INTERIM
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
FORMALDEHYDE
(CAS Reg. No. 50-00-0)

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Formaldehyde is a colorless flammable gas with a pungent, suffocating odor. It is ubiquitous in the atmosphere as a constituent of smog, in homes that contain urea-formaldehyde foam insulation or particle board construction, and at production sites. It is a naturally-occurring constituent of many foods and is a normal metabolite in the human body.

The data base on formaldehyde is robust, with human and animal studies that address various endpoints and cover acute through chronic exposure durations. The primary effect during short-term exposures is irritation of the eye, nose, and throat. At low concentrations of 1 to 3 ppm, formaldehyde is well scrubbed in the nasal passages of both humans and rodents and does not reach the lower respiratory tract. At higher concentrations, formaldehyde is an extreme irritant. Chronic studies with moderate concentrations (14 ppm) result in carcinomas of the anterior nasal passages of the rat. Formaldehyde is a weaker carcinogen in the mouse and is not carcinogenic in the hamster. Because formaldehyde is so highly reactive and rapidly metabolized/detoxified by the tissues of the nasal passages, inhalation is unlikely to result in cancers at remote sites. Epidemiology studies have failed to show a clear relationship between exposure and carcinogenicity.

The irritant properties of formaldehyde and its effects on pulmonary function parameters have been reported in 22 clinical studies with over 500 healthy and sensitive subjects (potentially sensitive subjects included both asthmatics and subjects who reported sensitivity to formaldehyde). In most of the studies, eye irritation was the most sensitive endpoint. At concentrations <1 ppm, there is no clear dose-response to the irritant properties of formaldehyde, and responses do not differ greatly from those of control atmospheres. At 1 ppm, the eye irritation response ranges from slight to moderate, with adaptation occurring with prolonged exposure. At 3 ppm for several hours, the response in heavily exercising individuals and moderately exercising individuals is similar (Green et al. 1987). Eye, nose, and throat irritation ranged from mild to moderate, and there were small, transient decrements in pulmonary function parameters in healthy subjects. In the absence of exercise, there are no decrements in pulmonary function parameters in either healthy or asthmatic subjects inhaling 3 ppm for 3 hours (Sheppard et al. 1984; Sauder et al. 1986; 1987).

The AEGL-1 was based on a NOAEL for eye irritation in a single study with subjects whose eyes were sensitive to formaldehyde (Bender et al. 1983). In this study, groups of 5 to 28 healthy subjects were exposed eye-only for 6 minutes to 0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm. The subjects had been selected for their response to formaldehyde at 1.3 or 2.2 ppm, i.e., subjects that did not report eye irritation during previous exposures to 1.3 or 2.2 ppm were excluded from the study. At 0.35 to 0.9 ppm, the subjects' subjective eye irritation responses ranged from none to slight, the same as their responses to clean air. The 0.9 ppm concentration was selected as the basis for the AEGL-1. No intraspecies uncertainty factor was applied as no additional sensitive populations were identified [there were no significant decrements in pulmonary function parameters in exercising asthmatic subjects at 2 or 3 ppm, and asthmatic subjects reported less than moderate eye irritation, the same as healthy subjects, at these concentrations (Green et al. 1987; Kulle et al. 1987; Sauder et al. 1987)]. Because several studies show there is adaptation to irritation at this low concentration, the 0.9 ppm concentration was applied across all exposure durations. This value is supported by the fact that animal studies show there is no damage to the

respiratory epithelium during single (Morgan et al. 1986b) or repeated exposures to 1 or 2 ppm (Rusch et al. 1983; Maronpot et al.1986; Woutersen et al. 1987).

The AEGL-2 was based on the clinical study of Sim and Pattle (1957). Twelve healthy male subjects inhaled 13.8 ppm for 30 minutes. Initially, the exposure caused considerable nose and eye irritation. Mild lacrimation continued for some period of time. The eye irritation was not considered severe, and adaptation occurred in about 10 minutes. Mild lacrimation at 13.8 ppm (rounded to 14 ppm) with adaptation was considered the threshold concentration for the inability to escape. The lacrimation experienced by Barnes and Speicher (1942) at 20 ppm during short exposures might impair the ability to escape. The 14 ppm concentration may also be close to the threshold for an increase in airways resistance (Douglas 1974). No intraspecies uncertainty factor was applied to the 14 ppm concentration because application of an uncertainty factor of ≥3 would lower the value to close to a no-effect concentration in several studies with exercising asthmatics. Because the endpoint is eye and nose irritation to which adaptation occurs, the same value was used across all exposure durations.

The AEGL-3 values were based on the highest non-lethal value for the rat following a 4-hour exposure to 350 ppm (Nagorny et al. 1979). The value was adjusted by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. These uncertainty factors, applied to irritants, are protective of sensitive populations. Furthermore, application of larger uncertainty factors, e.g., a total of 30, would reduce the value to the level of the AEGL-2. No data on time-scaling were found. Therefore, the default value of n = 3 when scaling to shorter exposure periods (NRC 2001) was applied. The 8-hour value was set equal to the 4-hour value because formaldehyde is well scrubbed in the nasal passages. Furthermore, application of the default of n = 1 when scaling to longer time periods would result in an 8-hour value of 18 ppm, similar to the 8-hour AEGL-2. The 8-hour value is supported by sublethal concentrations in additional animal studies. For example, no deaths occurred in rats that inhaled 35 ppm for 18 hours (Murphy et al. 1964).

The calculated values are listed in Table 1 below.

TABLE 1. Summary of AEGL Values for Formaldehyde

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1[a] (Nondisabling)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	NOAEL for eye irritation - sensitive human subjects (Bender et al. 1983)
AEGL–2 (Disabling)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	Mild lacrimation with adaptation - humans (Sim and Pattle 1957)
AEGL–3 (Lethal)	100 ppm (123 mg/m^3)	70 ppm (86 mg/m^3)	56 ppm (69 mg/m^3)	35 ppm (43 mg/m^3)	35 ppm (43 mg/m^3)	Highest non-lethal value - rat (Nagorny et all 1979)

[a]Most individuals will notice the distinct, pungent odor of formaldehyde at the AEGL-1. The Level of Distinct Odor Awareness is 3.6 ppm.

1. INTRODUCTION

Formaldehyde is a flammable colorless gas with a pungent, suffocating odor. Its high chemical reactivity, good thermal stability, and ability to polymerize make it a useful material in the synthesis of a wide variety of products. The most common form of the material is aqueous solutions (formalin), with a formaldehyde content of 37-50%, by weight. Paraformaldehyde is a solid polymer of formaldehyde which can be easily vaporized to its monomeric form (O'Neil et al. 2001). Chemical and physical properties are listed in Table 2.

Total annual capacity for production in the United States in 1998 was 11.3 billion pounds. The primary method of manufacture is from methanol with either silver or a metal oxide as catalyst (ATSDR 1999). Most formaldehyde produced in the United States (23%) is used in urea-formaldehyde resins. Other uses include phenolic resins (19%), acetylenic chemicals (12%), polyacetal resins (11%), methylene diisocyanate (6%), pentaerythritol (5%), urea-formaldehyde concentrates (4%), hexamethylenetetramine (4%), melamine resins (4%), and miscellaneous (12%) (ATSDR 1999). The phenolic, urea, and melamine resins are used in the manufacture of plywood, fiberboard, and particle board. Worldwide production in 2000 was 21, 547 thousand tons (IARC 2006).

Formaldehyde is ubiquitous in the environment as it is found in a great number of consumer products such as cosmetics, permanent press fabrics, particle board, plywood, floor coverings, office furniture, and urea-formaldehyde foam insulation. Cigarette smoke may contain up to 40 ppm formaldehyde (Turoski 1984). Outdoors, the major source of atmospheric formaldehyde is from auto emissions and from the photooxidation of hydrocarbons in auto emissions (NRC 1981).

Formaldehyde is found in a large number of common foods and drinks. It occurs as a natural constituent of raw fruits including pears, apples, tomatoes, and white radish in amounts varying from 3.7 to 60 ppm. It also occurs in raw vegetables such as cabbage, carrots, green onions, and spinach in amounts varying from 3.3 to 26.3 ppm. Its maximum oral intake is estimated to be 14.2 mg/person/day (Feron et al. 1991).

Formaldehyde is an essential metabolic intermediate in all cells. It is produced during the normal metabolism of serine, glycine, methionine, and choline and also by the demethylation of N-, S-, and O-methyl compounds. As such, it is a normal metabolite, and enters into the chain of biochemical events in humans and other animals to give rise to essential cellular substances (NRC 1981).

TABLE 2. Chemical and Physical Properties		
Parameter	**Value**	**Reference**
Synonyms	Methanal, oxomethane, oxymethylene, methylene oxide formic aldehyde, methyl aldehyde	O'Neil et al. 2001
Chemical formula	CH_2O	O'Neil et al. 2001
Molecular weight	30.03	O'Neil et al. 2001
CAS Reg. No.	50-00-0	ATSDR 1999
Physical state	Gas	O'Neil et al. 2001
Solubility in water	Very soluble, up to 55% 980 L/L water at 20°C	O'Neil et al. 2001 Andersen and Molhave 1983
Vapor pressure @ 25°C	3883 mm Hg	ATSDR 1999
Vapor density (air =1)	1.067	O'Neil et al. 2001
Liquid density (water =1)	0.815 g/mL	ATSDR 1999
Melting point	– 92°C	O'Neil et al. 2001
Boiling point	–19.5°C	O'Neil et al. 2001
Flammability limits @ 25°C	7-73%	ATSDR 1999
Ignition temperature	300°C	O'Neil et al. 2001
Conversion factors	1 ppm = 1.23 mg/m^3 1 mg/m^3 = 0.813 ppm	ATSDR 1999

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of deaths from short-term inhalation of formaldehyde were located.

2.2. Nonlethal Toxicity

Formaldehyde is an eye, upper respiratory tract, and skin irritant. Dermal contact may cause sensitization. Because it is extremely water soluble, it is extensively "scrubbed" in the anterior nasal passages. The irritant effects of formaldehyde from construction products in the home, occupational exposures, and controlled clinical studies have been reported.

2.2.1. Odor threshold

Formaldehyde has a distinct, pungent odor. The odor threshold has been studied by several groups. The odor of formaldehyde can be recognized by most individuals at concentrations below 1 ppm. The concentration at which a group of observers can detect the odor in 50% of the presentations is between 0.05 and 0.18 ppm. The individual odor detection threshold covers "over two powers of ten," and the distribution is extremely positively skewed (WHO 1989). Berglund et al. (1987) reported that the 50^{th} percentile detection threshold was 0.145 ppm, the 10-percentile threshold was 0.020 ppm and the 90-percentile threshold was 0.5 ppm. The Level of Distinct Odor Awareness (LOA) was derived using the data of Berglund et al. (1987). Calculations are contained in Appendix A. The LOA for formaldehyde is 3.6 ppm.

The odor threshold was measured for 64 subjects, ages 17-64 years, in a climate-controlled chamber (Pettersson and Rehn 1977). The subjects placed their heads in a hood during the exposures. The exposures were alternately to a formaldehyde-air mixture or clean air,

given in a random manner, and the subjects had to determine in which of the two exposures formaldehyde was present. Concentration ranged from 0.01 to 1.0 ppm. The lowest detectable odor was 0.04 ppm. There was a dose-response to odor detection above this level. At slightly greater than 1.0 ppm all 64 subjects could correctly detect the odor.

In another study that addressed the odor threshold as well as effects on the central nervous system, a panel of 12 persons, ages 19-64, judged 0.09 ppm as the threshold concentration for odor perception (Melekhina 1964). Following adaptation to a climate controlled chamber, the threshold for odor perception was 0.06 ppm. Additional odor threshold values cited in U.S. EPA (1992) range from 0.06 to 0.3. Amoore and Hautala (1983) cite 0.83 ppm and Billings and Jonas (1981) cite 1.0 ppm as odor thresholds. The threshold for odor recognition by a trained odor panel was 1.0 ppm (Leonardos et al. 1969). The odor was characterized as hay/straw-like, pungent.

2.2.2. Indoor Air Exposures

As noted, formaldehyde is a commonly encountered environmental chemical. Consumers may be exposed to formaldehyde from a number of sources, including cigarette smoke, formaldehyde-containing resinous products, and cooking. Formaldehyde is present indoors as an off-gassed product of construction materials such as plywood and urea-formaldehyde foam insulation. An important source of indoor formaldehyde is cigarette smoke (WHO 1989). The majority of complaints registered with the Consumer Product Safety Commission involved eye and upper respiratory tract irritation attributed to off-gassing from formaldehyde foam insulation, particle board, or plywood; concentrations ranged from 0.01 to 32 ppm (NRC 1980). Indoor air exposures can exceed 1.0 ppm (ATSDR 1999), but are generally lower than in the work environment. A study of nearly 2000 residents of mobile and conventional homes that reported symptoms related to formaldehyde was undertaken by Ritchie and Lehnen (1987). Measured concentrations ranged from <0.1 ppm to ≥0.3 ppm. The study reported a positive dose-response between formaldehyde concentrations and self-reported health complaints. In all cases complaints were substantially more frequent with concentrations above 0.3 ppm. The percentage of respondents reporting eye irritation at <0.1, 0.1 to <0.3, and ≥0.3 ppm were similar between mobile and conventional homes (2 vs 1%, 32 vs 12%, and 93 vs 89%, respectively). The contribution of smoking to eye irritation was noted in both types of homes, but exposure to other chemicals was not evaluated. The participants received a free medical test and so were self-selected with a potential bias.

2.2.3. Occupational Exposures

Occupational sources and concentrations have been reviewed by several agencies. Several such surveys are cited here as examples of past routine exposures. In some cases symptoms were also reported, but many of the survey results are complicated by the presence of other chemicals in the manufacturing process. Usually the frequency, exact concentration, and duration of exposure are not provided. A few recent occupational studies are also cited.

NIOSH (1976) reviewed early reports on occupational exposures to formaldehyde. In these reports, irritation of the upper respiratory tract was reported at formaldehyde concentrations between 0.09 and 11 ppm. Sampling periods varied, but periods of 15 and 30 minutes were

reported in some studies. Examples of occupations and workplace concentrations follow: handling flame-proof fabrics, 1-11 ppm; dress shop, 0.13-0.45 ppm; resin manufacturing and paper plant, 16-30 ppm; paper conditioning installation, 0.9-1.6 ppm; funeral home (use of formaldehyde and paraformaldehyde in embalming process), average 0.25-1.39 ppm with range up to 5.26 ppm; clothing store, 0.9-3.3 ppm; textile garment factory, 0.9-2.7 ppm (irritation noted followed by adaptation), wood processing plant, 2.1-8.9 ppm, ranging up to 31 ppm (illnesses noted); and two laminating plants using phenol-resorcinol glue (which emits formaldehyde), 0.04-10.9 ppm. Concentrations in the latter two plants depended on area of the plant and the specific glue used. The authors reported that employees objected when airborne concentrations exceeded 1 ppm, and the odor at concentrations of 4.2 to 10.9 ppm was considered unbearable. Dermatitis was a common complaint in workers handling formaldehyde-impregnated materials.

OSHA (1996) estimated that in the late 1980s over 2 million workers were exposed to formaldehyde. Most of these workers were in the garment industry. About 1.9 million workers in the apparel, furniture, paper mill and plastic molding industries were exposed to between 0.1 and 0.5 ppm. Approximately 123,000 workers were exposed to between 0.5 and 0.75 ppm, and about 84,000 were exposed to 0.75 to 1 ppm. A U.S. EPA (1982) survey of occupational exposures found mean concentrations of 0.1 to 0.9 ppm, with ranges up to 2.2 ppm. Exposures were highest during the direct manufacture of formaldehyde. IARC (2006) also summarized workplace concentrations. Mean concentrations in formaldehyde and resin manufacturing plants, plywood mills, particle-board mills, furniture factories, textile mills and garment factories, foundries, mortuaries, building sites, etc., ranged from 0.1 to 38 ppm (range, <0.01 to 61 ppm).

Horvath et al. (1988) conducted a well-designed study with a formaldehyde exposed group and an unexposed group. The exposed workers were employed in a particle board and molded plastics plant; the duration of exposure was from <1 to 20 years. Formaldehyde concentrations ranged from 0.17 to 2.93 ppm (mean 0.69 ppm). Formaldehyde concentrations were determined by both passive and active sampling procedures. On the day of examination, test subjects were monitored with formaldehyde monitors (3M, St. Paul, MN; lower limit of sensitivity of 0.1 ppm). Area samples were taken with an sampling train that employed a liquid medium impinger containing 1% sodium bisulfite. Both types of samples were analyzed according to NIOSH 77-157A. Nuisance particles of softwood dust were present at similar concentrations at the particle board plant and the two control plants. The control group was employed in the food-processing industry. A symptom questionaire and spirometry were administered to all participants before and after the workshift.

Spirometry results showed that exposed workers had some evidence of an acute decline in some pulmonary function parameters. The authors considered the respiratory changes “small and probably transient.” As baseline values were similar among controls and exposed workers, the authors concluded that exposure to these low levels for up to ten years did not appear to cause permanent respiratory impairment. Spirometry results showed that exposed workers had some evidence of an acute decline in some pulmonary function parameters. These consisted of statistically significant postshift decreases in forced expiratory volume in 1 second divided by percent forced vital capacity (1%), peak expiratory flow rate during the middle half of the forced vital capacity (5%), forced expiratory flow at 50% and 75% of the forced vital capacity (4% and 7%). The authors considered the respiratory changes “small and probably transient.” Controls

showed 1% declines in forced expiratory volume in 1 second and forced vital capacity (not significant in the control group). As baseline values were similar among controls and exposed workers, the authors concluded that exposure to the low levels of formaldehyde for up to ten years did not appear to cause permanent respiratory impairment. Respiratory complaints were higher in the exposed group than the control group for cough (35% vs 19%), chest pains (9% vs 2%), production of mucus (27% vs 10%) burning sensation of the nose (28% vs 2%), nasal congestion (34% vs 14%), and dry or burning throat (22 vs 4%). The exposed group also reported burning eyes with a greater frequency that the control group (40% vs 9%). Frequencies between the control and exposed group were similar for shortness of breath and wheezing.

The responses of medical students to formaldehyde in a gross anatomy laboratory compared with those of non-exposed students were reported in two studies. In the first study, Akbar-Khanzadeh et al. (1994) found no statistically significant differences in pulmonary function parameters (FVC, FEV_1, FEV_3 and $FEF_{25-75\%}$) in 12 subjects exposed to an estimated TWA of 1.24 ppm for 2- to 3-hour periods. In the second study (Akbar-Khanzadeh and Mlynek 1997), 50 medical students were exposed to a mean concentration of 1.88 ppm (range, 0.30-4.45 ppm) for 3 hours. These 157-minute samples were taken in the breathing zone of the students. The control group consisted of 36 nonexposed physical therapy students. Eye and nose irritation were reported by more than 70% of the exposed students. Respiratory function parameters for both groups increased in a manner related to diurnal variation, but there was no relationship between concentration of formaldehyde in the breathing zone and changes in respiratory function of exposed subjects.

2.2.4. Clinical Studies

Twenty-three clinical studies with human subjects were located (Table 3). Most of the studies were conducted with controlled environmental exposure chambers supplied with filtered air. Formaldehyde was generated from purified paraformaldehyde, although heated solutions of formaldehyde were used in some studies. In the older studies, analytical measurements involved the NIOSH-recommended chromotropic acid method, and more recent studies involved formaldehyde specific air monitors. Pulmonary function parameters were measured with a spirometer and included forced vital capacity (FVC or VC), forced expiratory volume in 1 second (FEV_1), forced expiratory flow during the middle half of the functional residual capacity (FEF_{25-75}), and PEF or PEFR (peak expiratory flow or flow rate). Airway resistance (Raw) and functional residual capacity (FRC) were measured with a whole-body pressure plethysmographic technique. Airway resistance was converted to specific airway conductance (SRaw or SGaw). Exercise was incorporated into some of the protocols in order to increase minute ventilation (V_E).

Entries in Table 3 are listed generally in order of increasing concentrations. Some of the studies address the response of healthy and asthmatic subjects as well as subjects sensitized to formaldehyde. Several studies address eye irritation only which has been identified as the most sensitive irritant response to formaldehyde (Paustenbach et al. 1997).

TABLE 3. Irritant Effects of Formaldehyde in Controlled Human Studies

Concentration (ppm)	Time	Subjects/Effect (number of subjects)	Reference
0, 0.35, 0.56, 0.7,	6 min	Healthy subjects (groups of 7-28), excluded	Bender et al. 1983

TABLE 3. Irritant Effects of Formaldehyde in Controlled Human Studies

Concentration (ppm)	Time	Subjects/Effect (number of subjects)	Reference
0.9, 1.0		non-responders at 1.3 or 2.2 ppm; Eye irritation evaluated: average scores of none to slight at 0.35 to 0.9 ppm; slight to moderate at 1.0 ppm; slight adaptation with time	
0, 0.10, 0.69	90 min	Asthmatic nonsmoking subjects (15): No significant change in pulmonary function parameters (FEV_1 and airway resistance) or in bronchial reactivity; no association of subjective ratings of asthmatic symptoms with increasing air concentrations	Harving et al. 1986; 1990
0, 0.41	2 h	Healthy occupationally exposed (5) and contact dermatitis subjects (13): No effect on pulmonary parameters (VC, FEV_1); immune response in subjects with contact dermatitis (increased chemiluminescense of neutrophils)	Gorski et al 1992
0, 0.41	2 h	Healthy (11) and patients with skin hypersensitivity to formaldehyde (9) (all nonsmokers): No differences in response between groups; transient increase in symptoms of sneezing, rhinorrhea, or eye irritation; nasal washings showed increases in eosinophils, albumin, total protein, but not neutrophil, basophil or mononuclear cells	Pazdrak et al. 1993
0, 0.41	2 h	Healthy, non-occupationally exposed (10) and occupationally exposed asthmatic subjects (10): No differences in response between groups; transient increase in symptoms of sneezing, rhinorrhea, edema, or itchy eyes; increases in leucocytes and eosinophils in nasal washings; no allergic response; no clinical symptoms of bronchial irritation or effects on pulmonary function parameters (FEV_1, PEF)	Krakowiak et al. 1998
0, 0.40	1 hr	12 volunteers with intermittent asthma and allergy to pollen: No change in lung function (FEV_1); no enhanced response to allergens	Ezratty et al. 2007
0, 0.17, 0.39, 0.9	5.5 h	Formaldehyde exposed workers (32); controls (29): subjective symptoms (headache, tiredness) did not correlate with exposure; no clear effect of concentration on memory; some concentration-related effects in a few tests (additional speed, response time) but limitations in experimental design and control issues	Bach et al. 1990
1.0	90 min	Healthy (9) and formaldehyde-sensitive (9) subjects (previously complained about non-	Day et al. 1984

TABLE 3. Irritant Effects of Formaldehyde in Controlled Human Studies

Concentration (ppm)	Time	Subjects/Effect (number of subjects)	Reference
		respiratory effects of urea formaldehyde foam insulation): No effects on pulmonary function parameters (FVC, FEV_1, max and mid-exploratory flow rate); complaints of eye irritation, nasal congestion, tearing, and throat irritation; no severity index	
0, 1.0	3 h	Control asthmatic subjects (4); subjects with asthma attributed to urea formaldehyde foam (23): no differences between groups in immunologic parameters, either before or after exposure; minor immunologic changes in both groups postexposure	Pross et al. 1987
0, 0.2, 0.4, 0.8, 1.6 (no concurrent control)	5 h	Healthy subjects (16): No differences in nasal airway resistance or pulmonary function parameters; decrease in nasal mucus flow at all concentrations; no discomfort at 0.2 or 0.4 ppm for 2 hours (some slight discomfort reported in the 3 to 5 hours period [conjunctival irritation, dryness of nose and throat] but discomfort rated higher at 0.2 ppm than at 0.4 ppm and only 5 or fewer subjects reported any discomfort); average discomfort scored as slight during exposure to 1.6 ppm and first noted in the latter part of the first hour but decreased somewhat after three hours; no effect on performance on mathematical tests or number transfer tasks	Andersen and Molhave 1983
0, 0.15, 0.3, 0.5 ppm; 0.3 with 4 peaks to 0.6 ppm; 0.5 ppm with 4 peaks to 1.0 ppm; some exposures combined with ethyl acetate as masking agent	4 h	Healthy volunteers, 11 males and 10 females: All concentrations: no significant effects on nasal flow and resistance, pulmonary function, and decision reaction time; slight to moderately increased blinking frequency and conjunctival redness at 0.5 ppm with peaks to 1.0 ppm; subjective eye and olfactory symptoms reported at 0.3 ppm (no-effect level when "negative affectively" considered); subjective nasal irritation at 0.5 ppm with peaks to 1.0 ppm	Lang et al. 2008
0, 2.0 (at rest) 0, 2.0 (exercise)	40 min	Healthy (15) and asthmatic (15) non-smoking subjects: No significant decrement in pulmonary function parameters (flow-volume parameters and airway resistance) or bronchial reactivity both at rest and with exercise; subjective symptoms ranged up to severe (but not incapacitating) for odor for some individuals, but median scores for nose, throat and eye irritation were ≤moderate; no increase in symptomology	Witek et al. 1986; 1987; Schachter et al. 1985; 1986

TABLE 3. Irritant Effects of Formaldehyde in Controlled Human Studies

Concentration (ppm)	Time	Subjects/Effect (number of subjects)	Reference
		with exercise	
0, 0.1, 1.0, 3.0	20 min	Asthmatic patients who suspected formaldehyde as the cause (13): No significant difference in pulmonary function parameters (FEV_1, VC); no asthmatic response to formaldehyde challenge	Frigas et al. 1984
0, 0.5, 1.0, 2.0, 3.0 at rest; 2.0 with exercise	3 h	Healthy non-smoking subjects (19): (9 exposed to 3 ppm and 10 exposed to 0.05 ppm) No significant decrements in pulmonary function parameters (FVC, FEV_1, $FEF_{25-75\%}$, SGaw) or increases in bronchial reactivity (methacholine challenge) at any concentration; nasal flow resistance increased at 3.0 ppm; significant dose-response relationship for odor sensation and eye irritation, but eye irritation scored mild (5/9) or mild to moderate 4/9) at 3 ppm; eye irritation began at 1 ppm	Kulle et al. 1987; Kulle 1993
0, 3.0 ppm With heavy exercise (healthy subjects); moderate exercise (asthmatic subjects)	1 h	Healthy (22) and asthmatic (16) non-smoking subjects: No difference in symptoms between groups; eye, nose and throat irritation scored mild to mild-moderate (group means); small decreases in some pulmonary function parameters in healthy individuals engaging in heavy exercise	Green et al. 1987
0, 3.0 With heavy exercise (15 minutes every half hour)	2 h	Healthy non-smoking subjects (24): Increase in subjective symptoms of eye, nose and throat irritation, rated mild to moderate on average; small, but statistically significant increase in two ($FEF_{25-75\%}$, SGaw) of several pulmonary function measurements at some time intervals (no effect on FEV_1, FVC, FEV_3), no increase in cough	Green et al. 1989
0, 3.0 With intermittent exercise	3 h	Healthy non-smoking subjects (9) non-biologically significant, transient change in some pulmonary function parameters (FEV_1, $FEF_{25-75\%}$); increase in nose/ throat and eye irritation, rated mild to moderate by individuals; only one subject rated eye irritation as moderate	Sauder et al. 1986
0, 3.0	3 h	Asthmatic non-smoking subjects (9): no significant group change in pulmonary function parameters (FEV_1, FVC, $FEF_{25-75\%}$, SGaw, or FRC) or airway reactivity; significant increase in nose, throat (at 30 minutes), and eye irritation (at 60 minutes), rated as none to mild-moderate except for one subject who reported severe eye irritation	Sauder et al. 1987

TABLE 3. Irritant Effects of Formaldehyde in Controlled Human Studies

Concentration (ppm)	Time	Subjects/Effect (number of subjects)	Reference
0, 1, 3	10 min	Asthmatic non-smoking subjects (7): Similar responses in airway resistance following exposure to 0, 1, or 3 ppm with and without exercise (exercise increased all responses)	Sheppard et al. 1984
0.03 to 3.2; 0, 1.0, 2.0, 2.9, 4.0 or 1.2, 2.1, 2.8, and 4.0	37 min (n = 33); 1.5 min (n = 48)	Healthy subjects (exposure groups of 33 and 48): Poorer air quality and greater nose irritation reported during the short exposures than during the 37-minute exposure, whereas the opposite was true for eye irritation; with increasing concentrations, both eye and nose irritation increased from none to "a little;" objectively-measured eye blinking not affected at 1.2 ppm, but was statistically significantly increased at 2.1 ppm	Weber-Tschopp et al. 1977
0, 1, 2, 4, 5	5 min except for 2 ppm (12 min)	Healthy students (groups of 7 to 75): Addressed eye irritation only (subjects exposed via goggles): 1 ppm considered threshold for detection; 5 ppm produced severe eye irritation	Stephens et al. 1961
8, 13	Short exposures (<15 sec)	Healthy/atopic subjects (1-6): Eye irritation for 5 of 6 subjects at 12 ppm but not at 8 ppm for 4 of 5; irritation of the throat at both concentrations; changes in airway resistance	Douglas 1974
13.8	30 min	Healthy male subjects (12): Nasal and eye irritation with mild lacrimation; adaptation to the eye irritation	Sim and Pattle 1957
20	Several min	Healthy subjects (2): Lacrimation (within 15-30 seconds); eye, nose, and throat irritation considered objectionable	Barnes and Speicher 1942

FVC =
FEV_1 =
$FEF_{25-75\%}$, =
FRC =
PEF =
SGaw =

In an early study that addressed the threshold for eye irritation, Shuck et al. (1966) reported that a linear relationship between reported eye irritation and formaldehyde concentration does not hold below 0.3 ppm. Most subjects experienced the same eye irritation at 0.05 and 0.5 ppm. The atmospheres in this study were generated by photooxidation of propylene or ethylene in order to simulate photochemical air pollution. Although formaldehyde was measured in the atmospheres, additional photochemical smog irritants were present.

In a similar study by the above group (Stephens et al. 1961), the eye irritation potential of both photochemical smog and its individual constituents was examined. Healthy students in groups of 7 to 75 were exposed to formaldehyde via eye goggles. Eye irritation (none, medium,

or severe) was reported every 30 seconds over 5- to 12-minute periods. Medium and severe irritation were considered positive responses. In a static flow system, positive responses ranged from 8% (6/75 individuals) during exposure to 1 ppm to 67% (18/27 individuals) at 5 ppm. In a dynamic flow system, positive responses ranged from 24% (9/37 individuals) for 2 ppm to 100% (7/7 individuals) for 4 ppm. One ppm was considered the threshold for detection and 5 ppm produced severe eye irritation.

In a study to determine the threshold for eye irritation, Bender et al. (1983) exposed a series of 7-member test panels to increasing concentrations of formaldehyde: 0, 0.35, 0.56, 0.7, 0.9, and 1.0 ppm. Several panels were used for most concentrations, i.e., groups of 5-28. The panelists were selected for their ability to respond to formaldehyde at 1.3 and 2.2 ppm (i.e., subjects that were unresponsive to these concentrations were not used). The exposures were eye-only for 6 minutes. Response time in seconds was used as a measure of irritation, and irritation was rated on a scale of 1-3, with 0 = none, 1 = slight, 2 = moderate, and 3 = severe. Response time decreased with increasing exposure concentration, becoming statistically significant, i.e., different from clean air, at 1.0 ppm. The severity index was similar for concentrations of 0.35 ppm to 0.9 ppm (none to slight). The 1.0 ppm was rated slightly to moderately irritating, both at first exposure and after 6 minutes of exposure. There was a slight diminution of response at the end of the 6-minute exposure.

Harving et al. (1986; 1990) exposed 15 male and female non-smoking asthmatic subjects (ages 15 to 36 years) to concentrations of formaldehyde typically found in the indoor air environment. The study was conducted in a double-blind fashion with the order of exposure randomized. The subjects were selected on the basis of their bronchial reactivity to histamine (mean provocation challenge of 0.37 mg/mL for a 20% reduction in peak expiratory flow rate) and all subjects except one required bronchodilator therapy regularly. Bronchodilator therapy was discontinued 4 hours prior to the study. Subjects were exposed once a week for 90 minutes to 0, 0.10, or 0.69 ppm. Pulmonary parameters consisting of FEV_1, Raw, SRaw, as well as the flow-volume curves showed no significant changes in the group as a whole or in any individuals. Histamine challenge tests performed for up to 24 hours after the exposures showed no increase in bronchial reactivity. There was no difference in subjective asthmatic symptoms (not described) among the exposure days.

Gorski et al. (1992) exposed 5 healthy subjects and 13 patients with formaldehyde-sensitive contact dermatitis to 0.41 ppm for 2 hours in order to measure pulmonary and immunological responses. All patients had smoked for 10-15 years. The immunological response was measured by of neutrophil chemiluminescence (due to the release of free radicals) in the blood. Ventilatory parameters, which were also measured (VC, FEV_1, and PEF), were not affected by exposure in either group. Chemiluminescence of neutrophils was higher in the sensitive group prior to exposure, increased to a greater degree than in the healthy subjects at 30 minutes postexposure, and remained elevated at 24 hours postexposure. Subjective symptoms were not studied.

In a second study by the above group (Pazdrak et al. 1993), 11 patients with specific skin sensitization to formaldehyde and 5 healthy subjects were evaluated for nasal response to 0.41 ppm as observed by changes in nasal lavage fluid. All subjects were nonsmokers. Nasal lavage (saline washings) was performed prior to, immediately after the 2-hour exposure period, and at 4

and 18 hours after exposure. Albumen, total protein, numbers of eosinophils and basophils, and the proportion of epithelial, neutrophil, eosinophil, basophil, and mononuclear cells were counted or computed. Symptoms of the upper respiratory tract including sneezing, rhinorrhea, mucosal edema, and itching, ranging on a scale 0-7, were summed. A positive clinical challenge was defined as >3. The exposure to formaldehyde caused increases in the number and proportion of eosinophils and elevated albumin and total protein levels in nasal lavage fluid. These elevations were still present 16 hours postexposure. There were no differences in the percent of neutrophil, basophil, or mononuclear cells. No differences in the nasal response between healthy subjects and patients with skin sensitization were observed. Clinical symptoms of itching, sneezing, and congestion were similar between the two groups (approximate score of 4 for both groups). Analytical measurements were not made on the day of testing.

In a third study by the above investigators, the airway response to 0.41 ppm formaldehyde for 2 hours in 10 asthmatic subjects with suspected formaldehyde allergy was compared to that of 10 healthy subjects (Krakowiak et al. 1998). The asthmatic subjects had been exposed to gaseous formaldehyde or formaldehyde solutions in the workplace. The primarily male subjects ranged in age from 19 to 52 years. Spirometry at rest and following bronchial provocation with histamine were recorded before and after the exposure. The study was conducted in a single-blind manner. Clinical symptoms of the upper and lower respiratory tract and evaluation of morphological and biochemical changes in the nasal washings were examined after placebo and formaldehyde exposures. Atopy of the workers was measured as formaldehyde specific serum antibody (IgE). Responses to the challenge were evaluated by saline washings (before and after exposure), nasal symptoms (sneezes, rhinorrhea, edema, and itching; rated on a scale of 0-7), respiratory tract symptoms, and pulmonary function testing. Nasal symptoms were scored on a scale of 0-7, with >3 considered a positive clinical challenge. The exposure "caused sneezing, itching and congestion in all subjects." Immediately after inhalation, nasal symptoms were scored 4.6 and 4.3 by asthmatic and healthy subjects, respectively, with no significant difference between the two groups. This effect was transient. There were no clinical symptoms of bronchial irritation as measured by FEV_1 PEF, and bronchial challenge with histamine. Statistically significant increases in eosinophils in the nasal washings 30 minutes after the exposure were similar in the healthy and asthmatic subjects; leucocytes were also increased in the nasal washings of healthy subjects. There was no increase in basophilic cells or in the mediators tryptase and eosinophil cationic protein. No specific IgE antibodies to formaldehyde were detected in the serum of workers with exposure to formaldehyde. The authors concluded that inhalation of formaldehyde did not induce a specific allergic response in either asthmatic or healthy subjects and that the observed rhinitis was transient.

Ezratty et al. (2007) found no change in lung function (measured as a change in FEV_1, FVC, or PEF) in volunteers exposed to 0.4 ppm formaldehyde for 1 hour. The 12 volunteers (7 men and 5 women) ranged in age form 18 to 44 years. All had been diagnosed with intermittent asthma and allergy to pollen. Exposure to formaldehyde had no effect on lung function. Pre-exposure to formaldehyde had no significant deleterious effect on air allergen responsiveness (methacholine challenge following inhalation of a standardized pollen extract) or sputum inflammatory markers including eosinophilic response. Subjective symptoms were similar between the air only and formaldehyde exposures. No distinct odor was reported by the volunteers.

Bach et al. (1990) compared the reaction performance of 32 subjects chronically exposed to formaldehyde in the workplace (>5 years) with that of 29 control subjects. The subjects (all male, ages 18-64) were exposed in groups of 4 for 5.5 hours, with the concentration reached within the chamber during the first 30-minutes; exposure concentrations were 0, 0.12, 0.33, or 1.0 ppm (measured concentrations of 0, 0.17, 0.39, or 0.9 ppm). Furfurylmercaptan, a coffee aroma constituent, was used to mask the odor of formaldehyde in the chamber. Exposures were arranged in a 4x4 balanced design, involving 4 days of exposure in each of four weeks. This computes to a total of 8 workers and 8 controls being exposed to each concentration. During the exposures, general comfort was assessed with a standard questionnaire with questions involving headache and physical and mental tiredness ("heavy head"). An earlier publication (Bach et al. 1987), summarized subjective ratings of irritation in this study. Subjective ratings of irritation did not correlate with a dose-response relationship. The performance tests consisted of digit span, digit symbols, graphic continuous performance, and a computerized addition test. These tests measure short-term memory, ability to concentrate, changes in psychomotor functions. Heavy head and headache, the latter late in the exposure, were reported more often by the control subjects than by the workers. On a linear scale of 60 mm, scores for these parameters for the respective worker and control populations were 6.0 and 8.0 (heavy head; $p<0.05$) and 2.0 and 5.5 (headache; $p<0.01$). Significant differences were found among the exposures and between the worker and control group, but the results were often confounded by the "inhomogeneity" of the dose-response. For example, the total time used for the graphic continuous performance test was longest for the worker population at the intermediate dose, 0.33 ppm. Performance was also poorest for the digit span test at 0.33 ppm.

Lang et al. (2008) conducted a double-blind study in which 21 healthy volunteers (11 males and 10 females; ages 19-39 years) were subjected to 10 different formaldehyde exposure conditions: (1) 0 ppm, (2) 0.15 ppm, (3) 0.3 ppm, (4) 0.3 ppm with 4 peaks to 0.6 ppm, (5) 0.5 ppm, (6), 0.5 ppm with 4 peaks to 1.0 ppm, (7) 0 ppm, (8) 0.3 ppm and 12-16 ppm ethyl acetate (used as a masking agent), (9) 0.5 ppm with 12-16 ppm ethyl acetate, and (10) 0.5 ppm with 4 peaks to 1.0 ppm plus ethyl acetate. Monitoring of the chamber atmospheres was carried out with an Interscan formaldehyde monitor (Asynco®). Two air samples were also taken during each exposure and analyzed using dinitrophenylhydrazine followed by HPLC with UV detection. Up to four subjects at a time were exposed in a $30m^3$ chamber; all exposures were for 4 hours. Groups were tested in a random fashion over a 2-week period. Exercise, three 15-minute sessions on a bicycle at 80 watts, took place at 0, 120, and 195 minutes. Objective symptoms (blinking frequency and conjunctival redness), and subjective symptoms (standard questionnaire; scored on 6 levels) were reported after 195 minutes. Reaction time to visual and acoustic stimuli was tested before and after exposure. There were no effects on nasal flow and resistance, pulmonary function or decision reaction time under any condition. There were no significant effects on nasal flow and resistance, pulmonary function, and decision reaction time. Slight to moderately increased blinking frequency and conjunctival redness were measured at 0.5 ppm with peaks to 1.0 ppm. Subjective eye and olfactory symptoms were reported at 0.3 ppm; however, when personality traits were evaluated (evaluated in a personality questionnaire) the concentration of 0.3 ppm was no longer an effect concentration. Subjective nasal irritation was reported during the exposure to 0.5 ppm with peaks to 1.0 ppm. Increased symptom scores were reversed 16 hours after exposure. The authors concluded that eye irritation was the most sensitive measurement of formaldehyde exposure.

In a double-blind, exposure-randomized study, Witek et al. (1986; 1987; see also Schacter et al. 1985; 1986) exposed 15 healthy male and female subjects, mean age 25, and 15 male and female subjects classified as mild asthmatics, mean age 22, to clean air or 2.0 ppm formaldehyde for 40 minutes. On a separate day, all subjects exercised for 10 minutes at 450 kpm/min prior to the exposure to 2.0 ppm. Subjects refrained from taking medications for 24 hours prior to the sessions. Pulmonary function parameters including FVC, FEV_1, peak expiratory flow rate (PERF), the maximal flow at 50% of the vital capacity, and Raw were measured. Baseline airway reactivity was assessed with progressive doses of methacholine. Subjects completed a symptom survey upon entering the exposure chamber and at 30 minutes into the exposure. Measurements were also taken at 24 hours after exposure. No significant bronchoconstriction or airway resistance was noted during or 24 hours following exposure, although methacholine challenge for some individuals showed non-significant lower thresholds during the exposures to 2.0 ppm. Ratings for respiratory symptoms averaged mild to moderate but ranged up to severe (non-incapacitating) for some individuals. This was especially true for unusual odor. There was no difference in symptomology between rest and exercise sessions.

Nine subjects that had previously complained of nonrespiratory adverse effects from the urea formaldehyde foam insulation (UFFI) in their homes and nine subjects that were either unaffected by the insulation or had not been exposed to insulation inhaled 1.0 ppm of formaldehyde for 90 minutes or the off-gas from UFFI (Day et al. 1984). The latter material yielded a formaldehyde concentration of 1.2 ppm; the exposure was for 30 minutes. None of the measured pulmonary parameters consisting of FVC, FEV_1, or $FEF_{25-75\%}$ showed any clinically or statistically significant response to exposure in either group. Incidences of subjective symptoms were equally divided between the two groups of subjects. Fifteen of 18 subjects complained of eye irritation during the exposure to 1.0 ppm formaldehyde (severity of symptoms was not described). Fewer subjects complained of nasal congestion (7), tearing (6), and throat irritation (5). Tolerance developed rapidly.

In a second study by this group (Pross et al. 1987), a broad range of immunologic parameters was studied in subjects with a history of asthma attributed to UFFI. Twenty-three asthmatic subjects came from homes insulated with urea-formaldehyde foam, and four asthmatic control subjects came from conventionally insulated homes. All subjects were exposed to room air for 30 minutes, formaldehyde gas at 1.0 ppm for 3 hours, or the UFFI off products for 3 hours as described in Day et al. (1984) above. Data from the UFFI group were not different from data of the subjects whose homes were insulated with conventional methods, either before or after the exposures. Minimal but statistically significant increases in the percent of eosinophils and T8 positive lymphocytes were observed after the exposures to urea-foam off-products (including mold) and formaldehyde. Natural killer lymphocyte response to α-interferon was decreased in both groups of subjects after exposure to UFFI. The authors stated that the significance of these changes is unclear.

A series of 5-hour exposures, during which 16 healthy male and female students, ages 20-33, inhaled 0.2, 0.4, 0.8, or 1.6 ppm, was conducted by Andersen and Molhave (1983). The students entered the chamber in groups of four, each group undergoing a different exposure on each of four days. Five of the subjects were smokers. Control data were generated each day during a 2-hour period in the chamber prior to the exposures. The following parameters were

measured: nasal mucociliary flow, nasal airflow resistance, FVC, FEV_1, and FEF_{25-75}. Subject airway irritation was noted by each subject using a scale of 1-100. Three times a day, once during the control session and twice during the exposures, the subjects performed two of three mathematical tests, each of 15-minutes duration. These tests involved addition, multiplication, and transfer of numbers to punchcards. The mucus flow rate slowed during exposures to 0.2 and 0.4 ppm, with no further slowing at the higher exposures or after 3 hours. The decrease in mucus flow was most pronounced in the anterior two thirds of the nose; the posterior nasal passage was unaffected. No significant differences were found in nasal airway resistance or pulmonary parameters. At 0.2 and 0.4 ppm, no discomfort was registered during the first two hours of exposure. Discomfort increased and was registered earlier with higher concentrations. For example, at the two higher concentrations, discomfort was reported during the first hour of exposure. Some subjects reported no discomfort at any time during any exposure. Although at least one individual reported a discomfort rating of 50 (described as "discomfort") during the exposure to 1.6 ppm, the average rating was 18 which fell in the middle of the "slight discomfort" range. Performance on the mathematical tests was unaffected by the exposures.

Frigas et al. (1984) studied 13 patients with symptoms suggestive of formaldehyde-induced asthma for response to a formaldehyde inhalation challenge. These patients had been exposed either occupationally or in the home to formaldehyde at concentrations of 0.1 to 1.2 ppm for 4 months to 9 years. Reported symptoms during the home or work exposure involved chest tightness, coughing, or wheezing. Five of the patients were being treated with bronchodilators. Treatment was discontinued 24 hours prior to the challenge, and patients were free of symptoms when tested. Patients were challenged with placebo (room air), 0.1, 1.0, or 3.0 ppm for 20 minutes via a face mask. Subjective symptoms were also noted. Following the challenge and for up to 24 hours after, no patient had a decrease in FEV_1 greater than during the room air challenge. Irritation of the eyes, nose, and throat and tightness of the chest were reported as frequently with the placebo as with the formaldehyde challenges. The authors were unable to substantiate that formaldehyde exposure in the home or workplace was the cause of the asthmatic symptoms.

The following series of studies (Kulle et al. 1987; Kulle 1993; Green et al. 1987; Sauder et al. 1986; 1987) were performed by the same group of investigators. Kulle et al. (1987) exposed 19 healthy nonsmoking male and female subjects, mean age 26.3 ± 4.7 years, to each of five randomly assigned exposures for three hours. Exposures were separated by one week. Ten subjects were exposed to 0, 0.5, 1.0, or 2.0 ppm at rest or 2.0 ppm with exercise; nine subjects were exposed to 0, 1.0, 2.0, or 3.0 ppm at rest or 2.0 ppm with exercise. The exercise consisted of an 8-minute session on a bicycle ergometer every half hour. Each subject served as his or her own control. Spirometric measurements including FVC, FEV_1, $FEF_{25-75\%}$ were performed at time = 0, 30, 60, 90, 120, 150, and 180 minutes and on the postexposure day. Airway resistance and thoracic gas volume were measured prior to and at completion of each exposure. Nonspecific airway reactivity was measured with a methacholine challenge at the completion of each exposure. Nasal resistance was measured prior to and following each exposure. Symptoms (nose or throat and eye irritation, chest discomfort, cough, and headache) were recorded via a questionnaire at six intervals during the exposures. Symptoms were scored as 0 = none, 1 = mild (not annoying), 2 = moderate (annoying), or 3 = severe (debilitating). There were no significant decrements in pulmonary function parameters or increases in bronchial reactivity at any concentration; nasal flow resistance increased at 3.0 ppm. The dose-response relationship for

odor sensation and eye irritation were both significant ($p<0.0001$), but respective scores were only mild (1.0) or mild to moderate (1.4) at 3 ppm. The nose/throat irritation dose-response was close to significant, but the mean subjective symptom score at 3.0 ppm was between none and mild (0.22). At 2.0 ppm with exercise, nose/throat irritation increased significantly ($p<0.05$), but the symptom score was <1 (less than mild irritation). Exercise had no effect on eye irritation or odor sensation. There was great variability in the odor threshold; four of nine subjects sensed the odor of formaldehyde at 0.5 ppm. In a reexamination of the above study, Kulle (1993) estimated the thresholds for odor and irritant responses. Estimated thresholds were <0.5 ppm for odor sensation, 0.5-1.0 ppm for eye irritation and 1.0 ppm for nose/throat irritation. No substantial differences were seen between the symptom responses of male and female subjects.

Green et al. (1987; see also Kulle et al. 1986) found small but significant decrements in lung function in healthy normal subjects inhaling 3.0 ppm while engaged in heavy exercise. Some individuals in the study exhibited decrements in FEV_1 of >10%. In this study, 22 healthy male and female subjects, average age 27, and 16 male and female asthmatic subjects, average age 27, were exposed to 3 ppm for 1 hour. All of the subjects were nonsmokers. Asthmatic subjects discontinued medications within 12 hours of the study. Asthmatic subjects performed intermittent moderate exercise (V_E = 37 L/min), so as to minimize exercise-induced bronchoconstriction, and healthy subjects engaged in intermittent heavy exercise (V_E = 65 L/min). The study was performed in a double blind fashion in that both subjects and pulmonary technicians were unaware of the exposure concentrations. Symptoms and pulmonary function were assessed during exposure and SGaw was assessed after the exposure (see Kulle et al. 1987). Both groups exhibited similar, significant increases in perceived odor, nose/throat irritation, and eye irritation throughout the exposure. Mean scores for both groups for each of the three parameters attained a score of approximately 1.8 (mild to mild/moderate) at 17 minutes which decreased only slightly throughout the remaining exposure. There were small but significant decrements in lung function in the healthy subjects near the end of the exposure. Although the mean decrement in FEV_1 was 2%, 2 healthy individuals had decrements of >10% as did 2 asthmatic subjects.

In a follow-up study, Green et al. (1989) exposed 24 non-smoking healthy male and female subjects, average age 24, to 3.0 ppm for 3 hours. For 15 minutes of each hour the subjects performed heavy exercise on a bicycle that raised their minute ventilation to 60-70 L/min. Symptom questionnaires were completed and spirometric measurements were made as in the study of Kulle et al. (1987). Symptoms ratings and scores ranged from none = 0 to severe = 5. All symptoms were significantly increased over the air exposures, but average scores were <0.5 for headache and chest discomfort (none to mild) and between 1.0 and 1.5 for eye, nose, and throat irritation (mild to mild-moderate) at all time points. There was no significant effect of formaldehyde on FEV, FEV_2 or FEV_3. There was a significant effect of formaldehyde exposure on $FEF_{25-75\%}$ at 50 and 80 minutes and a decrease in peak flow at 120 minutes. Although statistically significant, mean decrements were <6%. Formaldehyde exposure was not associated with increased cough compared to clean air exposure.

Sauder et al. (1986) exposed nine healthy nonsmokers to 3 ppm for 3 hours. Each subject served as his or her own control. Spirometric measurements (FVC, FEV_1, and FEF_{25-75}) were performed at 0, 20, 60, 90, 120, 150, and 180 minutes. A body plethysmograph technique was used to determine FRC and Raw; SGaw was computed from Raw. A bicycle ergometer exercise

was completed two minutes prior to each spirometric measurement (except at 0 time). Airway reactivity was measured with a methacholine challenge following the exposures to both clean air and 3 ppm. Odor and symptoms of irritation (nose or throat and eye irritation, chest discomfort, tingling in feet or hands, cough, and heart palpitations) were recorded via a questionnaire at six intervals during the exposures. Symptoms were scored as none (0), mild (1), moderate (2), or severe (3). Statistically significant changes in FEV_1 of 2% and $FEF_{25-75\%}$ of 7% were not biologically significant. No statistically significant changes were observed in FVC, FRC, SGaw, or airway reactivity. Odor and nose /throat irritation were scored as mild to moderate, 1.22 and 1.33, respectively. Eye irritation was scored as none to mild (0.78). Five of the subjects scored the nose/throat irritation as moderate whereas only one subject scored the eye irritation as moderate.

Using the same protocol as in the above study, Sauder et al. (1987) exposed nine nonsmoking subjects with a characteristic clinical history of asthma and airway hyperreactivity to 3 ppm of formaldehyde for 3 hours. The male and female subjects ranged in age from 26 to 40 years. Seven of the nine subjects were on regular medications prior to the study; all medications were discontinued 12 hours prior to the study. Based on prestudy pulmonary parameters, three subjects had mild airway obstruction and one subject had moderate airway obstruction. All subjects had marked airway hyperreactivity to methacholine. Eight of the nine subjects had a history of hayfever. During the study, each subject served as his or her own control and received clean air for 3 hours during day 1. The following week, each subject was exposed to 3 ppm formaldehyde for 3 hours (day 2). Pulmonary function parameters including FVC, FEV_1, FEF_{25-75}, SGaw, and FRC were recorded several times during the exposures. Airway reactivity was measured with a methacholine challenge following the exposures to both clean air and 3 ppm. Symptoms (nose or throat and eye irritation, chest discomfort, tingling in feet or hands, cough, and heart palpitations) were recorded via a questionnaire at six intervals during the exposures. Symptoms were scored as mild, mild/moderate, moderate, moderate/severe, or severe. Inhalation of 3 ppm resulted in no significant group change in pulmonary function parameters or airway reactivity. On an individual basis, none of the changes were biologically significant. There was a significant increase in some nose or throat and eye irritation during the 3-hour exposure to 3 ppm. But, the group mean value for nose or throat irritation, statistically significant at $p<0.05$ at only the 30-minute interval, was rated as mild. For the group, eye irritation was rated as mild/moderate beginning at 2 minutes into the exposure and continuing throughout the exposure. However, one subject scored the eye irritation as severe. This score was in response to a questionnaire (not self-reported) and the subject remained in the room for the entire 3-hour exposure. This subject did not experience bronchoconstriction or changes in pulmonary function during the entire exposure. It should be noted that in this study, 22% of the subjects reported eye irritation and 33% responded with nose/throat irritation during the exposure to clean air.

Sheppard et al. (1984) exposed 7 nonsmoking male and female subjects, ages 18 to 37 to 0, 1, or 3 ppm for 10 minutes at rest or while exercising on a bicycle ergometer at a work rate of 100 watts. The study was performed in a double-blind manner. Formaldehyde was delivered by a mouthpiece. All subjects had a history of mild asthma as evidenced by recurrent episodes of wheezing, chest tightness, and reversible airways obstruction. The subjects had marked airway hyperresponsiveness to histamine. Six of the 7 subjects had responded with airways resistance to <1 ppm sulfur dioxide in a previous study. All medications were discontinued prior to the

study. Inhalation of 1 or 3 ppm of formaldehyde at rest or during moderate exercise did not significantly increase airway resistance compared to the control exposure. In two subjects, exercise increased airway resistance in a similar manner following the control, 1, or 3 ppm exposure.

Weber-Tschopp et al. (1977) exposed a group of 33 healthy male and female students to concentrations that increased from 0.03 to 3.2 ppm over a period of 37 minutes. At discrete concentrations (0.03, 0.5, 1.2, 1.7, 2.1, 2.5, 2.8, and 3.2 ppm), eye, nose and throat irritation were rated on a scale of 1 to 4, with ratings of 1 = none, 2 = a little, 3 = moderate, and 4 = strong. Compared with control scores of approximately 1.2, 1.2, and 1.1, respectively for eye, nose and throat irritation (values read from graphs), respective scores for exposure to 3.2 ppm were approximately 2.0, 2.0, and 1.1, respectively. Average severity scores for exposure to 1.2 ppm were approximately 1.4, 1.3, and 1.1. In a second part of this study, 48 healthy students inhaled 0, 1, 2, 3, or 4 ppm, each for 1.5 minutes. Irritation as well as eye blinking were scored. Average rates of eye blinking were not significantly affected at 1.2 ppm, but significantly increased at higher exposures (from about 22 blinks/minute to 35 blinks/minute at 2.1 ppm and 38 blinks/minute at 3.2 ppm). Compared with the 37 minute exposure, eye irritation scores were lower during the 1.5 minute exposures, whereas nose irritation scores were higher. The lower scores during the longer exposure indicate some adaptation to the irritancy. The authors considered the threshold for both eye and nose irritation to be 1.2 ppm, the threshold for throat irritation to be 2.1 ppm, and the threshold for eye blinking to be 1.7 ppm.

The above authors (Weber-Tschopp et al. 1977) also compared the irritation scores during the formaldehyde exposures to the irritation scores of sidestream cigarette smoke from an earlier study (Weber et al. 1976). The atmosphere for the earlier exposure was generated by smoking cigarettes in a 30 m^3 controlled-air chamber. Mainstream smoke was directed out of the laboratory. Following smoking of 10 cigarettes, the carbon monoxide, formaldehyde, and acrolein levels in the room were 24, 0.46, and 0.11 ppm, respectively. On a scale of good (1), acceptable (2), and bad (3), the quality of the air was considered bad (3); whereas, for the formaldehyde exposure that ranged from 0.03 up to 3.2 ppm over 37 minutes, the highest score was 2.2, and the 1.5 minute exposure to 4.0 ppm approached a score of 3. Auerbach et al. (1977) notes that undiluted cigarette smoke may contain 32-114 ppm of formaldehyde.

In a study of eye irritation and reflex bronchoconstriction response to irritant gases, Douglas (1974) exposed 1-6 healthy and atopic male and female subjects individually to approximately 6, 8, 12, 18, 24, or 30 ppm (eye irritation) or 4, 8, 10, or 12 ppm (broncho–constriction). Atmospheres were generated by bubbling air through formalin solutions. Following collection of formaldehyde from the airstream in 3-methyl-2-benzothiazolone, measurements were made with a colorimetric/spectrophotometric system. Separate eye and inhalation exposures were conducted using goggles in the former case and a mouth tube in the latter. Eye exposures lasted for 15 seconds. Time to onset of eye irritation was measured; no symptom scores were recorded. During inhalation exposures, subjects inhaled 10 one-liter breaths. A body plethysmograph was used for measuring bronchoconstriction. A single subject exposed to 6 ppm reported no eye irritation. Four of five subjects reported no eye irritation at 8 ppm, whereas, 5 of 6 subjects exposed to 12 ppm reported undefined irritation (one within 5 seconds). Neither of two subjects exposed to 18 ppm reported eye irritation. Single subjects exposed to 24 or 30 ppm reported eye irritation within 10 seconds.

During mouth breathing (which bypasses the scrubbing capacity of the nose), the single subject exposed to 4 ppm reported no subjective throat symptoms. Subjects inhaling 8 or 10 ppm reported mild sensations in the throat and subjects inhaling 12 ppm reported "irritancy" in the throat. There was a drop of 0 to 43% in airway resistance at 8 ppm and a drop in airway resistance of 50-108% at 12 ppm. Neither eye irritation nor bronchoconstriction appeared related to atopy.

One of the earliest controlled studies aimed at assessing irritation from smog components was performed by Sim and Pattle (1957). They exposed 12 healthy males, ages 18 to 45 to 13.8 ppm of formaldehyde in a chamber for 30 minutes. Initially, the exposure caused considerable nose and eye irritation. Mild lacrimation continued for some period of time. The eye irritation was not considered severe, and adaptation occurred in about 10 minutes. Formaldehyde was dispersed into the chamber by bubbling air through a known volume of liquid until all the liquid had evaporated. Chamber atmospheres were measured with a titration technique.

During analytical determinations of chamber concentrations, Barnes and Speicher (1942) entered the chamber "a number of times." Analytical measurements by two procedures, a chemical method and the dropping mercury electrode method, both indicated a concentration of 20 ppm. Upon entering the chamber, the authors noticed irritation of the eyes and upper respiratory tract. Lacrimation started within 15 to 30 seconds, and irritation of the nose and throat became quite pronounced. On some occasions, sneezing occurred within a minute or two. The authors commented that they could continue the exposure "for some length of time but it was distinctly uncomfortable..." and objectionable. They suggested that formaldehyde in workroom air should be at a value somewhat less than 20 ppm.

A panel of experts, the Industrial Health Foundation Panel, identified an occupational exposure limit that would prevent irritation (Paustenbach et al. 1997). Following a critique of approximately 150 scientific articles, "the panel concluded that for most persons, eye irritation clearly due to formaldehyde does not occur until at least 1.0 ppm. Information from controlled studies involving volunteers indicated that moderate to severe eye, nose, and throat irritation does not occur for most persons until airborne concentrations exceed 2.0-3.0 ppm." The panel concluded that exposure to 0.3 ppm for several hours in controlled studies was no different than exposure to room air. At 0.5 ppm, eye irritation is not observed in the majority of workers. Consequently, the panel recommended an 8-hour TWA of 0.3 ppm with a ceiling concentration of 1.0 ppm. The panel failed to identify a hypersensitive population or individuals that could be sensitized. The panel also concluded that there was sufficient evidence to show that persons with asthma respond no differently than healthy individuals following exposures up to 3.0 ppm.

2.3. Neurotoxicity

Two studies on neurotoxicity are described in Section 2.2.3 above. Andersen and Molhave (1983) found no affect of 5-hour exposures to 0.2, 0.4, 0.8, or 1.6 ppm on performance of mathematical tests.

As noted in the Bach et al. (1990) study above, there was no concentration-response relationship for changes in performance tests consisting of digit span, digit symbols, graphic continuous performance, and addition during 5.5-hour exposures. These tests measure short-term memory, ability to concentrate, and changes in psychomotor functions. However, the investigators did attribute the poorer performance at the intermediate dose, 0.33 ppm (compared with 0, 0.12, or 1.0 ppm), to either CNS effects or to distraction due to irritation caused by the exposure.

2.4. Developmental/Reproductive Toxicity

Few studies addressed developmental or reproductive effects in humans. No effect on sperm number or morphology was found in a small group of pathologists (Ward et al. 1984). There was no evidence for increased rates of miscarriage among a group of 275 persons with presumed residential exposure to formaldehyde (Garry et al. 1980).

2.5. Genotoxicity

The genotoxicity of formaldehyde has been reviewed by many groups including NRC 1980, WHO (1989), Feron et al. (1991), ATSDR (1999), and IARC (2006). Results from occupational studies, which usually involved exposures to low concentrations, are conflicting. Where increased incidences of sister chromatid exchanges, chromosomal aberrations, or micronuclei formation were recorded in exposed workers, differences were small when compared with those of control workers. Formaldehyde easily haptenates human proteins (Maiback 1983). IARC (2006) reviewed studies that showed increased DNA-protein cross-links in workers exposed to formaldehyde.

2.6. Carcinogenicity

According to ATSDR (1999), there are over 40 epidemiology studies that examine the potential for occupational exposure to formaldehyde to cause cancer in humans. Various agencies and panels have reviewed the data and taken varying positions on this issue. The reviews all suggest that formaldehyde induces cancer (nasal squamous cell carcinoma) in rats and mice exposed to airborne levels that are associated with significant irritation resulting in hyperplasia and tissue damage with repeated exposure. In humans, the overall evidence for cancer is inconsistent and associations are relatively weak when significant.

Formaldehyde is carcinogenic to the Fischer 344 rat at dose levels that are within the same order of magnitude as those to which humans are exposed. However, epidemiology studies have failed to show any convincing evidence correlating formaldehyde exposure and nasal cancer in exposed populations (Federal Panel on Formaldehyde 1982; Starr et al. 1983; Blair et al. 1986; Ad Hoc Panel on Health Aspects of Formaldehyde 1988). Carcinogenicity risk has been evaluated in occupational groups with known exposure to formaldehyde; these include pathologists, anatomists, morticians, and chemical workers. Cancers at remote sites have occasionally been correlated with exposure, but because formaldehyde is so highly reactive and rapidly metabolized/detoxified, inhalation is unlikely to affect a distant site. The Industrial Health Foundation panel of experts concluded that cancer risk of formaldehyde is negligible at airborne concentrations that do not produce chronic irritation (Paustenbach et al. 1997).

An independent international panel of scientists, the Ad Hoc Panel on Health Aspect of Formaldehyde (1988) reviewed and evaluated more than 30 epidemiology studies. The panel concluded that "(1) for no malignancy in man is there convincing evidence of a relationship with formaldehyde exposure, and (2) furthermore, if a relationship does exist, the excess risk, in absolute terms, must be small."

The U.S. EPA (2003) in their Weight-of-Evidence characterization classifies formaldehyde as B1, probable human carcinogen. This classification is based on limited evidence in humans and sufficient evidence in animals. "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. An increased incidence of nasal squamous cell carcinomas was observed in long-term inhalation studies in rats and in mice. The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde." The discussion provided in the IRIS report points out the inadequacies and non-site specificity of many of the epidemiology studies. Although several studies were well-conducted, all suffered from one or more of the following problems: lack of control for smoking, lack of trend with increasing concentration or cumulative exposure, cancers at sites other than the nasopharynx, lack of atmospheric measurements, small sample size, and exposure to other agents.

In 2006, IARC reevaluated their previous assessment of cancer based on epidemiologic studies and concluded that there was "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans." They upgraded their evaluation from Group 2A, "probably carcinogenic to humans" to Group 1. IARC also concluded that "there is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde."

The Consumer Product Safety Commission has acted to ban formaldehyde in products as a cancer risk (Fed. Reg. 47:14366). This ban was set aside by a reviewing court in 1983.

In the carcinogenicity study of Kerns et al. (1983; see Section 3.6), the target dose of formaldehyde in the nasal mucosa of rats was not linearly proportional to the airborne concentration, so that a linear extrapolation of the target doses at concentrations above 5.6 ppm would overestimate the target doses at low concentrations (Starr 1990). Therefore, a quantitative risk assessment using airborne formaldehyde concentrations would overestimate the tumor risk at low exposure concentrations. This group (Kerns et al. 1983; Heck et al. 1990; Starr 1990) also found that at the same concentrations, doses in the monkey were about 5-10 times lower than those in the rat. This indicates that tumor risk for primates would be overestimated if the quantitative risk assessment were done using the dosimetry data in the rat. Animal studies are summarized in Section 3.6. A carcinogenicity assessment using the rat data of Section 3.6 is in Appendix B.

2.7. Summary

The discomfort of sensory irritation is difficult to measure with certainty. Studies with controlled human exposures indicate that short-term exposure to 1 to 3 ppm induces eye, nose,

and throat irritation that is generally described as slight to mild/moderate by most subjects (Weber-Tschopp et al. 1977; Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Witek et al. 1986; Kulle et al. 1987; ATSDR 1999). Sensory irritation below 1 ppm is difficult to distinguish from the control situation (Bender et al. 1983; 2002). At the upper end of the 1-3 ppm range, a greater number of subjects experience mild irritation, i.e., at 3 ppm most subjects rated eye, nose, or throat irritation mild. The multi-dose clinical studies (Weber-Tschopp et al. 1977; Andersen and Molhave 1983; Bender et al. 1983) show that minimal to no discomfort is observed at levels up to 1 ppm; at 1 ppm and above some subjects show definite signs of discomfort. Elevated eosinophil counts and protein in nasal lavage fluid consistent with mild irritation were observed following 4 hours of exposure to 0.41 ppm (Gorski et al. 1992; Pazdrak et al. 1993; Krakowiak et al. 1998; ATSDR 1999). There were no changes in pulmonary parameters at concentrations between 0.41 and 3 ppm in healthy subjects, asthmatics, or subjects with dermal sensitivity to formaldehyde (Andersen and Molhave 1983; Day et al. 1984; Frigas et al. 1984; Sheppard et al. 1984; Harving et al. 1986; 1990; Witek et al. 1986; 1987; Pross et al. 1987; Sauder et al. 1987). Furthermore, there were no biologically significant differences in pulmonary parameters or symptoms greater than moderate irritation in exercising healthy subjects (Witek et al. 1986; Green et al. 1987; Kulle et al. 1987), asthmatics at rest (Frigas et al. 1984; Sheppard et al. 1984), or exercising asthmatics (Sheppard et al. 1984; Witek et al. 1986; Green et al. 1987) exposed to 2 or 3 ppm for up to 3 hours. In all studies, symptoms were related to eye and upper respiratory tract irritation. There was no evidence of these low concentrations having an effect on the lower respiratory tract.

The studies of Gorski et al. (1992); Pazdrak et al. (1993); and Krakowiak et al. (1998) were not summarized with the above studies because (1) the authors found irritation at levels not found irritating in approximately 20 other well-conducted clinical studies (that included analytical measurements), and (2) the authors did not make chamber measurements on the days the study was conducted.

Concentrations of 5 to 13.8 ppm were considered extremely irritating to the eyes of some subjects (Stephens et al. 1961), but not others (Douglas 1974). Unfortunately, some of the procedures and methods of exposure in the Douglas (1974) study make it of limited relevance for AEGL consideration. Mild lacrimation occurred at 13.8 ppm, but adaptation took place during the 30-minute exposure (Sim and Pattle 1957). Barnes and Speicher (1942) considered short exposures to 20 ppm objectionable. Only one study addressed airway “conductance” (Douglas 1974). Air was inhaled through a mouth tube in this study, thus bypassing the scrubbing capacity of the nasal passages.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Salem and Cullumbine (1960) exposed groups of 50 mice, 20 guinea pigs, and 5 rabbits to 15.3 ppm formaldehyde vapor or 16.1 ppm formaldehyde aerosol for up to 10 hours or until the animals died. Exposure took place in 1 m^3 glass flow-through chamber. Most deaths occurred on subsequent days (not specified). Total mortalities for mice (deaths during exposures plus deaths on subsequent days) for the vapor and aerosol were 34% (17/50) and 96% (48/50), respectively. Total mortalities for guinea pigs for the vapor and aerosol were 40% (8/20) and 5% (1/20), respectively. Total mortalities for rabbits for the vapor and aerosol were 60% (3/5)

and 20% (1/5), respectively. At autopsy, all species displayed expanded, edematous, and hemorrhagic lungs and fluid in the pleural cavity. These lethal values appear low in comparison to the human experience and additional animal studies discussed below. Studies utilizing lethal concentrations are summarized in Table 4.

TABLE 4. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	820	30 min	LC_{50}	Skog 1950
Rat	350 478	4 h 4 h	No deaths LC_{50}	Nagorny et al. 1979
Rat	250	4 H	33-66% Mortality	Carpenter et al. 1949
Mouse	1000 2162	10 min 10 min	No deaths LC_{50}	Alarie 1981
Mouse	900 140	2 h 2 h × 4 d	100% Mortality No substantial distress	Horton et al. 1963
Mouse	320 320	100 min 55 min	Lt_{50} 5% Mortality	Bitron and Aharonson 1978
Mouse	98 410	2 h 2 h	No deaths LC_{50}	Nagorny et al. 1979

3.1.1. Rats

Skog (1950) exposed groups of 8 rats to concentrations ranging from approximately 490-1400 ppm for 30 minutes. Rats were observed for 3 weeks postexposure. Extreme respiratory difficulty was observed immediately after exposure. This sign lasted for several days. The first deaths occurred 6 hours postexposure. At autopsy, microscopic changes in the lungs included hemorrhages and intra-alveolar and perivascular edema. Hyperemia, perivascular edema, and necroses were found in the livers and perivascular edema was observed in the kidneys. The late death of one rat, 15 days postexposure, was attributed to purulent bronchitis and diffuse bronchopneumonia. The LC_{50} was 810 ppm. In referring to a series of experiments with aldehydes, the authors stated that the lowest doses generally produced 0% mortality, and the highest dose generally produced 100% mortality.

Nagorny et al. (1979) exposed 21 groups of 6-12 male rats to various concentrations for 4 hours. Concentrations of 228 to 350 ppm were not lethal. Some deaths may have occurred in groups exposed to 317 to 732 ppm (data not clear), and all rats died at >732 ppm with the exception of the group exposed to 764 ppm. The 4-hour LC_{50} was 478 ppm. Clinical signs preceding death included excitement, increased respiration, open mouth, and bloody discharge from the nose, followed by a prone position. Deaths occurred one or more days after exposure. Some of the deaths were attributed to the combination of toxicity and pneumonia.

Carpenter reported that 2 to 4 of 6 rats died following a 4-hour exposure to 250 ppm. The postexposure observation period was 14 days. No further details were reported in this screening study.

Kamata et al. (1996) exposed groups of 6 male Fischer rats to 0, 128, or 295 ppm for 6 hours in order to study effects on pulmonary surfactant. Dyspnea and closed eyes were observed immediately after the start of exposure, and lacrimation, bloody nasal discharge, and salivation were observed shortly afterwards. No mortalities occurred during the treatment, but one rat in the high-concentration group died just after completion of treatment. Autopsy showed the following dose-related findings: edema surrounding the trachea, hydrothorax, congestion of the lungs and nasal cavities and retention of mucus in the lungs. Lung washes showed that surfactant production was depressed. A number of hematological and clinical chemistry changes were also observed. Animals were sacrificed immediately after the exposures; therefore, the true mortality incidence could not be ascertained.

3.1.2. Mice

As part of a study on respiratory depression by irritant chemicals, Alarie (1981) also determined 10-minute LC_{50} values. The 10-minute LC_{50} for formaldehyde in Swiss-Webster mice was 2162 ppm (95% confidence interval, 1687-2770 ppm). Mortality was recorded during the following 3-hour period. From the concentration mortality graph provided in the report, the 10-minute concentration resulting in no deaths was estimated at 1000 ppm. The California Environmental Protection Agency (1999) estimated MLE_{05} and BC_{05} of 1440 and 778 ppm, respectively. Because deaths may occur later than 3 hours postexposure, these values should be considered estimates.

A single 2-hour exposure to 900 ppm resulted in deaths from massive pulmonary hemorrhage and edema in C3H mice. When mice were subjected to 163 ppm for three 1-hour periods each week, substantial deaths occurred after the 6^{th} exposure. Concentrations of 41 and 81 ppm were well tolerated for up to 35 weeks. Mice inhaling 114 ppm for 2 hours daily for 4 days did not show signs of substantial distress (Horton et al. 1963).

Nagorny et al. (1979) exposed 14 groups of 6-8 male and female mice to formaldehyde for 2 hours. Concentrations of 64 to 98 ppm were not lethal. Concentrations of 109 to 745 ppm caused 12.5-83.3% lethality. At 746 to 820 ppm all mice died. The 2-hour LC_{50} was 410 ppm. The authors also calculated a 2-hour LC_{16} of 126 ppm and a 2-hour LC_{84} of 695 ppm.

Bitron and Aharonson (1978) exposed groups of 28-112 mice to 320 ppm for varying periods of time and then calculated the Lt_{50}, the time at which 50% of the mice died. The mice were restrained in tight-fitting cylindrical chambers. The postexposure observation period was 45 days. The Lt_{50} was 100 minutes. Exposure durations of 55, 90, 150, and 320 minutes resulted in mortalities of approximately 5, 44, 81, and 100%, respectively (data read from a graph).

3.2. Nonlethal Toxicity

Few studies involving acute exposures were located. Those studies that did employ acute exposures were usually directed at histopathological changes in the nasal tissues, and animals were sacrificed immediately after exposures. A few repeat-exposure studies are included in the discussions below.

3.2.1. Nonhuman Primates

Groups of three Rhesus monkeys inhaled 0 or 6 ppm for 6 hours/day, for one week, or 6 ppm, 6 hours/day, 5 days/week, for 6 weeks in order to study effects on the respiratory epithelium (Monticello et al. 1989). The formaldehyde-exposed animals showed signs of ocular irritation - mild lacrimation and conjunctival hyperemia - throughout each exposure period. Open mouth breathing was observed during the first 15 minutes of each exposure. After one week of exposure, bilateral changes in the respiratory epithelium included loss of goblet cells and cilia, minimal to mild epithelial hyperplasia with or without early stages of squamous metaplasia, and an associated neutrophilic inflammatory response. After six weeks of exposure, there was minimal progression of lesions, although the affected area was more extensive. After one week of exposure, lesions showed a progression of severity with the anterior most sections being the most severely affected; the larnyx/trachea was little affected. After six weeks, lesions were more similar in the anterior and posterior areas of the nasal cavity. The maxillary sinuses showed no response to exposure, and there were no treatment-related lesions present in the lungs. Tritiated thymidine labeling indices of the nasal passages, larynx, trachea, and carina showed highest labeling indices in the transitional epithelium; the elevation was less than two-fold greater than that of the controls.

3.2.2. Rats

In an early study, Murphy et al. (1964) examined the biochemical effects in 8 adult male Sprague-Dawley rats following exposure to a "sublethal concentration" of 35 ppm for 18 hours. Dyspnea, eye and nasal irritation, and other signs of generalized debility were observed in the rats during the exposures. No further details of the clinical signs were given, and histopathological results were not reported. The level of serum alkaline phosphatase was unaffected by exposure, whereas, the liver alkaline phosphatase was elevated five-fold.

Tobe et al. (1985) exposed groups of 12 male Wistar rats to 0, 10, 20, or 30 ppm for 6 hours in order to observe behavioral as well as biochemical and hematological responses. Signs in the group exposed to 10 ppm were similar to those of the control group. In the group inhaling 20 ppm, rats sniffed the air about 1 minute after the start of exposure; this was followed by face-washing movements. Movements in the 30-ppm group were similar to those in the 20-ppm group. Yellowing of hair around the genital areas was observed in both the 20 and 30-ppm groups. Irritation of the nasal mucosa membrane and trachea (undefined) were observed in these two groups. Biochemical changes included a decrease in leukocytes and plasma alkaline phosphatase and an increase in lung alkaline phosphatase activity. The 10- and 30-ppm groups had a decrease in the mean corpuscular volume and mean corpuscular hemoglobin. The 30-ppm group has a decrease in white blood cells.

Boja et al. (1985) described the behavior and neurotoxicity of adult male Sprague-Dawley rats exposed to 0, 5, 10, or 20 ppm formaldehyde for 3 hours on 2 consecutive days. Rats were sacrificed after the second exposure and brains were analyzed for neurotransmitters. Data were presented for only the 5 ppm exposure. On day 1, motor activity decreased within 15 minutes of exposure with controls showing 80% activity at 15 minutes compared with 45% in the exposed group. Exposure to 5 ppm increased 5-hydroxyindoleacetic acid, 3,4-

dihydroxyphenylacetic acid, and dopamine in the hypothalmus, but did not affect norepinephrine or 5-hydroxytryptamine.

Chang et al. (1981) conducted an RD_{50} study (concentration that lowers the respiratory rate by 50%) with F-344 rats. The RD_{50} value was 31.7 ppm. The RD_{50} in male Wistar rats was 10.0 ppm (C.L., 4.7-13.7 ppm) (Cassee et al. 1996). A maximum decrease in breathing frequency was observed within three minutes of exposure followed by marked desensitization during the remaining exposure (total exposure 30 minutes). The RD_{50} in male Crl:Cd (Sprague-Dawley) rats was 13.8 ppm (Gardner et al. 1985). Concentrations of ≥5.5 ppm produced considerable depressions in respiratory rate within the first minute of exposure, reaching a maximum at about 3 minutes. Incomplete recovery took place during the remainder of the 15-minute exposure.

Chang et al. (1983) exposed groups of male Fischer 344 rats to 0, 6, or 15 ppm for 6 hours in order to study nasal cavity deposition, cell proliferation, and histopathology. Both exposures resulted in approximately a 15% depression in respiratory rate and minute volume. The nasal respiratory epithelium of control rats had a very slow rate of cell turnover. Eighteen hours after a single 6-hour exposure to 15 ppm, a 13-fold increase in cell proliferation was observed. The proliferative response was most pronounced in the basal cell layer. Treatment for 5 days almost doubled the labeling index. Early degeneration and sloughing of respiratory epithelial cells were observed immediately following the single 6-hour exposure. Necrobiotic cells were observed in the most anterior areas of nasal cavity. When rats were sacrificed 18 hours after the exposure, hyperplasia, characterized by a thickened epithelium, scattered degenerate cells, neutrophilic infiltrates, and isolated areas of epithelial sloughing were observed. The olfactory epithelium appeared normal. Lesions observed following a 5-day exposure were much more extensive and more severe. Lesions following the exposure to 6 ppm were not described.

Morgan et al. (1986a) evaluated the effect of exposure on the nasal mucociliary apparatus of groups of F-344 rats exposed to 0.5, 2, 6, or 15 ppm. for 6 hours. Additional groups of rats were exposed to the same concentrations for up to 3 weeks. The relationship between inhibition of the mucociliary clearance mechanism and histopathologic changes in the underlying epithelium was also evaluated. No signs of irritation were observed in rats exposed to 0 or 0.5 ppm. Rats exposed to 2, 6, or 15 ppm exhibited concentration-related evidence of eye and nose irritation including ocular and nasal discharge. These signs were minimal at 2 ppm. After a single 6-hour exposure to 15 ppm, direct impairment of nasal mucociliary function and cessation of ciliary activity were observed in the anterior region of the nose. Lesions in this area were characterized by separation of epithelial cells and intravascular margination and local tissue infiltration by neutrophils and monocytes. The investigators characterized the lesions as "minimal effects," but indicated that the lesions were followed by severe degenerative changes. In what appears to be the same group of animals, Swenberg et al. (1983) characterized the lesions as acute degeneration of the respiratory epithelium with edema and congestion... evident at the end of one day of exposure. Less severe changes were found in rats exposed to 6 ppm for 6 hours, and no epithelial lesions were detected in rats exposed to 2 or 0.5 ppm for 6 hours. Repeated exposures resulted in more extensive changes in the anterior nasal passages. The investigators considered inhibition of mucociliary function a more sensitive indicator of toxicity than epithelial lesions.

In a second study (Morgan et al. 1986b), rats were exposed to 0, 2, or 15 ppm for 10, 20, 45, or 90 minutes or 6 hours with recovery groups examined 1 hour after the 90-minute and 6-hour exposures. There was no evidence of impaired mucociliary function in rats exposed to 2 ppm for 90 minutes or 6 hours. A 90-minute or 6-hour exposure to 15 ppm followed by a 1-hour recovery period resulted in extensive recovery of both ciliary activity and mucus flow. Recovery was almost complete in the group exposed to 15 ppm for 90 minutes, whereas recovery was "considerable but incomplete" in the group exposed for 6 hours.

Groups of 48 male F-344 rats inhaled 0 (filtered air), 0.7, 2, or 6 ppm for 6 hours/day, 5 days/week for up to three weeks (Andersen et al. 2008). Atmospheres were generated by thermal depolymerization of paraformaldehyde into 8 m^3 steel and glass chambers. Atmospheres were monitored by infrared analysis (measured concentrations of 1, 0.6, 1.8, 5.0, and 14 ppm). Sacrifices (n = 8 for each group) took place after 6 hours of exposure, after 18 hours of exposure, at the end of six days of exposure, 18 hours after the sixth exposure, and at the end of 15 days of exposure. Minimal inflammatory infiltrates were frequently noted in controls and all treated groups, with consistent increases evident only in the 6 ppm group. Neither cell proliferation nor histopathology was observed at 0.6 ppm at any time point. Immediately following exposure on day 1, minimal inflammatory cell infiltrate of the maxilloturbinate was present in 6 of 8 rats that inhaled 1.8 ppm and in all rats that inhaled 5.0 ppm. At day 1 recovery, epithelial hyperplasia was observed in 0, 1, 3, and 8 rats in the control through 5.0 ppm groups, respectively. Following 15 days of exposure, rats in the 1.8 ppm and 5.0 ppm groups exhibited epithelial hyperplasia (2 of 8 and 7 of 8, respectively), but all rats failed to exhibit squamous metaplasia. Squamous metaplasia had been observed in 7 of 8 rats in the 5.0 ppm group at the end of the first week of exposure. Cell proliferation, evaluated only at days 5 and 15 was observed only in the 5.0 ppm group.

In the above study (Andersen et al. 2008), an additional group of 8 rats inhaled 15 ppm; sacrifice took place following the 6-hour exposure. Gene expression in rat nasal epithelium was evaluated and compared with that of the groups above. Both temporal and concentration-dependent transitions in genomic signatures were observed between 0.6 and 5.0 ppm. These concentration affected primarily genes associated with extracellular componenets and plasma membrane. The number of genes altered at 15 ppm (evaluated after only a single exposure) was 18-fold greater than those altered at 5.0 ppm.

Dubreuil et al. (1976) observed slight irritation in rats continuously exposed to 1.6 ppm for up to two months. Minimal adverse effects occurred at 4.6 ppm, and clear signs of nasal irritation were observed at 8.1 ppm.

3.2.3. Mice

Kane and Alarie (1977) evaluated sensory irritation in male Swiss-Webster mice. Percent decreases in respiratory rate were measured in groups of four mice inhaling 0.52 to 10 ppm formaldehyde for 10 minutes. From the data, a 50% decrease in respiratory rate, the RD_{50}, was calculated at 3.1 ppm. Chang et al. (1981) conducted a similar study with $B6C3F_1$ mice. The RD_{50} values in mice and rats were 4.9 and 31.7 ppm, respectively. The authors of the latter study point out that the ability of mice to depress their respiratory rate in response to irritants

results in minimization of the inhaled dose and may contribute to differences in respiratory tract toxicity between mice and rats.

A series of immune function and host resistance parameters ere examined in female B6C3F1 mice following inhalation exposure to 15 ppm of formaldehyde for 6 hours/day, 5 days/week for 3 weeks (Dean et al. 1984). There were no deaths, and no significant differences in body weight between the control and exposed group were observed. Lymphoid organ weight, bone marrow cellularity, and hematology parameters were unchanged in formaldehyde-exposed mice. The percentage of T and B lymphocytes and their proliferative responses to mitogens were not significantly altered. Antibody plaque-forming cell response following antigen challenge was unchanged. Macrophage function was normal although some evidence of enhanced hydrogen peroxide production associated with elevated bactericidal activity was observed in resident macrophages. Resistance to challenge with the bacteria *Listeria monocytogenes* was significantly enhanced, while resistance to tumor challenge remained unchanged.

3.2.4. Guinea Pigs

The airway reactivity of guinea pigs to formaldehyde was assessed in several studies. Amdur (1960) measured pulmonary mechanics in groups of 4 to 18 guinea pigs exposed to 0.05, 0.31, 0.58, 1.22, 3.6, 11.0, or 49 ppm for 1 hour. Preexposure values served as control values. An increase in resistance and a decrease in compliance, suggestive of bronchoconstriction, became statistically significant at 0.31 ppm. Decreases in respiratory rate and minute volume became statistically significant at 11 ppm. Delivery of formaldehyde directly to the trachea via a cannula increased the response to formaldehyde. In both cases, the resistance change was reversible in an hour after the exposure ended.

Inhalation of 6 or 10 ppm, 6 or 8 hours/day, for 5 consecutive days failed to elicit pulmonary hypersensitivity or produce antibodies in guinea pigs, although two of four animals that had inhaled 10 ppm for 8 hours over 5 days developed skin sensitivity (Lee et al. 1984). Pulmonary sensitivity, both immediate and delayed, was assessed by measurement of bronchial reactivity in response to a formaldehyde challenge. Dermal sensitivity was assessed with a topical challenge, and antibodies were assessed with formaldehyde-specific antigens. Respiratory rates of animals inhaling 10 ppm for 6 hours were measured over the course of the first day. Respiratory rates first decreased by 45% within the first hours of exposure and remained depressed during he following 5 hours of exposure. The pattern of respiration changed over the course of the exposure, with the first hour resembling that of animals exposed to a sensory irritant and the second hour characteristic of animals with tracheal cannulation, i.e., indicating the formaldehyde had reached the lower respiratory tract. Antibodies to formaldehyde were observed only in guinea pigs administered the material by injection.

In a another study, Swiecichowski et al. (1993) investigated the changes in pulmonary resistance and airway reactivity to intravenous acetylcholine in guinea pigs exposed to selected concentrations of formaldehyde. Groups of 5 to 7 male Hartley guinea pigs were exposed to 0, 0.86, 3.4, 9.4, or 31.1 ppm for 2 hours or to 0, 0.11, 0.31, 0.59, or 1.05 ppm for 8 hours. Baseline reactivities were measured prior to exposure and up to 24 hours postexposure. Tracheal histology was also examined immediately after exposure and for up to 96 hours after exposure to 3.4 ppm for 8 hours. Specific pulmonary resistance to infused acetylcholine increased by 31%

after exposure to 9.4 ppm for 2 hours, but not at the lower exposures. A similar increase was observed following an 8-hour exposure to 1.0 ppm. Microscopic examination of the trachea revealed no changes in the number of ciliated cells of the epithelium or in inflammatory cell infiltration into the lamina propria of the epithelium.

3.3. Neurotoxicity

No information on neurotoxicity in animals was located.

3.4. Developmental/Reproductive Toxicity

Inhalation, oral gavage, dietary, and drinking water studies have been used to study the effects of formaldehyde on reproduction and development. Study results published prior to 1982 were reviewed by the Federal Panel on Formaldehyde (1982). Many of the studies suffered from an unreported or inadequate number of animals in treated dose groups. Details in the studies were often conflicting. Dietary studies with dogs and rats, gavage studies with mice, and drinking water studies with rats, the latter with hexamethylenetetramine (which is metabolized to formaldehyde *in vivo*), were also conducted. Although formaldehyde was not teratogenic in these studies, the panel concluded that additional, well-conducted studies should be performed. In a multi-generation study with rats administered 1% hexamethylenetetramine in the drinking water (Della Porta et al. 1970), there was no effect of treatment on survival or body weight of any generation.

Saillenfait et al. (1989) exposed Sprague-Dawley rats to 0, 5, 10, 20, or 40 ppm for 6 hours/day from day 6 to 20 of gestation. On day 21 of gestation the fetuses were examined. There were no effects on embryo or fetal lethality and no teratogenic effects. The concentration of 40 ppm was maternally toxic as reflected by a significant reduction in dam body weight. Concentrations of 20 and 40 ppm were fetotoxic as reflected by reduced fetal weights, characterized as slight at 20 ppm and 20% at 40 ppm.

Morgan (1990) exposed 25 mated female Sprague-Dawley rats whole-body to 1.9, 4.9, or 9.5 ppm formaldehyde for 6 hours/day from day 6 through day 15 of gestation. Both an air and a room control group were included in the study. Dams were weighed and sacrificed, and examined for reproductive indices; fetuses were weighed and examined for malformations. A significant decrease in maternal food consumption and weight gain was observed in the 10 ppm group. Pregnancy rate, number of corpora lutea, implantation sites, live fetuses, dead fetuses and resorptions, and fetal weight, sex ratio, and preimplantation and postimplantation losses were unaffected by treatment. Incidences of litters and fetuses with major malformations, minor external visceral anomalies, and minor skeletal anomalies were unaffected by treatment. Incidences of reduced ossification of the pubic and ischial bones in the 5 and 10 ppm groups were significantly increased when compared to the air control group but not when compared to the room control group. This effect appeared to be related to the larger litter sizes in the higher exposure groups.

3.5. Genotoxicity

The genotoxicity of formaldehyde has been reviewed by many groups including NRC 1980, WHO (1989), Feron et al. (1991), ATSDR (1999), and IARC (2006). According to IARC (2006), formaldehyde "demonstrates positive effects in a large number of in vitro tests for genotoxicity, including bacterial mutation, DNA strand breaks, chromosomal aberrations, and sister chromatid exchange. Studies in humans showed inconsistent results with regard to cytogenetic changes (micronuclei, chromosomal aberrations, and sister chromatid exchange)." Formaldehyde induced DNA-protein cross-links *in vitro* in human bronchial epithelial cells, fibroblasts, and lymphocytes. Studies in formaldehyde-exposed workers revealed increased DNA-protein cross-links, consistent with results of inhalation studies with rats and monkeys.

In a dominant lethal test with mice, intraperitoneal injections of males with 16, 20, 32, or 40 mg/kg did not affect spermatogenesis or fertility, i.e., no dominant lethal mutations (Epstein et al. 1972). According to WHO (1989) formaldehyde is mutagenic in different test systems, especially at high concentrations. However, evidence that formaldehyde may induce mutations in vivo is lacking.??

Formaldehyde readily reacts with a variety of cellular nucleophiles including DNA. Reaction products with DNA include adducts and DNA-protein cross-links in vitro (WHO 1989). In inhalation studies of rats exposed to formaldehyde, formaldehyde induces the formation of DNA -protein cross-links in the nasal respiratory mucosa in vivo (Casanova-Schmitz and Heck 1983; Casanova-Schmitz et al. 1984). The concentration-response curve is sublinear below 6 ppm, but linear above. DNA-protein cross-links were not found at other sites.

3.6. Chronic Toxicity/Carcinogenicity

Studies of intermediate duration as well as chronic toxicity/carcinogenicity studies are summarized in Table 5. Subchronic studies show that precursor carcinogenic effects - pathologic lesions of the nasal mucosa occur if concentrations are sufficiently high. Generally no nasal lesions occurred in 13-week studies at concentrations of 1-4 ppm for 6-8 hours/day. Concentrations $\geq$10 ppm for at least 13 weeks caused lower respiratory tract damage as evidenced by nasal, laryngeal and tracheal lesions (Rusch et al. 1983; Maronpot et al. 1986; Woutersen et al. 1987; Feron et al. 1988; Wilmer et al. 1989). Respiratory tract lesions were always greater in rats than in mice and were generally absent in hamsters. Only the chronic studies are discussed in the following text.

Several studies addressed carcinogenicity in rodents at low levels of exposure. In the earliest such study (Swenberg et al. 1980; Kerns et al. 1983) groups of 120 male and 120 female Fischer 344 rats and groups of 120 male and 120 female B6C3F$_1$ mice inhaled measured concentrations of 0, 2.0, 5.6, or 14.3 ppm for 6 hours/day, 5 days/week for 24 months. Some animals were sacrificed at 6, 12, and 18 months. Rats exposed to all concentrations had a concentration-dependent yellow discoloration of the fur. Clinical signs were limited to the 14.3 ppm group and included dyspnea and emaciation. At the end of 24 months, body weights of male and female rats in the 5.6 and 14.3 ppm groups were decreased ($p<0.05$); body weight recovery took place during a 3-month postexposure non-treatment period. Concentration-dependent observations of rhinitis, epithelial dysplasia, and squamous metaplasia occurred in all exposure groups of rats. Squamous cell carcinomas were observed in the nasal cavities of 51 of 117 male rats (44%) and 52 of 115 female rats (45%) exposed to 14.3 ppm and in one male (of

119) and one female (of 116) rat exposed to 5.6 ppm (both approximately 1%). At 24 months, the adjusted incidence rates of squamous cell carcinomas in male and female rats in the 14.3 ppm exposure group were 67 and 87%. The nasal lesions were described as "squamous metaplasia with zones of squamous epithelial hyperplasia and increased keratin production that appeared to precede areas of squamous papillary hyperplasia with foci of cellular atypia." Carcinomas invaded the nasal turbinates. In many animals in this exposure group, the excessive accumulation of keratin and inflammatory exudate within the nasal cavity caused severe dyspnea and death. Polyploid adenomas of the nasal mucosa were seen in rats at all doses in a significant dose-related trend. At study termination, squamous cell carcinomas were found in 2 of 106 male mice exposed to 14.3 ppm (2%) and in none of the female mice (0/109) exposed to 14.3 ppm. Mouse survival was not affected by exposure.

TABLE 5. Summary of Subchronic and Chronic/Carcinogenicity Studies in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Monkey (male cynomolgus)	0, 0.19, 0.98, 2.95	22 h/d, 7 d/w, 26 wk	No effect at 0.19 or 0.98 ppm; hoarseness, congestion and squamous cell metaplasia in the nasal turbinates at 2.95 ppm	Rusch et al. 1983
Rat (male Sprague-Dawley)	0, 15	6 h/d, 5 d/wk, lifetime	Controls: epithelial or squamous hyperplasia of the nasal mucosa, 0/99 tumors; 15 ppm: squamous hyperplasia and metaplasia; nasal cavity tumors: 38/100 squamous cell carcinomas, 1/100 fibrosarcoma, 1/100 mixed carcinoma	Sellakumar et al. 1985; Albert et al. 1982
Rat (male and female Wistar)	0, 1, 9.7, 20	6 h/d 5 d/wk, 13 wks	1 ppm: minimal focal hyperplasia in the nose 9.7 ppm: moderate squamous metaplasia, nasal respiratory epithelium 19.8 ppm: growth retardation, squamous metaplasia, squamous cell carcinomas (4/44 vs 0/45 controls), carcinoma *in situ*, adenomas	Woutersen et al. 1987; Feron et al. 1988;
Rat (male Wistar)	1, 2 2,4	8 h/d, 5 d/wk, 13 wks 8 x 30-min/d, 30-min break, 13 wks	Continuous, 8 hours: 1, 2 ppm: no histopathology of the nose Interrupted, 4 hours: 2 ppm: rhinitis (considered incidental); 4 ppm: squamous metaplasia and hyperplasia, nasal turbinates, increased cell turnover	Wilmer et al. 1989
Rat (male and female Fischer 344)	0, 0.19, 0.98, 2.95	22 h/d, 7 d/w, 26 wks	No effect at 0.19 or 0.98 ppm; squamous metaplasia in the nasal turbinates, decreased body weight, and decreased liver weight at 2.95 ppm	Rusch et al. 1983
Rat (male Wistar)	0, 0.1, 1, 10	12 months	No adverse effects at 0.1 and 1 ppm; growth retardation, reduced urine production, and rhinitis accompanied by squamous metaplasia of the nasal respiratory epithelium at 10 ppm	Appleman et al. 1988
Rat (male Fischer 344)	0, 0.3, 2.0, 3.3, 15	6 h/d, 5 d/wk, 24-28 months	Dose-related incidences of rhinitis and nasal hyperplasia 15 ppm: 88% mortality; squamous cell carcinomas, 14/27 vs 0/27 controls surviving past 12 months	Tobe et al. 1985
Rat (male Fischer-344)	0, 0.3, 2.1, 14.9	6 h/d, 5 d/wk, 28 months	Inflammatory cell infiltration, erosion, or edema observed in all groups including controls; concentration dependent nasal epithelial cell hyperplasia with squamous cell metaplasia at all concentrations; 15 ppm: squamous cell carcinomas, papillomas in 8/32 by 24 months	Kamata et al. 1997
Rat (male Fischer 344)	0, 0.7, 2, 6, 10, 15 ppm	6 h/d, 5 d/wk, 24 months	0.7, 2 ppm: no squamous cell carcinomas 6, 10, 15 ppm: tumor incidences of 1, 22, and 47%, respectively	Monticello et al. 1996
Rat (male and female Fischer 344)	0, 2, 5.6, 14.3	6 h/d, 5 d/wk, 24 months	Rat: 2 ppm: no clinical signs, no carcinomas 5.6 ppm: rhinitis, increased mortality (males), nasal squamous metaplasia, squamous carcinomas (2/153 vs 0/156 controls) 14.3 ppm: dyspnea, emaciation, increased mortality, nasal squamous carcinomas (94/140 vs 0/156 controls)	Swenberg et al. 1980; Kerns et al. 1983
Rat (male Wistar)	0, 0.1, 1, 10	6 h/d, 5 d/wk, 28 months	No effect on nasal respiratory epithelium at 0.1 or 1 ppm; degenerative inflammatory, and hyperplastic changes at 10 ppm; nasal squamous cell carcinomas in 0/26, 1/26, 1/28, and 1/26 rats, respectively	Woutersen et al. 1989
Mouse (male and female B6C3F1)	0, 2, 4, 10, 20, 40	6 h/d, 5 d/wk 13 wks	2, 4 ppm: no histopathology of the nasal epithelium; 10 ppm: nasal lesions; 20 ppm: nasal, laryngeal, and tracheal lesions; 40 ppm: ataxia, body weight depression, inflammation and metaplasia of the	Maronpot et al. 1986

TABLE 5. Summary of Subchronic and Chronic/Carcinogenicity Studies in Laboratory Animals				
			nasal cavity, larynx, trachea, and lungs, 80% mortality	
Mouse (male and female B6C3F1)	0, 2, 5.6, 14.3	6 h/d, 5 d/wk, 24 months	2 ppm: no noteworthy lesions 5.6, 14.3 ppm: squamous cell carcinomas, 2/116 males	Kerns et al. 1983
Hamster (male and female golden Syrian)	0, 0.19, 0.98, 2.95 ppm	22 h/d, 7 d/w, 26 wk	No effect at any concentration (no increase in squamous metaplasia in the nasal cavity of treated hamsters)	Rusch et al. 1983
Hamster (male Syrian golden)	0, 10	5 h/d, 5 times/wk, lifetime	No increase in rhinitis; hyperplastic and metaplastic areas in nasal epithelium in 5% of hamsters exposed to 10 ppm; no tumors in treated or control group	Dalbey 1982

Studies are arranged by species followed by length of study.

Sellakumar et al. (1985; see also Albert et al. 1982) exposed groups of 100 male Sprague-Dawley rats to 15 ppm for a lifetime. Two additional groups were included in the experiment: a group exposed to air only and a group exposed to 15 ppm formaldehyde and 10 ppm hydrogen chloride (HCl). HCl was administered to see if tumor response was enhanced by an additional irritant effect or by the combination of the two chemicals to form bis-(chloromethyl)ether, a known carcinogen. Squamous cell carcinomas of the anterior nasal cavity were induced in 38/100 rats that received formaldehyde alone. Concurrent administration of HCl had no effect on the incidences of nasal cancers. In addition to rhinitis, hyperplasia and squamous metaplasia of the nasal mucosa, larynx and trachea were observed in all formaldehyde exposed group. Exposure to HCl alone resulted in only hyperplasia.

Tobe et al. (1985) conducted a 28-month study with male F-344 rats. Groups of 32 rats were exposed 6 hours/day, 5 days/week to 0, 0.3, 2.0, 3.3, or 15 ppm in aqueous methanol. Another group was exposed to the methanol only. Exposure to 15 ppm ended at 24 months at which point the mortality was 88%. Squamous cell carcinomas were observed in 14/27 rats in the 15 ppm group surviving past 12 months (controls, 0/27). No polyploid adenomas were observed. Incidences of rhinitis and hyperplasia were dose-related.

Using male Wistar rats, Woutersen et al. (1989) observed nasal squamous cell carcinomas in only 1/26, 1/28, and 1/26 exposed to 0.1, 1.0, or 10 ppm, respectively, for 6 hours/day, 5 days/week for 28 months. There were no carcinomas in 26 control rats. Physical damage to the nasal mucosa (electrocoagulation) increased the response in a group subsequently exposed to 10 ppm group (15/58 compared with 1/54 in controls treated with electrocoagulation).

Male F-344 rats inhaled 0.3, 2, or 15 ppm for 6 hours/day, 5 days/week for 28 months (Kamata et al. 1997). Clinical signs of irritation were observed in the 15 ppm group. No nasal tumors were observed in the groups that inhaled 0.3 or 2 ppm. By 14 months, nasal tumors were macroscopically evident in the in the 15-ppm group, and this group had early deaths. By 24 months, 8/32 rats had squamous cell papillomas and carcinomas.

Dalbey (1982) exposed male Syrian golden hamsters to 10 ppm formaldehyde 5 hours/day, 5 times/week, throughout their lifetimes. Beginning with the 20th week, survival time was reduced in the exposed group compared with unexposed controls. No tumors were observed in the respiratory tract of either the control or exposed group. Only a minimal increase in hyperplastic and metaplastic areas was observed in the nasal epithelium of 5% of the exposed group.

As noted in Section 2.6, the U.S. EPA (2003) in their Weight-of-Evidence characterization classifies formaldehyde as B1, probable human carcinogen. This classification is based on limited evidence in humans and sufficient evidence in animals. IARC (2006) concluded there is sufficient evidence in humans for the carcinogenicity of formaldehyde.

3.7. Summary

Lethal concentrations were available for the rat and mouse. LC_{50} values for the rat ranged from 820 ppm for 30 minutes (Skog 1950) to 250-482 ppm for 4 hours (Carpenter et al.

1949; Nagorny et al. 1979). For the mouse, the value was similar to the rat when the duration was shorter (Nagorny et al. 1979), whereas the Lt_{50} (similar to the LC_{50}) was 320 ppm for 100 minutes (Bitron and Aharonson1978). Mice survived a 4-day repeat exposure to 140 ppm with little signs of distress (Horton et al. 1963).

Few studies at sublethal concentrations were of acute duration. Murphy et al. (1964) reported that 35 ppm for 18 hours was a sublethal concentration for the rat. Rats exposed to 15, 20 or 30 ppm for 6 hours showed eye and nose irritation, inhibition of the mucociliary clearance mechanism, and damage of the nasal mucosa which extended to the trachea at the higher exposures (Chang et al. 1983; Tobe et al. 1985; Morgan et al. 1986a). There was no evidence of damage to the anterior respiratory epithelium after exposures to 2 ppm for up to 6 hours (Morgan et al. 1986b). Repeated exposures to 1 or 2 ppm for 6 hours/day also produced no histopathology in rats (Woutersen et al. 1987). It should be noted that rats are obligate nose breathers. Horton et al. (1963) observed no substantial distress in mice during a 4-day repeat exposure to 140 ppm (of 2 hours duration). The RD_{50} in mice is 3.1 ppm (Kane and Alarie (1977).

Guinea pigs are the only species to react with bronchoconstriction during exposure to low concentrations. A concentration of 0.3 ppm produced bronchoconstriction (Amdur 1960).

Formaldehyde has been evaluated for potential teratogenicity in several test systems. Inhalation studies with rats, although lacking in detail, indicate no teratogenic response. Inhalation exposure of pregnant rats to 20 or 40 ppm on days 6-20 of gestation reduced fetal body weight but failed to cause malformations (Saillenfait 1989). No teratogenic responses were observed in dogs or mice treated orally. The reviewed studies do not show any evidence of the embryo being unusually sensitive to formaldehyde, and there is no information that indicates formaldehyde is teratogenic to rodents when administered by a number of routes.

A 13-week repeat exposure to 2 or 4 ppm did not result in pathologic changes in the nasal epithelium of mice (Maronpot et al. 1986). However, repeat exposures to 10, 20, or 30 ppm produced squamous metaplasia and inflammation. The 40 ppm exposure was lethal to most mice during the 13-week exposure. Subchronic exposures were carcinogenic to the rat (Woutersen et al. 1987).

Chronic studies have been carried out with rats, mice, and hamsters. In these studies, formaldehyde-induced effects were restricted to non-neoplastic and neoplastic lesions in the anterior regions of the nasal epithelium. Non-neoplastic lesions in rats such as metaplasia were found at concentrations as low as 2 ppm (Kamata et al. 1997). Neoplastic lesions - squamous cell carcinomas, squamous cell papillomas, or polyploid adenomas - were observed in rats exposed to 5.6 ppm and in mice exposed to 14.3 ppm (Kerns et al. 1983). Neoplastic lesions were not found in hamsters exposed to 10 ppm (Dalbey 1982).

Studies with several species of animals confirm that the upper respiratory tract is a critical target for inhaled formaldehyde. These studies describe exposure-response relationships for upper respiratory tract irritation and epithelial damage. Inhaled formaldehyde damages epithelial tissue in specific regions of the upper respiratory tract in rats, mice, and monkeys. Lesions consist of hyperplasia and squamous cell metaplasia. Lung damage occurs at higher

concentrations than those affecting only the upper respiratory tract. Mice and hamsters are less susceptible to formaldehyde-induced upper respiratory tract epithelial damage than rats. Rats and monkeys may be equally susceptible to epithelial damage, but display damage in different regions of the respiratory tract.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Inhaled formaldehyde, being highly water soluble, is rapidly and almost completely absorbed from the respiratory tract. Studies with mongrel dogs exposed to 122-235 ppm of vapor showed that the retention of vapor is nearly 100%, with most of the absorption in the upper respiratory tract (Egle 1972; ATSDR 1999). Gastric absorption is also high, but dermal absorption is quite low. Although all tissues are capable of metabolizing formaldehyde, rapid local metabolism in the tissues of the respiratory tract results in little or no formaldehyde reaching the blood. Given the high absorption and metabolism in the tissues of the respiratory tract, storage or distribution to other tissues in unlikely.

Heck et al. (1985) measured the blood level of formaldehyde in six volunteers immediately following inhalation of 1.9 ppm for 40 minutes and compared the results to pre-exposure values. Although individual differences in blood concentrations were noted both pre- and post-exposure, differences in the mean values were not statistically significant following exposure (control value, 2.61 μg/g; postexposure, 2.77 μg/g). Similar results were found by Heck et al. (1985) following exposure of eight male F-344 rats to 0 or 14.4 ppm for 2 hours and sacrificed immediately after. Blood levels in the control and exposed groups were 2.24 and 2.25 μg/g, respectively. After intravenous injection of monkeys, formaldehyde is rapidly eliminated from the blood with a half-life of about 1.5 minutes (McMartin et al. 1982).

In the cell, the initial reaction of formaldehyde is with glutathione to form a hemiacetal. The hemiacetal is then metabolized to formate, primarily by formaldehyde dehydrogenase, although other aldehyde dehydrogenases are capable of metabolizing formaldehyde (ATSDR 1999). This enzyme is present in all animal tissues. The actual endproduct of the dehydrogenase reaction is S-formylglutathione which slowly hydrolyzes to formate. Formate can undergo three reactions: oxidation to carbon dioxide and water, elimination in the urine as a sodium salt, or entrance into the metabolic one-carbon cycle. Formaldehyde may also enter the one-carbon pool directly. Formaldehyde also reacts with protein and single-strand DNA.

4.2. Mechanism of Toxicity

Formaldehyde is a primary irritant that is extensively scrubbed in the anterior nasal passages. The mechanism of action of primary irritants involves activation of sensory nerve fibers which relay to the trigeminal nerve to reflexively induce bronchoconstriction through the vagus nerve. This mechanism of action has been observed in guinea pigs (Amdur 1960), but has not been observed at the low concentrations used in clinical studies with healthy subjects and asthmatics.

Formaldehyde is a highly cytotoxic respiratory tract irritant. The exact mechanism of formaldehyde's irritant, corrosive, and cytotoxic effects is unknown. Aldehydes as a group are

highly reactive chemicals. The highly electronegative oxygen atom and less electronegative carbon atoms convey a substantial dipole moment. The electrophilic carbonyl atom reacts easily with nucleophilic sites on cell membranes and in body tissue fluids. Formaldehyde also combines readily with free, unprotonated amino groups of amino acids to yield hydroxymethyl amino acid derivatives and a proton (H+). This action may be responsible for its germicidal properties. Higher concentrations will precipitate protein (ATSDR 1999).

The precursor of tumor formation for respiratory irritants is persistent tissue damage followed by sustained cell proliferation. Induction of nasal squamous carcinomas in rats by formaldehyde requires long-term exposure to concentrations of 10-20 ppm that result in epithelial degeneration and cell death accompanied by rhinitis, followed by regenerative hyperplasia and metaplasia, changes associated with increased cell proliferation (Feron et al. 2001). Studies of nasal epithelial lesions and cell proliferation in formaldehyde-exposed rats demonstrated a good correlation of cellular injury with cell proliferation and neoplasia. At concentrations of 10 and 15 ppm there is a 4- to 10-fold increase in cell proliferation in rat nasal tissue (Monticello et al. 1996). Formaldehyde is weakly genotoxic, inducing DNA cross-links in the nasal respiratory epithelium of rats and monkeys (Casanova and Heck 1991). At 10 ppm, the major pathway for detoxification in the rat is saturated. And above 10 ppm there is a 7-fold greater level of formation of DNA-protein cross-links per ppm of exposure than what occurs at lower concentrations. Areas of DNA-protein cross links are correlated with regional sites of formaldehyde-induced epithelial damage in the nose of rats. Inhibition of mucociliary function, epithelial degeneration, inflammation, squamous metaplasia, and increased cell proliferation in the nasal tissue all correlate with the site-specific uptake and cancer pattern observed in experimental studies (Paustenbach et al. 1997).

4.3. Structure-Activity Relationships

In their study of the irritancy of six aldehydes, Sim and Pattle (1957) reported that acrolein and crotonaldehyde were highly irritant, and acetaldehyde, propionaldehyde, butyraldehyde, and isobutryaldehyde were almost nonirritant. The irritancy of formaldehyde was intermediate between that of the highly irritant and nonirritant groups. Pattle and Cullumbine (1956) reported formaldehyde toxicity to be between the unsaturated aldehydes and acetaldehyde. U.S. EPA (2003) notes that when inhaled, acetaldehyde causes cancers in the nose and trachea of hamsters and nasal cancers in rats.

Kane and Alarie (1977) compared the irritancy of formaldehyde and acrolein. The respective RD_{50} values were 3.1 and 1.7 ppm, demonstrating that formaldehyde is approximately half as irritating as acrolein.

4.4. Other Relevant Information

Dermal exposure to formaldehyde produces allergic contact dermatitis. This is a delayed hypersensitivity reaction in which only minute quantities of a material are necessary to elicit an overt reaction. Allergic contact dermatitis is preceded by sensitization to the allergen. Subsequent exposures elicit clinical effects (Cohen and Rice 2001).

4.4.1. Species Variability

The carcinogenic response to formaldehyde is species specific. Formaldehyde was carcinogenic to F-344 rats and Wistar rats, but not hamsters. Wistar rats were much less responsive than F-344 or Sprague-Dawley rats. Mice were much less susceptible than F-344 rats. Both the rat and monkey reacted to subchronic exposure with squamous metaplasia (Rusch et al. 1983). There are differences in the deposition of formaldehyde in the nasal regions of the rat and monkey, due to anatomical differences which influence air-flow patterns. In addition, monkeys develop much lower amounts of DNA-protein crosslinks than rats after exposure to formaldehyde (Casanova et al. 1991). For mice, differences in the carcinogenic response appear due to differences in dose. Mice respond to formaldehyde with decreased minute volume and therefore have less formaldehyde available for deposition in the nasal epithelium than rats (Chang et al. 1983).

Nasal airflow patterns appear to play a dominant role in determining olfactory lesions (Morgan and Monticello 1990). To estimate local formaldehyde dose in rat and monkey nasal passages and in the human respiratory tract, researchers at the CIIT developed and applied three-dimensional nasal airflow models and computational fluid dynamics modeling (Bush et al. 1998; Frederick et al. 1998; Kimball et al. 2001; Conolly et al. 2003; 2004). Additional key elements of their approach were (1) association of the flux of formaldehyde into the nasal mucosa with formation of DNA-protein cross-links and with cell death and cell proliferation, and (2) use of a two-stage clonal growth model to link DNA-protein cross-links and cell proliferation with tumor formation. Based on this computer modeling maximum likelihood estimates of cancer risk are *de minimis* at relevant human exposures.

4.4.2. Susceptible Populations

Several studies indicate that there is wide variation in subjective response to irritation. Response of subjects exposed to 1.6 ppm ranged from no discomfort to discomfort (Andersen and Molhave 1977). Subjects were excluded from the study of Bender et al. (1983) if they did not respond to 1.3 or 2.2 ppm. Green et al. (1987) reported that during exposure of 38 exercising healthy and asthmatic subjects to 3 ppm, scores for odor, nose/throat irritation, and eye irritation ranged from none to severe. Slightly less than a third of the subjects scored odor and eye and nose/throat irritation as moderate or above and approximately 18% of the subjects reported no odor perception. Up to 3 ppm, exercising asthmatics were not more susceptible to the irritant effects of formaldehyde than exercising healthy subjects.

A small proportion of the population may develop formaldehyde asthma as a result of occupational exposure. Of a total of 230 patients who had been exposed to formaldehyde and suffered from asthma-like respiratory symptoms, 12 were considered a result of specific sensitization to asthma (Nordman et al. 1985). Exposures ranged from 1 month to 19 years. Diagnosis was made on the basis of bronchial reactivity to formaldehyde at a challenge concentration of 2 ppm. In another study, 13 patients who had been chronically exposed to formaldehyde in the home or workplace and had asthmatic-like symptoms at the site of exposure, were tested with a challenge dose of formaldehyde or room air (Reed and Frigas 1984). One to several concentrations were administered: 0.1, 1.0, and 3 ppm. Reactivity was measured as a decline in FEV_1 of greater than 20%; a dose-response to formaldehyde and a lack of response to room air were also considered in the positive response. These patients did not response to the

formaldehyde bronchial challenges. Furthermore, it has been difficult to demonstrate antibodies to formaldehyde in individuals affected by asthma (Hendrick et al. 1982).

4.4.3. Concentration-Exposure Duration Relationship

The slight to moderate irritation that accompanies low concentrations of formaldehyde is concentration rather than concentration x time dependent. Based on a review of several studies including the subchronic study of Rusch et al. (1983), the Industrial Health Foundation expert panel concluded that irritant effects of formaldehyde are concentration rather than concentration x time dependent. They noted that nasal irritation did not occur below 0.98 ppm for three animal species, even after 22 hours of exposure, and that no lower respiratory tract effects were observed at 2.95 ppm, i.e., squamous metaplasia was confined to the nasal epithelium.

A number of studies indicate that adaptation takes place during continuous exposure. For example, Weber-Tschopp et al. (1977) demonstrated that continuous exposure was subjectively less irritating than discontinuous exposures to identical concentrations. Longer-term animal studies also show a concentration effect. For example, in a 26-week inhalation study with rats, monkeys and hamsters (Rusch et al. 1983), no nasal irritation or lower respiratory effects occurred at or below 0.98 ppm, whereas, nasal lesions (squamous metaplasia) was observed in rats and monkeys at 2.95 ppm.

Exposure duration has little effect on pulmonary function changes. In the clinical study of Sauder et al. (1986), the maximal pulmonary response in healthy subjects inhaling 3 ppm for 3 hours (a 2% decrease in FEV_1 and a 7% decrease in $FEF_{25-75\%}$) occurred during the first 30 minutes of exposure and was no longer detectable between 60 and 180 minutes.

However, for a carcinogenic effect, exposure must be of sufficient duration. A 13-week exposure at 10 ppm produced non-neoplastic changes in the nasal mucosa of rats (Woutersen et al. 1987; Feron et al. 1988), whereas a 13-week exposure at 20 ppm caused squamous cell carcinoma, carcinoma in situ, and polyploid adenomas in rats (Feron et al. 1988). A 4- or 8-week exposure at 20 ppm failed to produce nasal cancers in rats (Feron et al. 1988).

Conolly et al. (2002) presented a dose-response analysis for formaldehyde-induced respiratory tract cytotoxicity. Regenerative cellular proliferation data (secondary to cytotoxicity) from F-344 rats inhaling 0, 0.7, 2.0, 6.0, 10, or 15 ppm 6 hours/day, 5 days/week for up to 2 years (Monticello et al. 1996) was extrapolated to humans (human flux model) to predict the extent and intensity of the cytotoxic response throughout the human respiratory tract. The dose-response to regenerative cellular proliferation was J-shaped, with the rates of regenerative cellular proliferation at 0.7 and 2.0 ppm not statistically different from control. Both the J-shaped and hockey-stick-shaped curves were fitted to the raw data to predict human dose response for regenerative cellular proliferation. A computational fluid dynamics model of air flow and gas transport in the human nasal airways was linked to a typical path model of the human lung to provide site-specific flux. Three working levels (respiratory rates) were considered. Using the most vigorous working level, the lowest concentrations of formaldehyde predicted to exert any cytotoxic effects in humans were 1.0 and 0.6 ppm for the J-shaped and hockey-stick-shaped curves, respectively.

For the endpoint of lethality, a time-scaled concentration-response probably occurs. However, the diverse lethality data, including the LC_{50} values of Skog (1950), Carpenter et al. 1949), Bitron and Aharonson (1978), and Nagorny et al. (1979) do not show a good relationship.

4.4.4. Concurrent Exposure Issues

Particulate matter may enhance the irritant effects of chemicals. Green et al. (1989) tested the acute response of healthy nonsmoking subjects inhaling both 3.0 ppm formaldehyde and 0.5 mg/m^3 respirable activated carbon aerosol (see Section 2.2.2 for results of exposure to 3.0 ppm formaldehyde alone). Synergistic increases in cough, but not in other irritant respiratory tract symptoms were observed. Small (<5%) synergistic decreases in FVC and FEV_3 were also seen. The authors could draw no conclusions concerning the clinical significance of these effects.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

A number of controlled exposure studies have been conducted. These 22 clinical exposure studies with controlled atmospheres and involving over 500 subjects provide the most scientific evidence for dose-response effects. The most sensitive endpoint in these studies is eye and upper respiratory tract irritation. These studies show that irritation ranges from none to mild to moderate at concentrations up to 1 ppm. Below 1 ppm many studies show no dose-response relationship. Above 1 ppm, definite symptoms of discomfort are reported. However, even at 3 ppm, the majority of subjects reported only mild-moderate eye and upper respiratory tract irritation (Green et al. 1987; 1989; Kulle et al. 1987; Sauder et al. 1986; 1987; Weber-Tschopp et al. 1977). Of the 180 subjects tested in these latter studies, only one reported severe eye irritation at 3 ppm (Sauder et al. 1987). Occupational studies report symptoms at lower levels than in clinical studies, but the occupational studies have concomitant exposures to other chemicals and particulates which increases irritancy.

Individuals may differ greatly in their response to the irritancy of formaldehyde. Several of the studies were designed to include presumably sensitive individuals such as asthmatics. At concentrations up to 3 ppm, asthmatics engaged in moderate exercise suffered no decrements in several pulmonary function parameters (Sheppard et al. 1984; Green et al. 1987). This and additional studies with asthmatics indicate that at $\leq$3 ppm, formaldehyde is scrubbed in the upper respiratory passages. In evaluating eye irritation, Bender et al. (1983) excluded nonsusceptible individuals, i.e., individuals that did not report eye irritation at 1.3 or 2.2 ppm were excluded from the study. The sensitive subjects in the Bender et al. (1983) reported the same irritant response (none to slight) during exposures to clean air and to formaldehyde concentrations $\leq$0.9 ppm.

5.2. Summary of Animal Data Relevant to AEGL-1

Several animal studies addressed low concentrations and damage to the respiratory epithelium. A concentration of 2 ppm for 6 hours did not damage the anterior respiratory epithelium in obligate nose-breathing rats (Morgan et al. 1986b). A 13-week repeat exposure to 2 or 4 ppm did not result in pathologic changes in the nasal epithelium of mice (Maronpot et al.

1986). Repeated exposures to 1 or 2 ppm for 6 hours/day filed to induce lesions in rats (Woutersen et al. 1987). Concentrations of 2 or 4 ppm did not damage the respiratory epithelium in mice exposed for 13 weeks (Maronpot et al. 1986) or rats exposed to 3 ppm for 22 hours/day, 7 days/week, for 26 weeks (Rusch et al. 1983). Rodents have higher respiratory rates than humans, which increases the dose delivered to the target tissues.

5.3. Derivation of AEGL-1

Rather than a weight-of-evidence approach, the AEGL-1 was based on a NOAEL for eye irritation in a single study with sensitive subjects (Bender et al. 1983). In this study, groups of 5 to 28 healthy subjects were exposed eye-only for 6 minutes to 0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm. The subjects had been selected for their response to formaldehyde at 1.3 or 2.2 ppm, i.e., subjects that did not report eye irritation during previous exposures to 1.3 or 2.2 ppm were excluded from the study. At 0.35 to 0.9 ppm, the subjects' subjective eye irritation responses ranged from none to slight, the same as their responses to clean air. The 0.9 ppm concentration was selected as the basis for the AEGL-1. No intraspecies uncertainty factor was applied as no additional sensitive populations were identified [there were no significant decrements in pulmonary function parameters in exercising asthmatic subjects at 2 or 3 ppm, and asthmatic subjects reported <moderate eye irritation, the same as healthy subjects, at these concentrations (Green et al. 1987; Kulle et al. 1987; Sauder et al. 1987)]. Because several studies show there is adaptation to irritation at this low concentration, the 0.9 ppm concentration was applied across all exposure durations (Table 6).

The 0.90 ppm value is supported by the fact that animal studies show there is no damage to the respiratory epithelium during single (Morgan et al. 1986b) or repeated exposures to 1 or 2 ppm (Rusch et al. 1983; Maronpot et al.1986; Woutersen et al. 1987). Derivations of AEGL values are in Appendix C and a category graph of human and animal toxicity data in relation to AEGL values is in Appendix D.

TABLE 6. AEGL-1 Values for Formaldehyde

10-min	30-min	1-h	4-h	8-h
0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)	0.90 ppm (1.1 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Only a few studies with controlled exposures addressed effects defined by the AEGL-2. Stephens et al. (1961) reported that 5 ppm delivered via goggles produced severe eye irritation , whereas, Douglas (1974) reported eye irritation for 1 of 5 subjects at 8 ppm and for 5 of 6 subjects at 13 ppm during short exposures. Delivery to the eye was also via goggles. During 100% mouth breathing, airway resistance was increased at both concentrations. The decrement was less than 50% at 8 ppm and 50-108% at 13 ppm. Lacrimation was mild and adaptation occurred during a 30-minute exposure to 13.8 ppm (Sim and Pattle 1957). Two healthy investigators considered the lacrimation and eye, nose, and throat irritation during several short exposures to 20 ppm objectionable (Barnes and Speicher 1942). Average concentrations in

occupational situations have ranged up to 38 ppm (IARC 2006). Exposure durations and concomitant exposures to other chemicals or particles were unknown.

6.2. Summary of Animal Data Relevant to AEGL-2

Few animal acute studies addressed effects that meet the definition of the AEGL-2. Several studies reported on exposures of rats to concentrations as high as 15 ppm for 6 hours (Chang et al. 1983; Morgan et al. 1986a; 1986b). These exposures inhibited mucociliary clearance and resulted in histopathologic lesions of the respiratory epithelium, but little effect on the olfactory epithelium. When exposure was discontinued, extensive recovery took place.

6.3. Derivation of AEGL-2

The AEGL-2 was based on the clinical study of Sim and Pattle (1957). Twelve healthy male subjects inhaled 13.8 ppm for 30 minutes. Initially, the exposure caused considerable nose and eye irritation. Mild lacrimation continued for some period of time. The eye irritation was not considered severe, and adaptation occurred in about 10 minutes. Mild lacrimation at 13.8 ppm (rounded to 14 ppm) with adaptation was considered the threshold concentration for the inability to escape. The lacrimation experienced by Barnes and Speicher (1942) at 20 ppm during short exposures might impair the ability to escape. The 14 ppm concentration may also be close to the threshold for an increase in airways resistance (Douglas 1974). No intraspecies uncertainty factor was applied to the 14 ppm concentration because application of an uncertainty factor of ≥3 would lower the value to close to a no-effect concentration in several studies with exercising asthmatics. Because the endpoint is eye and nose irritation to which adaptation occurs, the same value was used across all exposure durations (Table 7).

TABLE 7. AEGL-2 Values for Formaldehyde

10-min	30-min	1-h	4-h	8-h
14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethal concentrations were available for the rat and mouse. LC_{50} values for the rat ranged from 820 ppm for 30 minutes (Skog 1950) to 250-482 ppm for 4 hours (Carpenter et al. 1949; Nagorny et al. 1979). For the mouse, the Lt_{50} (similar to the LC_{50}) was 320 ppm for 100 minutes (Bitron and Aharonson 1978). These assorted studies did not show a good concentration-response relationship.

Few studies at sublethal concentrations were of acute duration. Mice survived a 2-hour, 4-day repeat exposure to 140 ppm with little signs of distress (Horton et al. 1963). Murphy et al. (1964) reported that 35 ppm for 18 hours was a sublethal concentration for the rat. Rats exposed to 15, 20 or 30 ppm for 6 hours showed eye and nose irritation, inhibition of the mucociliary clearance mechanism, and damage of the nasal mucosa which extended to the trachea at the higher exposures (Chang et al. 1983; Tobe et al. 1985; Morgan et al. 1986a). Pregnant rats inhaling 20 or 40 ppm on days 6-20 of gestation suffered no mortalities, but delivered fetuses of reduced body weight (Saillenfait 1989). Mice did not survive a 13-week, 5 hour/day, exposure to 40 ppm (Maronpot et al. 1986). In chronic studies, mice survived 5 hour/day exposures to 14 ppm (Swenberg et al. 1983).

7.3. Derivation of AEGL-3

The AEGL-3 values were based on the highest non-lethal value for the rat (350 ppm) during a 4-hour exposure (Nagorny et al. 1979). The value was adjusted by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. These uncertainty factors, applied to irritants, are protective of sensitive populations. Furthermore, application of larger uncertainty factors, e.g., a total of 30, would reduce the value to the level of the AEGL-2. No data on time-scaling were found. Therefore, the default value of n = 3 when scaling to shorter exposure periods (NRC 2001) was applied (Table 8).

The 8-hour value was set equal to the 4-hour value because formaldehyde is well scrubbed in the nasal passages. Furthermore, application of the default of n = 1 when scaling to longer time periods would result in an 8-hour value of 18 ppm, similar to the 8-hour AEGL-2. The 8-hour value is supported by sublethal concentrations in additional animal studies. Rats were exposed to the sublethal concentration of 35 ppm for 18 hours in the study of Murphy et al. (1964), and no deaths were attributable to effects of formaldehyde on the lungs during chronic exposures of mice to 15 ppm (Swenberg et al. 1983).

TABLE 8. AEGL-3 Values for Formaldehyde

10-min	30-min	1-h	4-h	8-h
100 ppm (123 mg/m^3)	70 ppm (86 mg/m^3)	56 ppm (69 mg/m^3)	35 ppm (43 mg/m^3)	35 ppm (43 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 9. Derivation summary tables are in Appendix E.

TABLE 9. Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.90 ppm (1.1mg/m^3)	0.90 ppm (1.1mg/m^3)	0.90 ppm (11.mg/m^3)	0.90 ppm (1.1mg/m^3)	0.90 ppm (1.1mg/m^3)
AEGL-2 (Disabling)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)	14 ppm (17 mg/m^3)
AEGL-3 (Lethal)	100 ppm (123 mg/m^3)	70 ppm (86 mg/m^3)	56 ppm (69 mg/m^3)	35 ppm (43 mg/m^3)	35 ppm (43 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 10. Emergency Response Planning Guidelines (ERPGs) are similar to AEGLs, but are set for only 1-hour exposures. The ERPG-1 of 1 ppm is based on human exposure data including the studies of Weber-Tschopp et al. (1977), Kulle et al. (1987), and Sauder et al. (1987). At the exposure of 1 ppm, it is felt that nearly all individuals would experience no greater health effects than odor or mild sensory irritation. The ERPG-2 of 10 ppm is based on the studies of Kulle et

al. 1987 and Sim and Pattle (1957). Concentrations greater than this might impair the ability to escape. The ERPG-3 of 25 ppm is based on acute exposure data in animals (Carpenter et al. 1946, Skog 1950) and human data cited in Patty's Industrial Hygiene and Toxicology (Morandi and Maberti. 2001).

The NIOSH IDLH of 20 ppm is based on a report that exposure to 10 to 20 ppm produces almost immediate eye irritation and a sharp burning sensation of the nose and throat which may be associated with sneezing, difficulty in taking a deep breath, and coughing; recovery is prompt from these transient effects (personal observations reported in Morandi and Maberti 2001). NIOSH standards carry carcinogen notations. NIOSH (1976) notes that their recommended standard is not designed to protect an individual already sensitized to formaldehyde.

The NRC (1994) SMAC of 0.4 ppm is based on the prevention of mucosal irritation. In setting this value, the NRC considered complaints of workers and residents in mobile homes. It should be noted that exposure to 0.4 ppm was not irritating in most of the clinical studies and that the exposures in mobile homes and factories were to a mixture of chemicals.

The NRC (2007) 1-hour EEGL of 2 ppm was based on a range of 1-3 ppm in multiple controlled human studies which allowed for up to moderate irritation with reversible symptoms.

Noisel et al. (2007; IRSST 2006) addressed the impact of lowering the occupational standard for exposure to formaldehyde in Quebec, Canada. They assessed the exposure-response relationship from a pooled analysis of published controlled human studies on the incidence of the most sensitive effects related to acute formaldehyde exposure (irritation of the eyes, nose, and throat). The exposure-irritating effect relationship compiled from concentration ranges and by degree of severity was best described by quadratic regression. The authors concluded that workers exposed to formaldehyde concentrations <0.75 ppm should not experience moderate or severe irritating effects to the eyes, nose, or throat that may be attributed to formaldehyde.

TABLE 10. Extant Standards and Guidelines for Formaldehyde

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
AEGL-2	14 ppm	14 ppm	14 ppm	14 ppm	14 ppm
AEGL-3	100 ppm	70 ppm	56 ppm	35 ppm	35 ppm
ERPG-1 (AIHA)[a]			1 ppm		
ERPG-2 (AIHA)			10 ppm		
ERPG-3 (AIHA)			25 ppm		
SMAC (NRC)[b]			0.4 ppm		
EEGL (NRC)[c]			2 ppm		
PEL-TWA PEL-STEL (OSHA)[d]					0.75 ppm 2 ppm (15 minute)
IDLH (NIOSH)[e]		20 ppm*			
REL-TWA REL-STEL (NIOSH)[f]					0.016 ppm* 0.1 ppm (15 minute)
TLV-Ceiling (ACGIH)[g]					0.3 ppm*
MAK Peak Limit (Germany)[h]					0.3 ppm* 1 ppm
MAC Peak Limit (The Netherlands)[i]					1 ppm 2 ppm

*potential occupational carcinogen

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2004)

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**SMAC (Spacecraft Maximum Allowable Concentration**) (NRC 1994)

SMACs provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The one-hour SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposure may cause reversible effects such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

[c]**EEGL (Emergency and Continuous Exposure Levels for Chemicals in Submarines)** (NRC 2007)

EEGLs provide guidance on chemical exposures during normal operations of submarines. The one-hour EEGL is a concentration that would allow up to moderate irritation in some individuals, but would not interfere with critical duties. These exposures are for healthy adults.

[d]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (NIOSH 1997) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week. The OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit) is defined analogous to the ACGIH-TLV-STEL.

[e]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1997) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1997) is defined analogous to the ACGIH-TLV-TWA. The NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) is defined analogous to the ACGIH TLV-STEL.

[g]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2004) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[h]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** List of MAK and BAT Values 2007 (Deutsche Forschungsgemeinschaft [German Research Association] 2007) is defined analogous to the ACGIH-TLV-TWA. In the case of formaldehyde a momentary value of 1 ppm should not be exceeded. The MAK Spitzenbegrenzung (Peak Limit [give category]) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[i]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA. The peak limit is defined analogous to the ACGIH ceiling.

8.3. Data Adequacy and Research Needs

Formaldehyde has a robust data set of controlled human exposures. Data from 22 well-conducted clinical studies involving over 500 subjects form a reliable basis for setting AEGL-1 and AEGL-2 values. The data base for lethality involves relatively old animal studies that lack details of methodology as well as clear results. However, the data, with support from repeat-exposure studies with animals, can be used to set non-lethal values for humans.

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APPENDIX A: Level of Distinct Odor Awareness

The LOA derivation follows the guidance given by van Doorn et al. (2002).

The odor detection threshold (OT_{50}) for formaldehyde reported by Berglund et al. (1987) is 0.145 ppm.

The concentration C leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = k_w \times \log © /OT_{50}) + 0.5$

For the Fechner coefficient, the default of $k_w = 2.33$ was used due to the lack of chemical-specific data:

$3 = 2.33 \times \log C /0.145) + 0.5$ which can be rearranged to
$\log C /0.145) = (3 - 0.5) / 2.33 = 1.266$ and results in
$C = (10^{1.266}) \times 0.145 = 2.675$ ppm

The resulting concentration is multiplied by an empirical field correction factor of 1.33.

LOA = C x 1.33 = 2.675 ppm x 1.33 = 3.6 ppm

The LOA for formaldehyde is 3.6 ppm.

APPENDIX B: Carcinogenicity Assessment

The U.S. EPA (2003) in its Integrated Risk Information System (IRIS) has calculated dose levels for cancer risk levels of 1 in 10,000, 1 in 100,000, and 1 in 1,000,000 individuals. The calculations are based on the study of Kerns et al. (1983) with Fischer 344 rats (see Section 3.6 for discussion of this study). The concentration over a lifetime of 70 years that would result in a risk level of 1 in 10,000, a virtually safe dose, is 8 $\mu g/m^3$ (6.5 ppb).

To convert a 70-year exposure to a 24-hour exposure, multiply by the number of days in 70 years (25,600):

24-hour exposure = dose x 25,600
= 8 $\mu g/m^3$ x 25,600
= 205 mg/m^3

To account for uncertainty regarding the variability in the stage of the cancer at which formaldehyde or its metabolites may act, a multistage factor of 6 is applied(Crump and Howe 1984:

205 mg/m^3/6 = 34.17 mg/m^3 (28 ppm)

Therefore, based upon the potential carcinogenicity on formaldehyde, an acceptable 24-hour exposure would be 34 mg/m^3. If the exposure is limited to a fraction of a 24-hour period, the values are adjusted accordingly:

24-hour exposure = 34 mg/m^3 (28 ppm)
8-hour exposure = 103 mg/m^3 (83 ppm)
4-hour exposure = 205 mg/m^3 (167 ppm)
1-hour exposure = 820 mg/m^3 (667 ppm)
30-min exposure = 1640 mg/m^3 (1333 ppm)
10-min exposure = 4920 mg/m^3 (6052 ppm)

APPENDIX C: Derivation of AEGL Values

Derivation of AEGL-1

Key Study:	Bender et al. 1981
Toxicity endpoint:	0.9 ppm: NOAEL for eye irritation in sensitive subjects
Time scaling:	not applied; there is adaptation to the slight irritation defined by the AEGL-1
Uncertainty factors:	1 - the subjects had been selected for their eye sensitivity to slightly higher concentrations of formaldehyde
Modifying factor:	none applied
Calculations:	none; 0.90 ppm used across all exposure durations

10-minute AEGL-1: 0.90 ppm
30-minute AEGL-1: 0.90 ppm
1-hour AEGL-1: 0.90 ppm
4-hour AEGL-1: 0.90 ppm
8-hour AEGL-1: 0.90 ppm

Derivation of AEGL-2

Key Study:	Sim and Pattle 1957
Toxicity endpoints:	14 ppm for 30 minutes
Time scaling	none applied; there was adaptation to the eye and mild nose irritation
Uncertainty factors:	none applied; application of an uncertainty factor would lower the value to a no-effect level in exercising asthmatics
Modifying factor:	none applied
Calculations:	none; 14 ppm used across all exposure durations

10-minute AEGL-2: 14 ppm
30-minute AEGL-2: 14 ppm
1-hour AEGL-2: 14 ppm
4-hour AEGL-2: 14 ppm
8-hour AEGL-2: 14 ppm

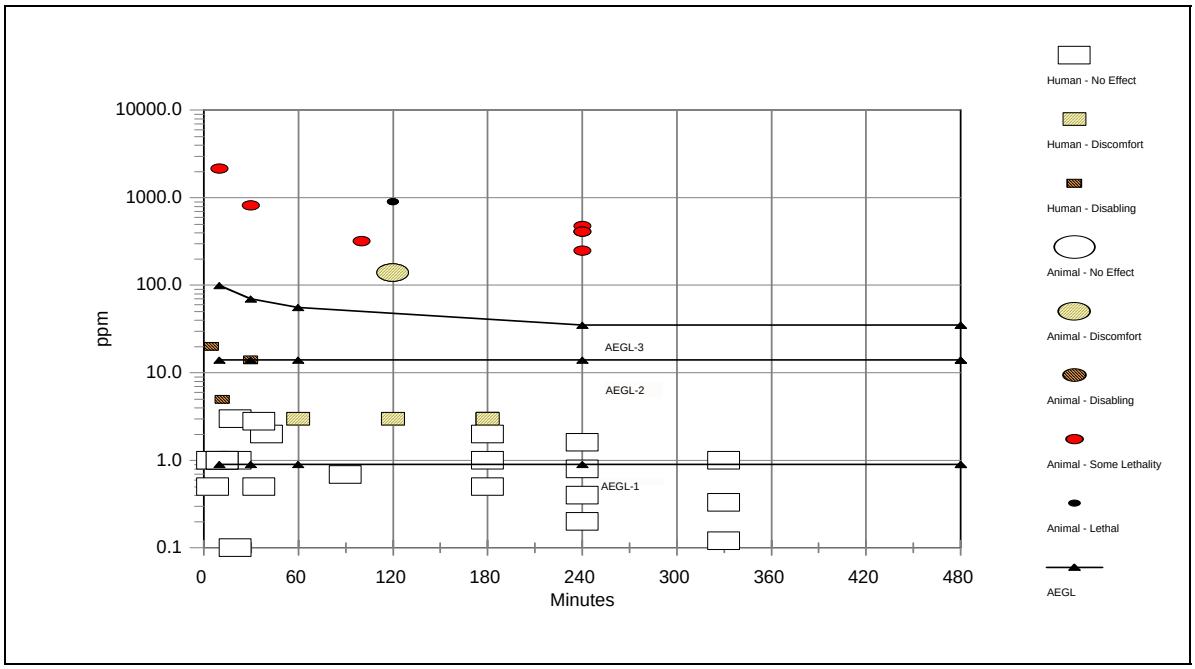
Derivation of AEGL-3

Key Study:	Nagorny et al. 1979
Toxicity endpoint:	350 ppm for 4 hours: highest non-lethal value in the rat
Time scaling	default value of 3 when extrapolating to shorter exposure durations (NRC 2001)
Uncertainty factors:	interspecies and intraspecies of 3 each for a total of 10; these factors have been protective of sensitive subjects exposed to irritants
Modifying factor:	none applied
Calculations:	$C^3 \times t = k$ $(350 \text{ ppm}/10)^3 \times 240 \text{ minutes} = 10290000 \text{ ppm}^3 \bullet \text{minutes}$

10-minute AEGL-3: 100 ppm
30-minute AEGL-3: 70 ppm
1-hour AEGL-3: 56 ppm
4-hour AEGL-3: 35 ppm
8-hour AEGL-3: 35 ppm

The 8-hour AEGL-3 was set equal to the 4-hour value because formaldehyde is well-scrubbed in the nasal passages.

APPENDIX D: Category Graph of Toxicity Data and AEGL Values



APPENDIX E: Derivation Summary for Formaldehyde AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR FORMALDEHYDE (CAS Reg. No. 50-00-0) DERIVATION SUMMARY

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.90 ppm	**0.90 ppm**	**0.90 ppm**	**0.90 ppm**	**0.90 ppm**
Key Reference: Bender, J.R., L.S. Mullin, G.J. Grapel, and W.E. Wilson. 1983. Eye irritation response of humans to formaldehyde. Am. Ind. Hyg. Assoc. J. 44:463-465.				
Test Species/Strain/Number: Humans, sensitive subjects/groups of 5-28; subjects whose eyes were not sensitive to 1.3 or 2.2 ppm were excluded from the study				
Exposure Route/Concentrations/Durations: Eye exposure/ 0, 0.35, 0.56, 0.7, 0.9, 1.0 for 6 minutes				
Effects: 0.35-0.90 ppm: responses same as those to clean air 1.0 ppm: slight irritation, adaptation with time				
Endpoint/Concentration/Rationale: NOAEL for irritation/0.90 ppm				
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: not applicable Intraspecies: 1 - subjects whose eyes were sensitive to formaldehyde were used				
Modifying Factor: not applied				
Animal to Human Dosimetric Adjustment: not applied				
Time Scaling: not applied; there was no irritation; in other cases, there is adaptation to the slight irritation that defines the AEGL-1				
Data Adequacy: There over 22 clinical studies involving 500 subjects that show that concentrations <1 ppm are generally non-irritating.				

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
14 ppm	**14 ppm**	**14 ppm**	**14 ppm**	**14 ppm**
Key Reference: Sim, V.M. and R.E. Pattle. 1957. Effect of possible smog irritants on human subjects. J. Amer. Med. Assoc. 165:1908-1913.				
Test Species/Strain/Number: Humans/male/12				
Exposure Route/Concentrations/Durations: Inhalation/14 ppm/30 minutes				
Effects: Initial nose and eye irritation with mild lacrimation; adaptation in 10 minutes				
Endpoint/Concentration/Rationale: mild irritation at 14 ppm for 30 minutes meets the definition of the AEGL-2				
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: not relevant Intraspecies: 1 - application of an uncertainty factor would lower the value to a no-effect level in exercising asthmatics				
Modifying Factor: not applied				
Animal to Human Dosimetric Adjustment: not relevant				
Time Scaling: not applied; there was adaptation to the irritation in 10 minutes				
Data Adequacy: The abundance of clinical studies at lower concentrations and involving over 500 subjects support the 14 ppm concentration as a reasonable value.				

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
100 ppm	**70 ppm**	**56 ppm**	**35 ppm**	**35 ppm**
Key Reference: Nagorny, P.A., Zh.A. Sudakova and S.M. Schablenko. 1979. On the general toxic and allergic action of formaldehyde. Gig. Tr. Prof. Zabol. 1:27-30.				
Test Species/Strain/Number: rat/not given/groups of 6-12				
Exposure Route/Concentrations/Durations: Inhalation/not given/4 hours				
Effects: 228-350 ppm, no deaths; ≤732 ppm, some lethality; >732 ppm, 100% lethal				
Endpoint/Concentration/Rationale: highest non-lethal value, 350 ppm for 4 hours, meets definition of AEGL-3				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 - rodents with higher respiratory rates than humans have greater uptake Intraspecies: 3 - applied to irritants; protective of the sensitive population				
Modifying Factor: none applied				
Animal to Human Dosimetric Adjustment: not applied				
Time Scaling: default values of 3 and 1 when extrapolating to shorter and longer exposure durations, respectively				
Data Adequacy: The lethality studies are old and lack details of methodology and results. Longer-duration and repeat-exposure studies (Horton et al. 1963; Murphy et al. 1964; Tobe et al. 1985) support the 4 and 8-hour values.				