in embryos of rats that had been exposed to formaldehyde by inhalation 4 h/d, 5 d/wk for 4 months. At 1.5 mg/m³, but not at 0.5 mg/m³, there was a significant increase in the proportion of degenerate embryos. By comparison, the bone marrow cells of the mothers appeared to be more sensitive to formaldehyde as shown by significant increases in the numbers of cells with aberrations, and the numbers of chromosomes with aberrations and aneuploidy at both dose levels.

In the context of developmental susceptibility to formaldehyde exposure, as noted above, the respiratory tract lining fluid (RTLFL) protecting the lungs is often lower in glutathione levels than is the RTLFL of adult lungs (Reise et al., 1997). This is especially true in premature infants who later develop chronic lung disease (Grigg et al., 1993). As glutathione is central to the lungs' antioxidant defenses, and is involved in the metabolism of inhaled formaldehyde, this relative deficiency may make the neonate's and infant's developing lungs more susceptible to toxic insult. Indeed, alterations in lung development following early life air toxicant exposure has been shown for environmental tobacco smoke (Wang and Pinkerton, 2007) and ozone (Plopper et al., 2007). Whether early life exposure to formaldehyde has similar effects on lung development remains to be demonstrated. However, there is concern that allergen exposure can modulate trophic interactions of conducting airway epithelial and interstitial wall components (Finkelstein and Johnston, 2004) and alter postnatal development of the airways (Plopper et al., 2007). This, coupled with the ability of formaldehyde to enhance the immune response to proteins/allergens with which it binds (Thrasher et al., 1987, 1990), may render developing lungs more susceptible to formaldehyde exposure. If evidence of such developmental effects associated with formaldehyde exposure becomes available, a re-evaluation of the REL for formaldehyde may be necessary.

8. Derivation of Reference Exposure Levels

8.1 Formaldehyde Acute Reference Exposure Level

<i>Study</i>	Kulle et al., 1987
<i>Study population</i>	19 nonasthmatic, nonsmoking humans
<i>Exposure method</i>	Whole body to 0.5-3.0 ppm
<i>Exposure continuity</i>	Single exposure per concentration
<i>Exposure duration</i>	3 hr
<i>Critical effects</i>	mild and moderate eye irritation
<i>LOAEL</i>	1 ppm
<i>NOAEL</i>	0.5 ppm
<i>Benchmark concentration</i>	0.44 ppm
<i>Time-adjusted exposure</i>	not applied
<i>Human Equivalent Concentration</i>	not applied
<i>LOAEL uncertainty factor (UF_L)</i>	not applied
<i>Subchronic uncertainty factor (UF_s)</i>	not applied
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1 (default, human study)
<i>Toxicodynamic (UF_{A-d})</i>	1 (default, human study)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (site of contact; no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10 (asthma exacerbation in children)
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	55 µg/m³ (44 ppb)

Acute Reference Exposure Levels are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Technical Support Document).

Kulle et al (1987) was chosen as the critical study for the determination of the acute REL as it used a sensitive endpoint, eye irritation. It featured human subjects showing significant ($p < 0.05$) responses with short-term exposures to a range of formaldehyde concentrations, and the data permitted the use of a benchmark concentration (BMC) approach. As described in the technical support document, OEHHA recommends the use of the BMC approach whenever the available data support it as the BMC method provides a more statistically sound estimate of the point of departure in the REL determination.

The proposed acute REL was based on a BMCL₀₅ for eye irritation, estimated using log-probit analysis (Crump, 1984). The BMCL₀₅ is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BMCL₀₅ from this analysis was 0.44 ppm (0.53 mg/m³) formaldehyde. The endpoint of eye irritancy appears to be more a function of formaldehyde concentration rather than duration of exposure (Yang et al., 2001), so no time correction factor was applied. An uncertainty factor (UF_{H-k}) of 1 was used since sensory irritation is not expected to involve large toxicokinetic differences among individuals. Although the toxicological endpoint is eye irritation, the REL should protect against all possible adverse effects. The respiratory irritant effect, with documented potential to exacerbate asthma, is clearly an effect with the potential to differentially impact infants and

children. [In addition, the ability of formaldehyde to exacerbate the immune response to aeroallergens is of especial concern during development of the lungs.](#) The toxicodynamic component of the intraspecies uncertainty factor UF_{H-d} is therefore assigned an increased value of 10 to account for potential asthma exacerbation. These considerations are applied equally to the acute, 8-hour and chronic REL.

As noted in Section 5.1, contact lens wearers appear to be at greater risk for ocular irritation with formaldehyde exposure. However, since contact lens users, and infants and children are generally mutually exclusive groups, it is expected that with the ten-fold toxicodynamic UF_{H-d} described above, the acute REL should be adequately protective of these individuals as well.

8.2 Formaldehyde 8-Hour Reference Exposure Level

<i>Study</i>	Wilhelmsson and Holmstrom, 1992
<i>Study population</i>	66 chemical plant workers
<i>Exposure method</i>	Discontinuous occupational exposure
<i>Exposure continuity</i>	8 hr/day, 5 days/week (assumed)
<i>Exposure duration</i>	10 years (average); range 1-36 years
<i>Critical effects</i>	Nasal obstruction and discomfort, lower airway discomfort, and eye irritation.
<i>LOAEL</i>	Mean 0.26 mg/m ³ (range 0.05 – 0.6 mg/m ³) (described as exposed group)
<i>NOAEL</i>	Mean of 0.09 mg/m ³ (described as control group of office workers)
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	0.09 mg/m ³ (time adjustment not applied)
<i>Human Equivalent Concentration</i>	not applied
<i>LOAEL uncertainty factor (UF_L)</i>	1 (NOAEL observed)
<i>Subchronic uncertainty factor (UF_s)</i>	not applied
<i>Interspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1 (default, human study)
<i>Toxicodynamic (UF_{A-d})</i>	1 (default, human study)
<i>Intraspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (site of contact; no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10 (asthma exacerbation in children)
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	9 µg/m³ (7 ppb)

The 8-hour Reference Exposure Level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures (see Section 6 in the Technical Support Document).

The 8-hour REL is based on the occupational study by Wilhelmsson and Holmstrom (1992). This study evaluated the effects of formaldehyde on the upper airways of adult human subjects exposed to a mean formaldehyde concentration of 0.26 mg/m³ during the work day compared with a referent group exposed to 0.09 mg/m³. The critical effects in this study included nasal

obstruction and discomfort, lower airway discomfort, and eye irritation. A NOAEL and a LOAEL may be derived from these data but no other dose-response information was provided. This study included only adults, but there is evidence that children may be more susceptible to long term exposures to formaldehyde than are adults. Thus, in the absence of child-specific data, an intraspecies uncertainty factor of 10 for toxicodynamic variability [and developmental susceptibility](#) was applied.

For comparison, the 8-hour REL of 9 $\mu\text{g}/\text{m}^3$ is similar to the value of 10 $\mu\text{g}/\text{m}^3$ based on increased pulmonary resistance in guinea pigs following an 8 hr exposure to 0.11 – 1.05 ppm formaldehyde (Swiecichowski et al., 1993). The NOAEL of 0.59 ppm in guinea pigs was adjusted to a Human Equivalent Concentration (HEC) of 0.49 ppm with a regional gas dose ratio (RGDR) of 0.826. Use of the HEC adjustment entails an interspecies uncertainty factor of 6, while an intraspecies uncertainty factor of 10 addresses toxicodynamic variability.

<i>Study</i>	Swiecichowski et al., 1993
<i>Study population</i>	25-35 adult male guinea pigs
<i>Exposure method</i>	Whole body exposure
<i>Exposure continuity</i>	
<i>Exposure duration</i>	8 hr
<i>Critical effects</i>	Increased specific pulmonary resistance
<i>LOAEL</i>	1.0 ppm
<i>NOAEL</i>	0.59 ppm
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	not applied
<i>Human Equivalent Concentration</i>	0.49 ppm (610 $\mu\text{g}/\text{m}^3$) (0.59 * RGDR 0.826 for pulmonary effects)
<i>LOAEL uncertainty factor (UF_L)</i>	1 (default: NOAEL observed)
<i>Subchronic uncertainty factor (UFs)</i>	not applied
<i>Interspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	6 (with HEC adjustment)
<i>Toxicodynamic (UF_{A-d})</i>	1 (with HEC adjustment)
<i>Intraspecies Uncertainty Factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (no systemic effect)
<i>Toxicodynamic (UF_{H-d})</i>	10 (potential asthma exacerbation in children)
<i>Cumulative uncertainty factor</i>	60
<i>Reference Exposure Level</i>	10 $\mu\text{g}/\text{m}^3$ (8 ppb)

8.3 Formaldehyde Chronic Reference Exposure Level

<i>Study</i>	Wilhelmsson and Holmstrom, 1992 supported by Edling et al., 1988
<i>Study population</i>	66 human chemical plant workers
<i>Exposure method</i>	Discontinuous occupational exposure
<i>Exposure continuity</i>	8 hr/day, 5 days/week (assumed)
<i>Exposure duration</i>	10 years (average); range 1-36 years
<i>Critical effects</i>	Nasal obstruction and discomfort, lower airway discomfort.
<i>LOAEL</i>	Mean 0.26 mg/m ³ (range 0.05 – 0.6 mg/m ³) (described as exposed group)
<i>NOAEL</i>	Mean of 0.09 mg/m ³ (described as control group of office workers)
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	0.09 mg/m ³ for NOAEL group
<i>Human Equivalent Concentration</i>	not applied
<i>LOAEL uncertainty factor (UF_L)</i>	not applied
<i>Subchronic uncertainty factor (UFs)</i>	not applied
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1 (default, human study)
<i>Toxicodynamic (UF_{A-d})</i>	1 (default, human study)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10 (potential asthma exacerbation in children)
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	9 µg/m³ (7 ppb)

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from chronic exposures (see Section 7 in the Technical Support Document).

The study by Wilhelmsson and Holmstrom (1992) was selected for development of the chronic REL as it investigated long-term exposure to formaldehyde relatively free of other confounding exposures. From this study it was possible to determine both a NOAEL and a LOAEL. Since this study included only adults, a combined intraspecies uncertainty factor of 10 for toxicodynamic variability was applied to account for the possibly greater susceptibility of children with long term exposures to formaldehyde.

The susceptibility of young children was examined in a study by Rumchev et al. (2002) that compared children (mean age 25 mo) with a clinical diagnosis of asthma to children without this diagnosis. The LOAEL used (60 µg/m³) represents the formaldehyde level at which the authors found a statistically elevated risk for asthma-related respiratory symptoms. For this comparison, the NOAEL was taken to be 30 µg/m³, the lower end of the NOAEL range. Intraspecies uncertainty factors of 3.16 for potential toxicodynamic variability and 1 for toxicokinetic differences give a cumulative uncertainty factor of 3.16 for an inhalation chronic REL of 10 µg/m³ (8 ppb), similar to the chronic REL calculated from the critical study.

<i>Study</i>	Rumchev et al., 2002
<i>Study population</i>	88 asthmatic children (mean age 25 mo); 104 nonasthmatic controls (mean age 20 mo)
<i>Exposure method</i>	Ambient in home
<i>Exposure continuity</i>	Continuous assumed
<i>Exposure duration</i>	range 0.5-3 years
<i>Critical effects</i>	Parent-reported respiratory symptoms (cough, shortness of breath, wheeze, trouble breathing)
<i>LOAEL</i>	60 $\mu\text{g}/\text{m}^3$
<i>NOAEL</i>	30 $\mu\text{g}/\text{m}^3$ (lower limit of NOAEL range)
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	not applied
<i>Human Equivalent Concentration</i>	30 $\mu\text{g}/\text{m}^3$
<i>LOAEL uncertainty factor (UF_L)</i>	1
<i>Subchronic uncertainty factor (UF_s)</i>	not applied
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1 (default, human study)
<i>Toxicodynamic (UF_{A-d})</i>	1 (default, human study)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (study performed in children)
<i>Toxicodynamic (UF_{H-d})</i>	$\sqrt{10}$ (inter-individual variation)
<i>Cumulative uncertainty factor</i>	$\sqrt{10}$
<i>Reference Exposure Level</i>	10 $\mu\text{g}/\text{m}^3$ (8 ppb)

The Rumchev study supports an association with exposure to formaldehyde and the observation of asthma symptoms (cough, shortness of breath, wheeze, trouble breathing) in children. However, it was not selected for REL development due to the difficulties in distinguishing asthma from other wheezing conditions in the clinical diagnoses in such a young population. There are additional uncertainties associated with the exposure continuity, and the possibility of observational and/or recall bias in the parental reports of respiratory symptoms characteristic of asthma.

For comparison with the chronic REL of 9 $\mu\text{g}/\text{m}^3$ (7 ppb) presented above, Table 8.3.1 below presents a summary of potential formaldehyde RELs based on chronic and subchronic animal studies originally presented in OEHHA (2000). The toxicological endpoint was nasal lesions, consisting principally of rhinitis, squamous metaplasia, and dysplasia of the respiratory epithelium.

The most striking observation is the similarity of potential RELs among the rat chronic studies (exposures ≥ 26 weeks) that contain a NOAEL. The range of RELs from these animal studies, 1.5 – 24.9 ppb, includes the proposed REL (7 ppb) based on a human study. Another related observation is that the NOAEL and LOAEL are similar among all the studies, regardless of exposure duration. The NOAEL and LOAEL are generally in the range of 1 - 4 ppm and 1 – 10 ppm, respectively, with the exception of the study by Kamata et al. (1997) that may be due to the absence of a dose level between 2 and 0.3 ppm. It is also of interest that the studies of Rusch et

al (1983) indicate that monkeys and rats are of about the same sensitivity. In addition, the results of the Rusch studies suggest that, at least for the endpoint of squamous metaplasia, formaldehyde concentration is more important than the total dose since these animals, receiving more continuous exposure, exhibited the same adverse effects seen in studies using more intermittent exposures.

ATSDR has estimated minimum risk levels (MRLs), defined as “an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure” (ATSDR, 1999). For formaldehyde inhalation exposures they describe as “acute” (≤ 14 days), the MRL is 40 ppb based on a LOAEL of 0.4 ppm from a study by Pazdrak et al. (1993), and a 9-fold uncertainty factor (3 for use of a LOAEL; 3 for intraspecies variability). This exposure period is much longer than the acute REL of one hour, but the acute REL represents possibly repeated exposures. The MRL for an “intermediate” exposure period of 15-364 days is 30 ppb based on a NOAEL of 0.98 ppm for clinical signs of nasopharyngeal irritation and lesions in the nasal epithelium in monkeys (Rusch et al., 1983). A chronic MRL (≥ 365 d) of 8 ppb was developed based on damage to nasal epithelium in chemical factory workers (Holmstrom et al., 1989). This number is similar to the chronic REL of 7 ppb reported here. The MRLs are more similar to the chronic RELs developed by OEHHA in that they assume continuous exposure over the specified time period rather than regular but periodic exposures, as assumed for the 8-hour RELs considered above. [For 8-hr exposures, NIOSH \(1988\) suggested a TWA 8-hr REL of 16 ppb based on sensory irritation.](#)

8.4 Formaldehyde as a Toxic Air Contaminant

Formaldehyde was identified by the ARB as a toxic air contaminant (TAC) in accordance with sections 39660-39662 of the California Health and Safety Code on March 12, 1992 (Title 17, California Code of Regulations, section 93001)(CCR, 2007). In view of the differential impacts on infants and children identified in Section 6.2, OEHHA recommends that formaldehyde be listed as a toxic air contaminant which may disproportionately impact children pursuant to Health and Safety Code, Section 39669.5(c).

Table 8.3.1. Summary of Chronic and Subchronic Formaldehyde Studies in Experimental Animals

Study	Animal	Duration	Exposure	LOAEL ppm	NOAEL ppm	Time adj	LOAEL DAF	LOAEL						Cum UF	REL ppb	REL µg/m ³
								UF	UFak	UFad	UFhk	UFhd	UFsc			
Woutersen 89	rat	28 mo	6 h 5 d	9.8	1	0.179	0.148	1	1	3.16	1	10	1	30	4.9	6.1
Kerns 83	rat	24 mo	6 h 5 d	2	n/a	0.357	0.296	6	1	3.16	1	10	1	200	1.5	1.8
Monticello 96	rat	24 mo	6 h 5 d	6.01	2.05	0.366	0.304	1	1	3.16	1	10	1	30	10.1	12.6
Kamata 97	rat	24-28 mo	6 h 5 d	2	0.3	0.054	0.044	1	1	3.16	1	10	1	30	1.5	1.8
Appelman 88	rat	52 wk	6 h 5 d	9.4	1	0.179	0.148	1	1	3.16	1	10	1	30	4.9	6.1
Rusch 83	rat	26 wk	22 h 7d	2.95	0.98	0.898	0.746	1	1	3.16	1	10	1	30	24.9	30.8
Kimbell 97	rat	26 wk	6 h 5 d	6	2	0.357	0.296	1	1	3.16	1	10	1	30	9.9	12.3
Wilmer 89	rat	13 wk	8 h 5 d	4	2	0.238	0.198	1	1	3.16	1	10	1	30	6.6	8.2
Woutersen 87	rat	13 wk	6 h 5 d	9.7	1	0.179	0.148	1	1	3.16	1	10	1	30	4.9	6.1
Zwart 88	rat	13 wk	6 h 5 d	2.98	1.01	0.180	0.15	1	1	3.16	1	10	1	30	5.0	6.2
Kerns 83	mouse	24 mo	6 h 5 d	5.6	2	0.357	0.296	1	2	3.16	1	10	1	60	4.9	6.1
Maronpot 86	mouse	13 wk	6 h 5 d	10.1	4.08	0.729	0.605	1	2	3.16	1	10	1	60	10.1	12.5
Rusch 83	monkey	26 wk	22 h 7d	2.95	0.98	0.898	not used	1	2	2	1	10	1	40	22.5	27.8

9.0 References

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