2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of formaldehyde. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure— inhalation, oral, and dermal; and then by health effect—death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods—acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of

exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of formaldehyde are indicated in Tables 2-1, 2-4, and 2-5 and Figures 2-1 and 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for formaldehyde. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Formaldehyde vapors used in controlled-exposure inhalation studies can be generated by heating commercial formalin, aqueous solutions containing 30–50% formaldehyde by weight plus methanol or other substances to inhibit intrinsic polymerization, or by heating solid paraformaldehyde, a formaldehyde polymer. Unless noted otherwise, inhalation studies used in the preparation of this profile provided clear evidence that formaldehyde was the only added gas in the experimental atmosphere.

2.2.1.1 Death

Reports of deaths in humans from short-term inhalation exposure to formaldehyde were not located. Increased rates of cancer-related mortality associated with occupational exposure to formaldehyde have been found in some epidemiological studies, but not in others. A more thorough discussion of available epidemiological studies is available in Section 2.2.1.8.

Repeated exposure to formaldehyde vapors at 40 ppm, 6 hours/day, 5 days/week for up to 13 weeks produced 80% mortality in B6C3F1 mice, whereas mice exposed with the same protocol to 20 ppm showed no mortalities within the exposure period (Maronpot et al. 1986). Deaths occurred predominately in the fifth and sixth week of exposure and were associated with ataxia, severe body weight depression, and inflammation and metaplasia in the nasal cavity, larynx, trachea, and lungs. Deaths were attributed to occlusive tracheal lesions and/or prominent seropurulent rhinitis (Maronpot et al. 1986).

In other intermediate duration inhalation bioassays, no exposure-related deaths or early mortalities were found in Wistar rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), in F344 rats, Cynomolgus monkeys, or Golden Syrian hamsters exposed to up to 2.95 ppm, 22 hours/day, 7 days/week for 26 weeks (Rusch et al. 1983), or in Wistar rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 4, 8, or 13 weeks and subsequently observed for 117 weeks without exposure (Feron et al. 1988). No exposure-related maternal or fetal deaths occurred in studies that exposed pregnant Sprague-Dawley rats to up to 10 ppm formaldehyde, 6 hours/day on gestation days

6 through 15 (Martin 1990) or up to 40 ppm, 6 hours/day on gestation days 6 through 20 (Saillenfait et al. 1989).

In chronic inhalation bioassays, increased mortality (compared with controls) was found in Sprague-Dawley rats exposed to 14.2 ppm formaldehyde, 6 hours/day, 5 days/week for up to 588 days (Albert et al. 1982), in F344 rats exposed to 5.6 or 14.3 ppm (but not 2 ppm), 6 hours/day, 5 days/week for up to 24 months (Kerns et al. 1983b; Swenberg et al. 1980), in F344 rats exposed to 15 ppm (but not to 0.7, 2, 6, or 10 ppm) 6 hours/day, 5 days/week for 24 months (Monticello et al. 1996), and in F344 rats exposed to 15 ppm (but not to 0.3 or 2 ppm), 6 hours/day, 5 days/week for up to 28 months (Kamata et al. 1997). In general, observations of increased mortality in the rat bioassays occurred after about one year of exposure and were associated with the development of nasal squamous cell carcinomas. Golden Syrian hamsters exposed to 10 ppm formaldehyde, 5 hours/day, 5 days/week for life showed a small, but statistically significant, increase in mortality compared with controls, but no increased incidence of nasal tumors and only a minimal (5% versus zero in controls) increased incidence of hyperplasia or metaplasia in the nasal epithelium (Dalbey 1982). No exposure-related increased mortality was found in B6C3F1 mice exposed to up to 14.3 ppm for 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b).

The LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Human (anatomy students)	3 hr	Resp		1.88	(nose irritation; increase in FEV_1 & $FEFR_{25-75}$ during class period less than in controls)	Akbar-Khanzadeh and Mlynek 1997
			Ocular		1.88	(eye irritation)	
2	Human (anatomy students)	2-3 hr	Resp		1.24	(nose irritation; 1.2% decrease in FEV_3 during class period)	Akbar-Khanzadeh et al. 1994
			Ocular		1.24	(eye irritation)	
3	Human (normal)	4 hr	Resp		0.2	(3/16 nasal irritation)	Andersen and Molhave 1983
			Ocular		0.2	(3/16 eye irritation)	
4	Human (normal)	6 min	Ocular		0.35	(decreased eye irritation response time in 5/12)	Bender et al. 1983
5	Human (normal)	90 min	Resp		1	(4/9 nasal congestion)	Day et al. 1984
			Ocular		1	(8/9 eye irritation)	

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
6	Human (w/health complaints)	90 min	Resp		1 (3/9 nasal congestion)		Day et al. 1984
			Ocular		1 (7/9 eye irritation)		
7	Human (w/contact dermatitis)	2 hr	Resp		0.4 (3/13 nasal irritation & sneezing)		Gorski et al. 1992
			Ocular		0.4 (3/13 eye irritation)		
8	Human (normal)	2 hr	Resp		0.4 (1/5 nasal irritation)		Gorski et al. 1992
			Ocular	0.4			
9	Human (healthy & asthmatics)	1 hr	Resp		3 (nose/throat irritation; dec FEV_1 >10% in 5/38)		Green et al. 1987
			Ocular		3 (eye irritation)		
10	Human (particle-board workers)	8 hr	Resp		0.69 (small decrease in FEFR during workshift)		Horvath et al. 1988
11	Human (non-preexposed)	2 hr	Resp		0.4 (increased eosinophils & protein in nasal lavage fluid)		Krakowiak et al. 1998
12	Human (asthmatics)	2 hr	Resp		0.4 (increased eosinophils & protein in nasal lavage fluid)		Krakowiak et al. 1998

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
13	Human (normal)	3 hr	Resp	1	2 (7/19 with nose/throat irritation)		Kulle et al. 1987; Kulle 1993
			Ocular	0.5	1 (4/19 with eye irritation)		
14	Human (purported asthmatics)	30 min	Resp	1	2 (12/230 w/decreased PEFR > 15%)		Nordman et al. 1985
15	Human (w/contact dermatitis)	2 hr	Resp		0.4 [b] (increased eosinophils and protein in nasal lavage fluid, increased itching, sneezing, and congestion)		Pazdrak et al. 1993
16	Human (healthy)	2 hr	Resp		0.4 (increased eosinophils & protein in nasal lavage fluid, increased itching, sneezing, and congestion)		Pazdrak et al. 1993
17	Human (healthy)	30 min	Resp		3 (small average decreases in FEV, FVC, & FEV_3)		Sauder et al. 1986
			Ocular		3 (increase in eye irritation)		
18	Human (normal)	35 min	Resp	0.5	1.2 (nasal irritation)		Weber-Tschopp et al. 1977
			Ocular	0.5	1.2 (eye irritation)		
19	Human (healthy)	40 min/d	Resp		2 (5/15 nasal irritation)		Witek et al. 1986; Witek et al. 1987
			Ocular		2 (8/15 eye irritation)		

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
20	Human (asthmatics)	40 min/d	Resp		2 (5/15 nasal irritation)		Witek et al. 1986; Witek *et al. 1987*
			Ocular		2 (8/15 eye irritation)		
21	Monkey (Rhesus)	5 d 6 hr/d	Resp			6 M (hyperplasia & squamous metaplasia in nasal epithelium, extending to trachea & carina)	Monticello et al. 1989
			Cardio	6 M			
			Gastro	6 M			
			Hepatic	6 M			
			Renal	6 M			
			Endocr	6 M			
			Ocular		6 M (mild lacrimation and conjunctival hyperemia)		
			Bd Wt	6 M			
22	Rat (Sprague-Dawley)	4 hr	Resp			10 M (ciliary destruction and cell separation in naso- and maxillo-turbinates, celluar swelling throughout turbinates, mucous releasing goblet cells in naso-turbinates)	Bhalla et al. 1991
23	Rat (Wistar)	3 d 2 x/day 8 hr	Resp			3.6 M (necrosis, hyperplasia and squamous metaplasia in nasal respiratory epithelium and rhinitis)	Cassee and Feron 1994

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
24	Rat (Fischer- 344)	10 min	Resp		31.7	(RD_{50})			Chang et al. 1981
25	Rat (Fischer- 344)	1 or 5 d 6 hr/d	Resp				15 M	(increased nasal epithelial cell turnover; degeneration and sloughing of epithelial cells, necrobiotic cells with inclusions, hyperplasia, and focal neutrophil infiltration in nasal cavity, severe ulcerative rhinitis)	Chang et al. 1983
26	Rat (Sprague-Dawley)	4 d 6 hr/d	Resp		10	(clinical signs of nasal irritation)			Dinsdale et al. 1993
			Ocular		10	(clinical signs of eye irritation)			
27	Rat (Fischer- 344)	6 hr	Resp				128	(bloody nasal discharge and pulmonary edema)	Kamata et al. 1996b
28	Rat (Fischer- 344)	1, 2, or 4 d 6 hr/d	Resp				6	(hypertrophy in nasal passages)	Monteiro-Riviere and Popp 1986
29	Rat (Fischer- 344)	1, 4, or 9 d 6hr/d	Resp	2 M			6 M	(nasal epithelial cell necrosis; neutrophil infiltration; epithelial hyperplasia; squamous metaplasia; increased cell proliferation)	Monticello et al. 1991

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
30	Rat (Fischer- 344)	once 10 min - 6 hr	Resp	2 M	15 M (decreased nasal mucous flow and ciliary activity)		Morgan et al. 1986a
31	Rat (Fischer- 344)	1, 2, 4, 9, or 14 d 5 d/wk 6 hr/d	Resp	0.5 M	2 M (minimal mucostasis)	6 M (severe mucostasis and nasal ulcerations)	Morgan et al. 1986c
			Ocular	0.5 M	2 M (eye irritation)		
32	Rat (Wistar)	3 d 8 hr/d	Resp			5 M (increases in nasal cell turnover rates; squamous metaplasia with cellular hyperplasia)	Wilmer et al. 1987
33	Rat (Wistar)	3 d 8 x 30 min/d	Resp			10 M (increased nasal epithelial cell turnover rates; squamous metaplasia with cellular hyperplasia)	Wilmer et al. 1987
34	Mouse (B6C3F1)	10 min	Resp		4.9 (RD_{50})		Chang et al. 1981
35	Mouse (B6C3F1)	1 or 5 d 6 hr/d	Resp			15 M (increased nasal respiratory epithelial cell turnover; mild to serious rhinitis and focal degeneration of the respiratory epithelium; congestion of the olfactory blood vessels, focal erosion and ulceration; hyperplasia)	Chang et al. 1983

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
36	Mouse (Swiss-Webster)	10 min	Resp		3.1 (RD_{50})		Kane & Alarie 1977
37	Gn Pig (Hartley)	2 hr	Resp	3.4 M	9.4 M (increased airway resistance)		Swiecichowski et al. 1993
38	Gn Pig (Hartley)	8 hr	Resp	0.1	0.3 M (increased airway resistance)		Swiecichowski et al. 1993
	Immunological/Lymphoreticular						
39	Human	3 hr		1.0			Pross et al. 1987
40	Human	3 hr		1.0			Pross et al. 1987 (UFFI)
41	Mouse (BALB/c)	10d 6 hr/d			1.6 (increased IgE response to inhaled ovalbumin)		Tarkowski and Gorski 1995
42	Gn Pig (Dunkin-Hartley)	5d 8 hr/d			0.25 (10/12 with allergic response to ovalbumin vs. 3/12 in controls)		Riedel et al. 1996
	Neurological						
43	Human	5.5 hr			0.12 (decreased performance on short term memory tests)		Bach et al. 1990

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
44	Rat (Sprague-Dawley)	1-2 d 3 hr/d			5 M (decreased motor activity; increased concentrations of 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenyl- acetic acid, & dopamine in the hypothalamus)		Boja et al. 1985
45	Rat (Fischer- 344)	once 10 min - 6 hr			15 M (restlessness)		Morgan et al. 1986a
	INTERMEDIATE EXPOSURE						
	Death						
46	Rat (Fischer- 344)	9 mo 5d/wk 6hr/d				15 M (significantly reduced survival after 9 months)	Kamata et al. 1997
47	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d				40 (80% mortality)	Maronpot et al. 1986

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
48	Monkey (Rhesus)	6 wk 5 d/wk 6 hr/d	Resp			6 M (in the nasal epithelium: loss of goblet cells & cilia; epithelial hyperplasia; squamous metaplasia; neutrophil inflammatory response; erosion of the metaplastic epithelium; increased cell proliferation in nasal transitional epithelium, nasal passage epithelium, trachea & carina. Larynx/trachea/carina: loss of cilia, goblet cells, mild epithelial hyperplasia, early squamous metaplasia.)	Monticello et al. 1989
			Cardio	6 M			
			Gastro	6 M			
			Musc/skel	6 M			
			Hepatic	6 M			
			Renal	6 M			
			Endocr	6 M			
			Ocular		6 M (mild lacrimation and conjunctival hyperemia)		
			Bd Wt	6 M			

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
49	Monkey (Cynomolgus)	26 wk 7 d/wk 22 hr/d	Resp	0.98[c]		2.95 M (hoarseness; nasal congestion and discharge; increased incidence of squamous metaplasia and hyperplasia in the nasoturbinates)	Rusch et al. 1983
			Bd Wt	2.95			
50	Rat (Wistar)	13 or 52 wk 5 d/wk 6 hr/d	Resp	1 M		10 M (rhinitis; hyperplasia and metaplasia of nasal epithelium)	Appelman et al. 1988
			Cardio	10 M			
			Gastro	10 M			
			Hemato	10 M			
			Hepatic	10 M			
			Renal	1 M	10 M (increased incidence of oliguria)		
			Endocr	10 M			
			Ocular	10 M			
			Bd Wt	1 M	10 M (10% decrease in body weight)		
51	Rat (Fischer- 344)	81 d 5 d/wk 6 hr/d	Resp	2 M	6 M (increased DNA-protein crosslinkage in lateral, medial & posterior meatuses of the nose)		Casanova et al. 1994

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
52	Rat (Fischer- 344)	6 wk 5 d/wk 6 hr/d	Resp	2 M		6 M (nasal epithelial cell necrosis; neutrophil infiltration; epithelial hyperplasia; squamous metaplasia; increased cell proliferation)	Monticello et al. 1991
53	Rat (Fischer- 344)	26 wk 7 d/wk 22 hr/d	Resp	0.98		2.95 (increased incidence of: nasal squamous metaplasia & hyperplasia; basal cell hyperplasia; rhinitis)	Rusch et al. 1983
			Bd Wt	0.98 M 2.95 F	2.95 M (average 13% decreased body weight)		
54	Rat (Sprague-Dawley)	gd 6-20 15 d 6 hr/d	Bd Wt	20 F		40 F (51% decrease in maternal weight gain)	Saillenfait et al. 1989
55	Rat (Wistar)	4 wk 5 d/wk 8 hr/d	Resp			5 M (nasal cavity squamous metaplasia with cellular hyperplasia; minimal to moderate rhinitis)	Wilmer et al. 1987
56	Rat (Wistar)	4 wk 5 d/wk 8 x 30 min/d	Resp			10 M (increased cell turnover rates; thinning & disarrangement of the nasal epithelium; squamous metaplasia with cellular hyperplasia; minimal to moderate rhinitis)	Wilmer et al. 1987

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
57	Rat (Wistar)	13 wk 5 d/wk 8 hr/d	Resp	2 M			Wilmer et al. 1989
58	Rat (Wistar)	13 wk 5 d/wk 8x 30 min/d	Resp	2 M		4 M (increased cell proliferating rates in nasal epithelium; squamous metaplasia with basal cell hyperplasia in nasal epithelium)	Wilmer et al. 1989
59	Rat (Wistar)	13 wk 5 d/wk 6 hr/d	Resp	1		10 (metaplasia, with keratinization of the epithelial lining the larynx; cell turnover, squamous metaplasia & hyperplasia in the nasal turbinates)	Woutersen et al. 1987
			Cardio	20			
			Gastro	20			
			Hemato	20			
			Hepatic	10 M 20 F	20 M (increased plasma AST, ALT, and ALP levels)		
			Renal	20			
			Endocr	20			
			Ocular	20			
			Bd Wt	10 M 20 F	20 (18.2% decrease in body weight)		
60	Rat (Wistar)	3 mo 5 d/wk 6 hr/d	Resp	1 M		10 M (increased nasal squamous metaplasia and rhinitis)	Woutersen et al. 1989

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
61	Rat (Wistar)	13 wk 5 d/wk 6 hr/d	Resp	1	3 (disarranged and hyperplastic nasal epithelial cells; increased cell proliferation)		Zwart et al. 1988
			Bd Wt	3			
62	Mouse (B6C3F1)	3 wk 5 d/wk 6 hr/d	Hemato		15 F (decrease in the absolute number of monocytes)		Dean et al. 1984
			Bd Wt	15 F			
63	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	2 M 4 F		4 M (squamous metaplasia; 10 F keratinization; suppurative inflammatory and serous exudate; & epithelial degeneration in nasal sections; dyspnea)	Maronpot et al. 1986
			Cardio	40			
			Gastro	40			
			Musc/skel	40			
			Hepatic	40			
			Renal	40			
			Endocr	40			
			Dermal	20	40 (loss of skin elasticity)		
			Ocular	40			
			Bd Wt	10 M 20 F	20 M (18% decrease in body weight)	40 M (50% decrease in body weight) 40 F (33% decrease in body weight)	

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
64	Hamster (Golden Syrian)	26 wk 7 d/wk 22 hr/d	Resp	2.95			Rusch et al. 1983
			Bd Wt	2.95			
	Immunological/Lymphoreticular						
65	Monkey (Rhesus)	6 wk 5 d/wk 6 hr/d		6			Monticello et al. 1989
66	Rat (Fischer- 344)	13 or 52 wk 5 d/wk 6 hr/d		10			Appelman et al. 1988
67	Rat (Wistar)	13 wk 5 d/wk 6 hr/d		20			Woutersen et al. 1987
68	Mouse (B6C3F1)	3 wk 5 d/wk 6 hr/d			15 F (increased ability of macrophages to release reactive oxygen intermediates)		Adams et al. 1987
69	Mouse (B6C3F1)	3 wk, 5 d/wk 6 hr/d		15 F			Dean et al. 1984
70	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		40			Maronpot et al. 1986
	Neurological						
71	Rat (Wistar)	13 or 52 wk 5 d/wk 6 hr/d		10 M			Appelman et al. 1988

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
72	Rat (Wistar)	13 wk 5 d/wk 6 hr/d		10	20	(temporary uncoordinated movement & wall-climbing)			Woutersen et al. 1987
73	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		10	20	(listlessness, hunched appearance)	40	(ataxia)	Maronpot et al. 1986
	Reproductive								
74	Human	1 to 11 mo to several years		0.97 M					Ward Jr. et al. 1984
75	Rat (Sprague-Dawley)	15 d gd 6-20 6 hr/d		40 F					Saillenfait et al. 1989
76	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		20 F 40 M	40 F	(decreased prominence of endometrial glands & stroma; decrease in ovarian luteal tissue)			Maronpot et al. 1986
	Developmental								
77	Rat (Sprague-Dawley)	15 d gd 6-20 6 hr/d		10	20 M	(5% decrease in fetal weight)	40	(21% decrease in fetal weight)	Saillenfait et al. 1989
	Cancer								
78	Rat (Wistar)	4 wk 5 d/wk 6 hr/d					20 M	(CEL: nasal tumors; squamous cell carcinoma & polypoid adenoma)	Feron et al. 1988

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
79	Rat (Wistar)	13 wk 5 d/wk 6 hr/d				10 M (CEL: nasal tumors; squamous cell carcinoma, cystic squamous cell carcinoma, carcinoma in situ and meloblastoma)	Feron et al. 1988
	CHRONIC EXPOSURE						
	Death						
80	Rat (Sprague-Dawley)	588 d 5 d/wk 6 hr/d				14.2 M (38% mortality)	Albert et al. 1982
81	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				15 M (decreased survival rate)	Monticello et al. 1996
82	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				5.6 M (significantly reduced survival after 17 months) 14.3 M F (significantly reduced survival after 12 months)	Swenberg et al. 1980, Kerns et al. 1983b;
83	Hamster (Golden Syrian)	lifetime 5 d/wk 5 hr/d				10 M (significantly reduced survival times)	Dalbey 1982

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
84	Human (plywood factory workers)	6.8 yr (range: 2-19 yr)	Resp		0.39 (increased lesions [nonciliated cells, metaplasia, dysplasia] in nasal epithelium samples)		Ballarin et al. 1992
85	Human (particleboard workers)	10.5 yr (range: 1-39 yr)	Resp		0.49 M (increased lesions [nonciliated cells, metaplasia, mild dysplasia] in nasal epithelium cells)		Edling et al. 1988
			Ocular		0.49 M (running eyes - 75%)		
86	Human (chemical workers)	7.3 yr (range: 1-36 yr)	Resp		0.24 [d] (increased lesions [nonciliated cells, metaplasia, mild dysplasia] in nasal epithelium samples)		Holmstrom et al. 1989c
87	Human (furniture factory workers)	7.3 yr (range: 1-36 yr)	Resp	0.2			Holmstrom et al. 1989c
88	Human (embalmers)	8.2 yrs (average, range not reported)	Resp		0.36 (increased reporting of symptoms of respiratory irritation)		Holness and Nethercott 1989
			Dermal		0.36 (increase in past skin problems and contact dermatitis)		
			Ocular		0.36 (increase in eye irritation)		

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
89	Human (particleboard workers)	10.3 yr (range <1-20 yr)	Resp		0.69	(increased reporting of respiratory symptoms)			Horvath et al. 1988
			Ocular		0.69	(increased reporting of itchy eyes and burning/watery eyes)			
90	Rat (Fischer- 344)	28 mo 5d/wk 6hr/d	Resp	0.3	2	(significant increased incidence of squamous cell metaplasia in nasal respiratory epithelium)	15	(hyperplasia or squamous metaplasia of nasal epithelium observed in all rats)	Kamata et al. 1997
			Gastro	15					
			Hemato	15					
			Musc/skel	15					
			Hepatic	15					
			Renal	15					
			Endocr	15					
			Bd Wt	2	15	(>10% decrease in body weight after 4 months)			
91	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d	Resp	2 M			6 M	(nasal inflammatory cell infiltrate; nasal epithelial hyperplasia & squamous metaplasia)	Monticello et al. 1996

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
92	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d	Resp		2	(restricted areas of dysplasia & metaplasia in nasal epithelium rhinitis)	5.6	(dyspnea; rhinitis, epithelial dysplasia and squamous metaplasia of nasal epithelium; epithelial hyperplasia or dysplasia or squamous metaplasia of the tracheal mucosa)	Swenberg et al. 1980, Kerns et al. 1983b
			Cardio	14.3					
			Gastro	14.3					
			Hemato	14.3					
			Musc/skel	14.3					
			Hepatic	14.3					
			Renal	14.3					
			Endocr	14.3					
			Ocular	14.3					
			Bd Wt	5.6	14.3	(approximate 10% decrease in body weight)			
93	Rat (Wistar)	28 mo 5 d/wk 6 hr/d	Resp	1 M			10 M	(increased squamous metaplasia and basal cell/ pseudoepithelial hyperplasia of the nasal epithelium; thinning & disarrangement of olfactory epithelium, & rhinitis)	Woutersen et al. 1989
			Bd Wt	1 M	10 M	(approximate 10% decrease in body weight)			

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	LOAEL	Reference Chemical Form
94	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d	Resp	2.0		5.6	(inflammatory, dysplastic & squamous metaplastic alterations of the nasal epithelium; serous rhinitis)	Kerns et al. 1983b
			Cardio	14.3				
			Gastro	14.3				
			Hemato	14.3				
			Musc/skel	14.3				
			Hepatic	14.3				
			Renal	14.3				
			Endocr	14.3				
			Ocular	14.3				
			Bd Wt	14.3				
95	Hamster (Golden Syrian)	lifetime 5 d/wk 5 hr/d	Resp			10 M	(hyperplastic & metaplastic areas in the nasal epithelium)	Dalbey 1982
	Immunological/Lymphoreticular							
96	Rat (Sprague-Dawley)	22 mo 5 d/wk 6 hr/d		12.6 F				Holmstrom et al. 1989b
97	Rat (Fischer- 344)	28 mo 5 d/wk 6 hr/d		15				Kamata et al. 1997
98	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d		14.3				Swenberg et al. 1980; Kerns et al. 1983b

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
99	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d		14.3			Kerns et al. 1983b
	Neurological						
100	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d		14.3			Swenberg et al. 1980, Kerns et al. 1983b
101	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d		14.3			Kerns et al. 1983b
	Cancer						
102	Rat (Sprague-Dawley)	588 d 5 d/wk 6 hr/d				14.2 M (CEL: squamous cell carcinomas 10/100 rats)	Albert et al. 1982
103	Rat (Fischer- 344)	28 mo 5 d/wk 6 hr/d				15 (CEL: nasal squamous cell carcinoma in 13/32 rats)	Kamata et al. 1997
104	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				10 M (CEL: nasal tumors - 20/90 rats)	Monticello et al. 1996
105	Rat (Sprague-Dawley)	lifetime 5 d/wk 6 hr/d				14.8 M (CEL: nasal cavity tumors; 38/100 squamous cell carcinomas, 1/100 fibrocarcinoma, & 1/100 mixed carcinoma)	Sellakumar et al. 1985

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
106	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				14.3	(CEL: squamous cell carcinomas of nasal cavity - 106/235 rats)	Swenberg et al. 1980, Kerns et al. 1983b

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute duration inhalation minimal risk level (MRL) of 0.04 ppm; concentration, 0.4 ppm, was divided by an uncertainty factor of 9 (3 for the use of a minimal LOAEL and 3 to account for variability among a group of potentially sensitive individuals).

[c]Used to derive an intermediate duration inhalation MRL of 0.03 ppm; concentration, 0.98 ppm, was divided by an uncertainty factor of 30 (3 for extrapolation from monkeys to humans and 10 to account for human variability).

[d]Used to derive chronic duration inhalation MRL of 0.008 ppm; concentration , 0.24 ppm, was divided by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 to account for human variability).

ALAT = alanine amino transferase; ALP = alkaline phosphatase; AST = aspartate amino transferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; FEFR = forced expiratory flow rate; FEFV = forced expiratory flow volume; FVC = forced vital capacity; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; GGT = gamma-glutamyl transpeptidase; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); mo = months; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; OR = odds ratio; Resp = respiratory; wk = week(s); x = times; yr = year(s)

Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation

Acute (≤14 days)

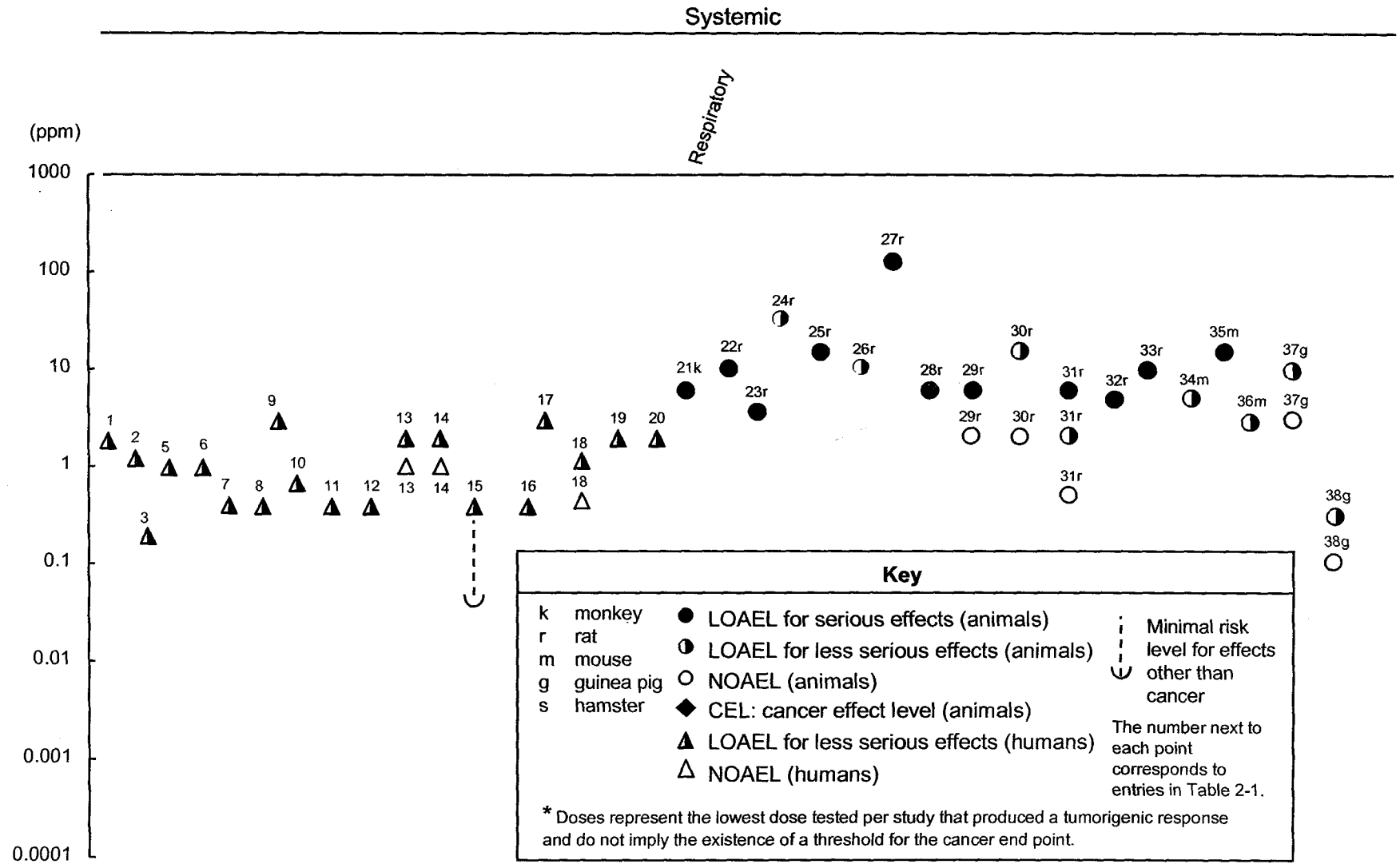


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Acute (≤14 days)

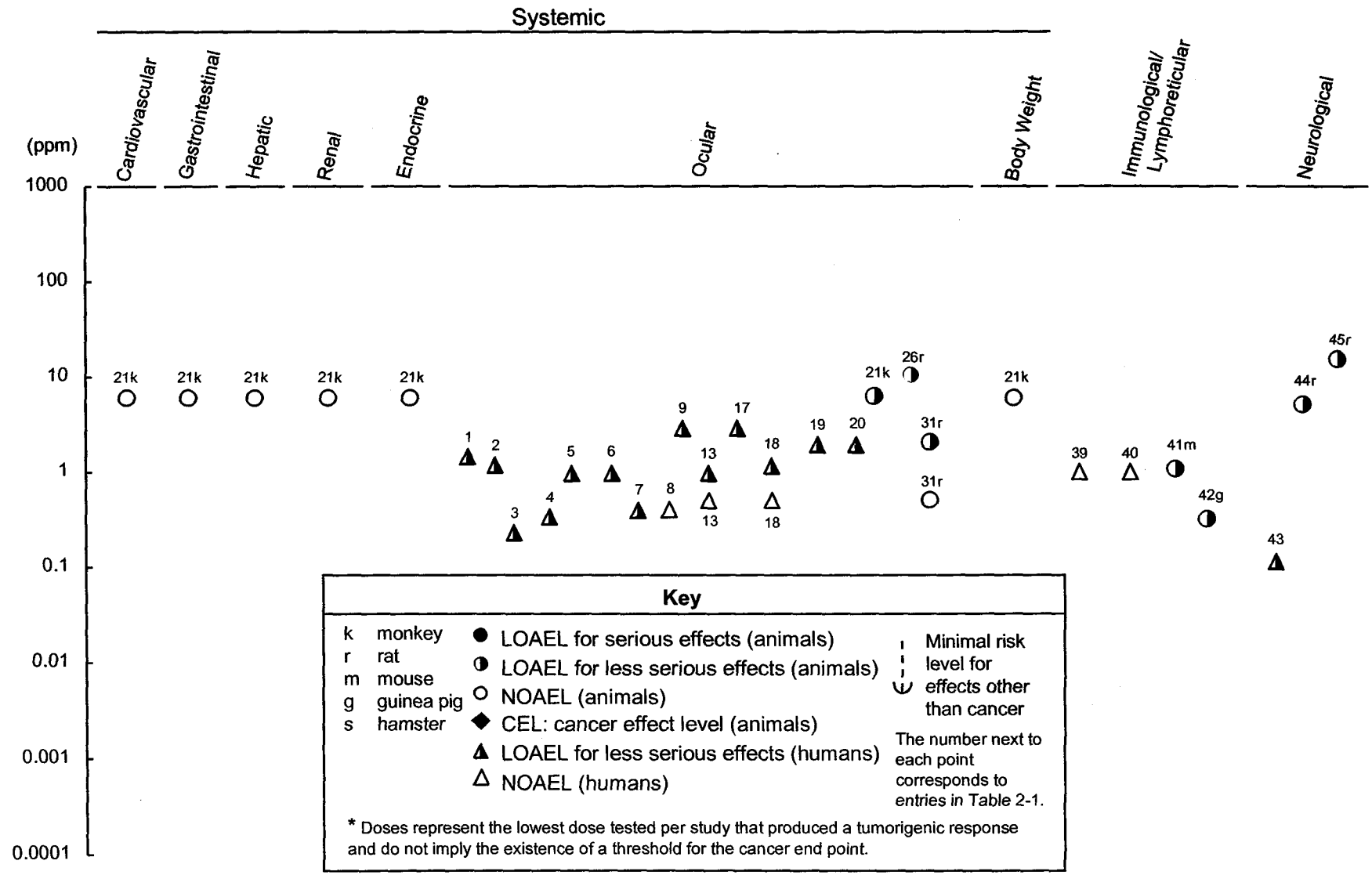


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Intermediate (15-364 days)

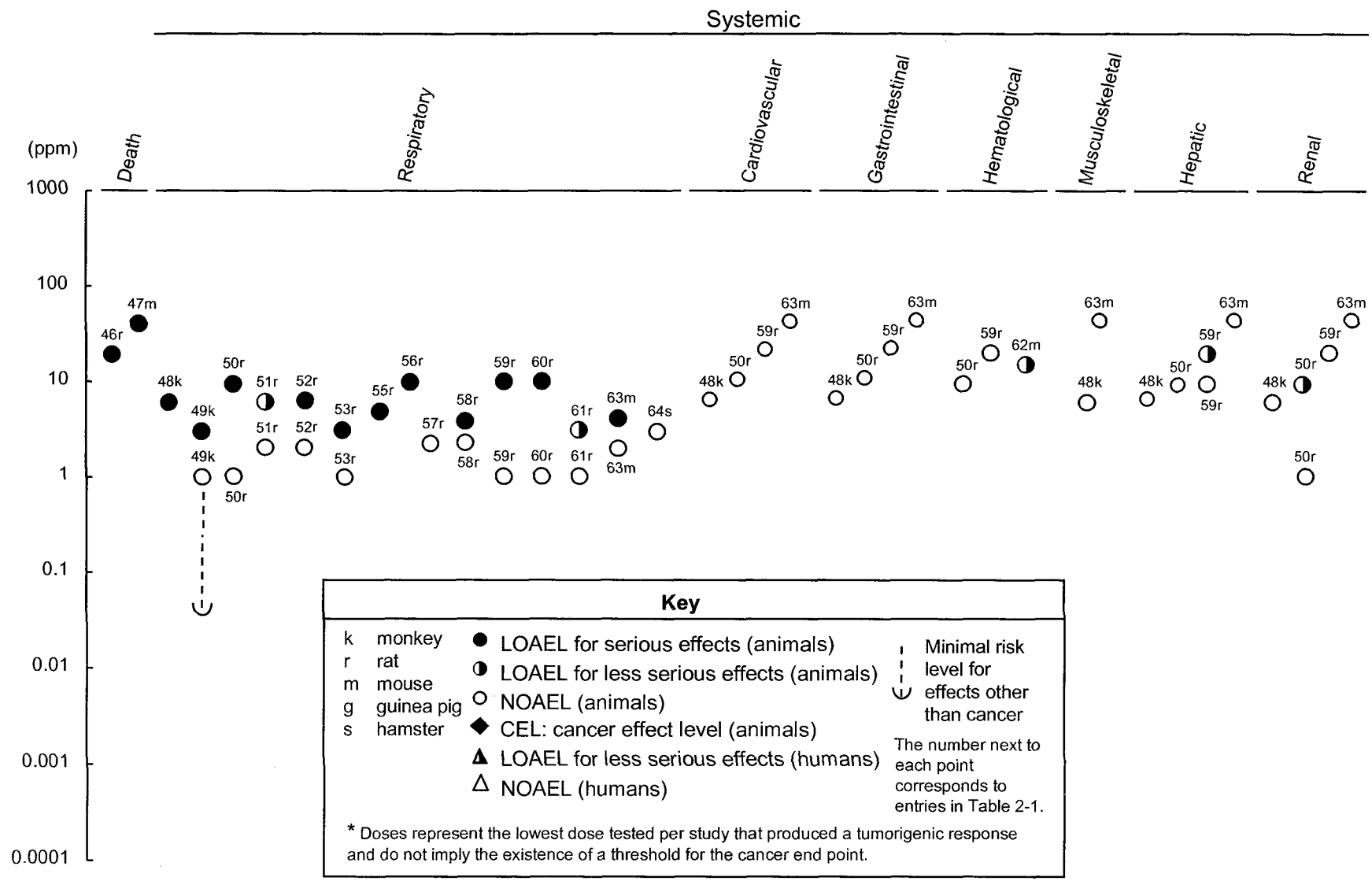


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Intermediate (15-364 days)

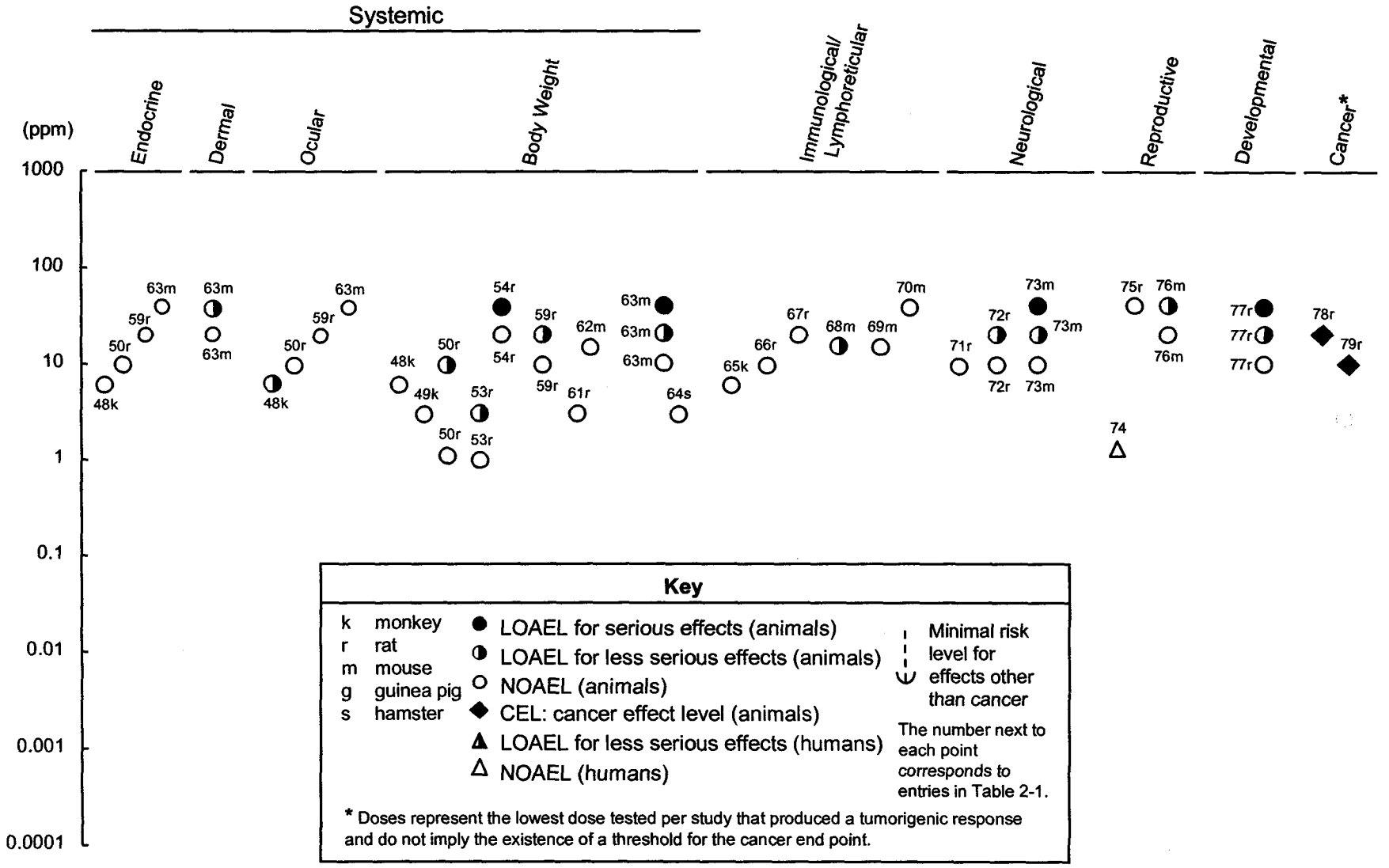


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Chronic (≥365 days)

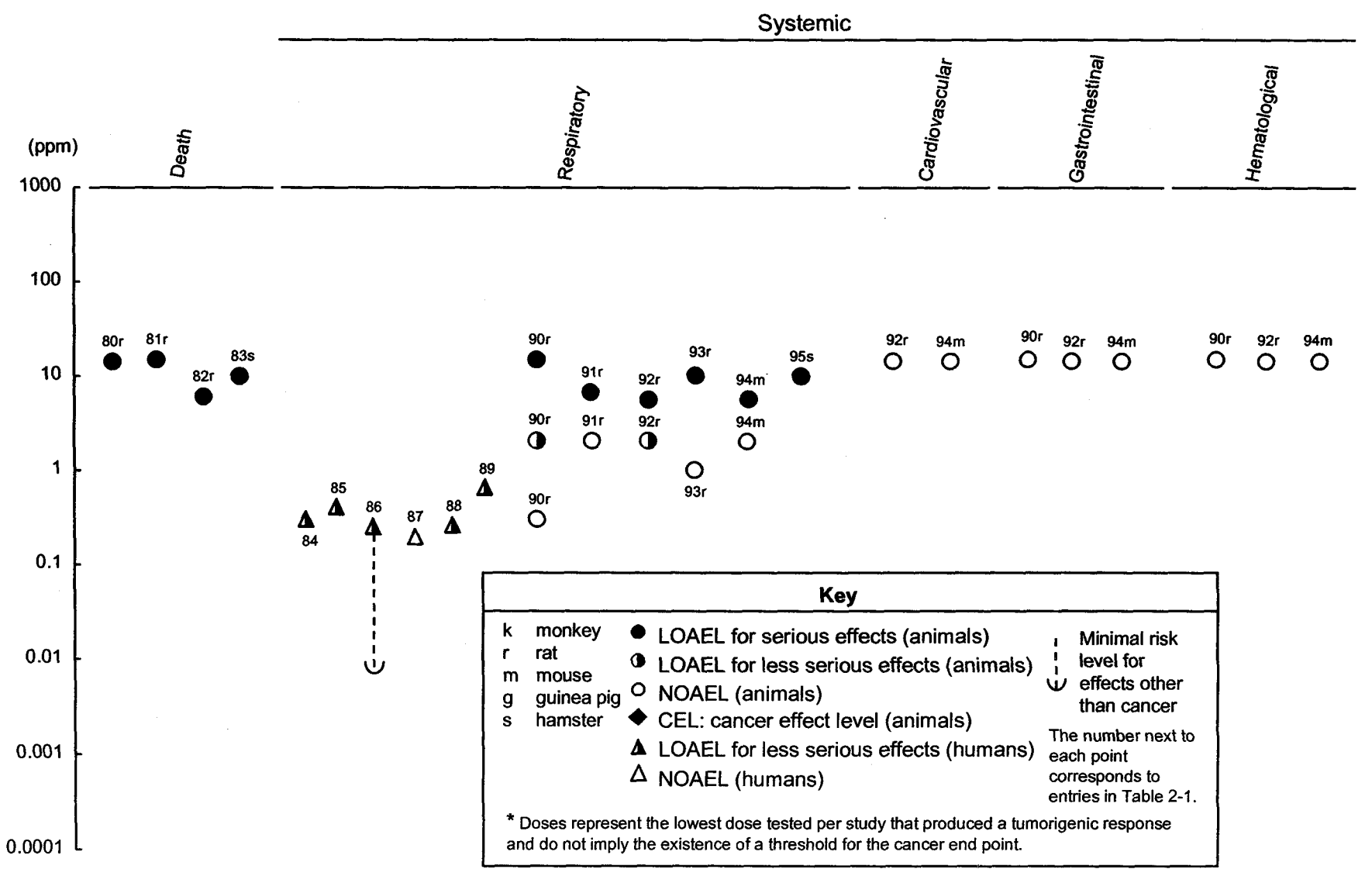
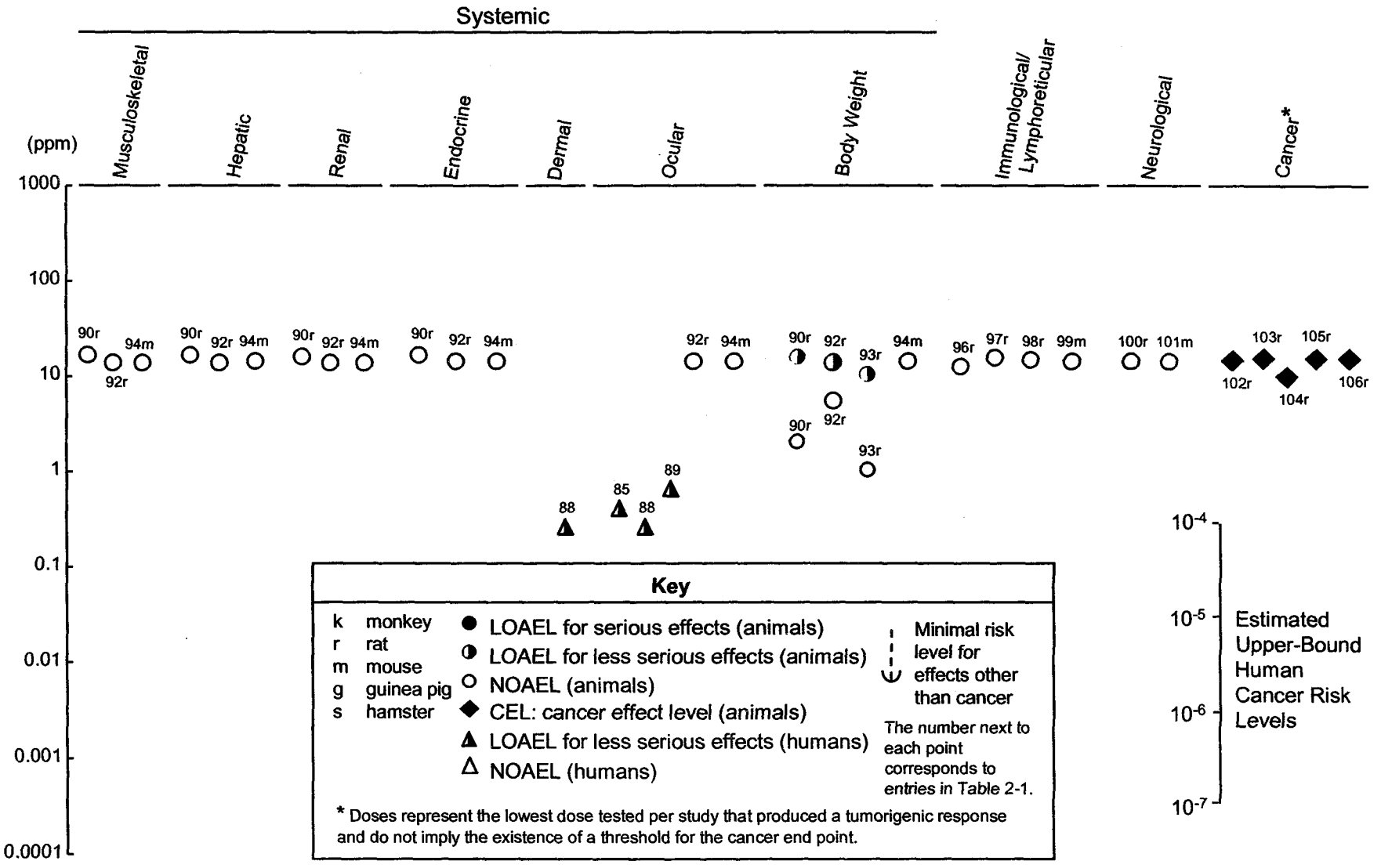


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Chronic (≥365 days)



Results from human and animal studies indicate that the critical target organs to airborne formaldehyde are the nose and the eyes, with the lungs being a secondary target at high exposure levels. Due to rapid, detoxifying metabolism of formaldehyde by most, if not all, cells, tissues, and organs distant from portals of entry are spared toxic effects from formaldehyde at concentrations normally expected to be encountered in the ambient or workplace atmosphere.

Respiratory Effects.

The respiratory tract, especially the upper respiratory tract, is a critical target of the toxicity of airborne formaldehyde as shown by acute controlled exposure human studies, by studies of humans exposed acutely or repeatedly under occupational or residential conditions, and by studies of animals (including primates) exposed by inhalation for acute, intermediate, and chronic durations.

Acute Controlled Exposure Human Studies. More than 15 published studies of respiratory function and/or irritation of the nose, eyes, and throat are available involving acute controlled exposure of volunteers, generally at formaldehyde concentrations #3 ppm. Recent reviews of these studies include those by ACGIH (1992), Krivanek and Imbus (1992), and Paustenbach et al. (1997).

Controlled exposure human studies have found that short-term inhalation exposures to concentrations ranging from 0.4 to 3 ppm can produce symptoms of mild to moderate irritation of the eyes, nose, and throat. The odor threshold for formaldehyde in humans has been reported to be 1 ppm (Leonardos et al. 1969), but others have noted that it may range as low as 0.05 ppm (ACGIH 1992). Descriptions follow of findings for irritation of the eyes, nose, and throat from a sampling of available controlled exposure studies of acute irritation, emphasizing studies that examined symptoms of irritation at the lower end of this concentration range (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Weber-Tschopp et al. 1977). Several of these studies reported that the initial severity of irritation lessened to some degree with continued exposure (Bender et al. 1983; Day et al. 1984; Green et al. 1987; Weber-Tschopp et al. 1977).

Weber-Tschopp et al. (1977) exposed a group of 33 healthy subjects for 35 minutes to concentrations of formaldehyde that increased during the period from 0.03 to 3.2 ppm; another group of 48 healthy subjects was exposed to 0.03, 1.2, 2.1, 2.8, and 4.0 ppm for 1.5 minute intervals. Eye and nose irritation were reported on a 1–4 scale (1=none to 4=strong) in both experiments, and eye blinking rate was measured in

the second experiment. Average indices of eye and nose irritation were increased in both experiments to a small, but statistically significant, extent at 1.2 ppm compared with indices for nonexposed controlled conditions. The published report of this study graphically showed average severity scores of about 1.3–1.4 for both indices at 1.2 ppm compared with 1.0–1.1 for nonexposed conditions. The average severity score was increased to a greater degree at higher concentrations, but was less than about 2.5 at the highest exposure concentration, 4 ppm. Average rates of eye blinking were not significantly affected at 1.2 ppm, but were statistically significantly increased at 2.1 ppm (about 35 blinks/minute at 2.1 ppm versus about 22 blinks/minutes under nonexposed conditions).

Andersen and Molhave (1983) exposed a group of 16 healthy subjects to 0.3, 0.5, 1.0, and 2.0 mg/m^3 (0.2, 0.4, 0.8, and 1.6 ppm) for 4-hour periods preceded by a nonexposed period of two hours. Subjects were asked to assess "discomfort" on a 0–100 scale ranging from 0=no discomfort to 100=intolerable discomfort (scores between 1 and 33 were rated as "slight discomfort"). Average peak discomfort scores for the group generally increased with exposure concentration, but the average discomfort score for the highest exposure concentration (1.6 ppm) never exceeded 18. Numbers of subjects who reported "No discomfort" ratings at the end of exposure periods were 7, 13, 10, and 6, respectively for 0.2, 0.4, 0.8, and 1.6 ppm; respective numbers of subjects reporting "conjunctival irritation and dryness in the nose and throat" were 3, 5, 15, and 15 of the 16 subjects exposed to each respective concentration. A statistical analysis of these data was not reported.

Bender et al. (1983) exposed groups of 5–28 healthy subjects to 0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm for 6-minute periods and asked them to note when they experienced eye irritation and to rate eye irritation on a 0–3 scale (0=none to 3=severe, with 1=slight). The subjects were selected from a larger group of subjects in a preliminary screening test as those who "responded to 1.3 and 2.2 ppm". Upper respiratory tract irritation was not rated in this study. Average initial severity scores for the five exposure concentrations in increasing order were 0.71, 0.79, 0.86, 0.80, and 1.56; no irritation was noted with "clean air" exposure. The median times to noting eye irritation (response time measured in seconds) generally decreased with increasing concentration as follows: 360 (clean air), 268, 217, 72, 119, and 78 seconds. Numbers of subjects who reported response times that were less than their clean air response time were: 5/12 at 0.35 ppm, 14/26 at 0.56 ppm, 4/7 at 0.7 ppm, 3/5 at 0.9 ppm, and 20/27 at 1.0 ppm. The elevation in percentage of subjects with shortened response time was only statistically significant at the 1 ppm level.

Kulle et al. (1987; Kulle 1993) exposed 19 healthy subjects to 0, 1.0, and 2.0 ppm for 3-hour periods and asked them to note symptoms of eye and nose/throat irritation and to rate severity on a 0–3 scale: 0=none; 1=mild (present but not annoying); 2=moderate (annoying); and 3=severe (debilitating). Ten of the subjects were also exposed to 0.5 ppm and nine were exposed to 3 ppm for 3-hour periods. The frequencies of subjects reporting eye irritation or nose/throat irritation increased with increasing exposure concentration, especially at concentrations $1 ppm. Under nonexposed conditions, 3/19 subjects noted mild nose/throat irritation and 1/19 noted mild eye irritation. At 0.5 ppm, 1/10 subjects noted mild nose/throat irritation, but none reported eye irritation. Frequencies for subjects with mild or moderate eye irritation were 4/19 at 1 ppm (1 was moderate), 10/19 at 2 ppm (4 were moderate), and 9/9 at 3 ppm (4 were moderate). The increased frequency for eye irritation (compared with controls) was statistically significant at $2 ppm. Frequencies for mild nose/throat irritation were 1/19 at 1 ppm, 7/19 at 2 ppm, and 2/9 at 3 ppm. Compared with control frequency for nose/throat irritation, only the response at 2 ppm was significantly elevated.

In a study of volunteers exposed to 1 ppm for 90 minutes, seven subjects reported eye irritation and three reported nasal congestion among nine subjects who had previously complained of health effects from exposure to urea-formaldehyde insulation in their homes (Day et al. 1984). A similar response to 1 ppm formaldehyde was noted among the other nine subjects in this study who had no previous complaints: eight reported eye irritation and four reported nasal congestion from the 90-minute exposure.

In groups of 15 healthy subjects and 15 asthmatics exposed to 2 ppm for 40 minutes while exercising, “mild” eye irritation (average severity scores of 1.1 and 1.6 on a 5-point scale ranging from 0=none to 4=incapacitating, with 1=mild) was reported by eight healthy and five asthmatic subjects (Schachter et al. 1986; Witek et al. 1986, 1987). Nasal irritation was reported by 5/15 healthy and 5/15 asthmatics subjects with average severity scores of 1.2 and 1.8, respectively.

Gorski and colleagues have reported that symptoms of upper respiratory tract irritation occurred in three studies comparing respiratory responses to 2-hour exposures to placebo or 0.5 mg formaldehyde/m^3 (0.4 ppm) in healthy, nonexposed subjects, in subjects with formaldehyde-sensitive contact dermatitis (Gorski et al. 1992; Pazdrak et al. 1993), and in formaldehyde-exposed workers with bronchial asthma (Krakowiak et al. 1998). Krakowiak et al. (1998) noted that, for these studies, formaldehyde vapors were generated by evaporating 10 µL of a 10% aqueous solution of formaldehyde in a 12-m, temperature- and humidity-controlled, exposure chamber. Measured airborne concentrations of formaldehyde ranged from

0.2 to 0.7 mg/m^3 with a mean of 0.5 mg/m^3 (0.4 ppm). Gorski et al. (1992) reported that, after exposure to 0.4 ppm, 1/5 healthy subjects and 3/13 subjects with formaldehyde-sensitive contact dermatitis experienced nose irritation, sneezing, or eye irritation. Similar exposure produced statistically significant increases in the average number and proportion of eosinophils and the concentration of albumin and total protein in nasal lavage fluid, both in groups of 9 sensitized subjects and in groups of 11 nonexposed subjects; the responses in the two groups were not significantly different (Pazdrak et al. 1993). Pazdrak et al. (1993) reported that exposure "caused itching, sneezing, and congestion", but did not indicate the number of subjects reporting these symptoms. In another experiment, exposure to 0.4 ppm also produced similar statistically significant increases in eosinophils and protein in nasal lavage fluid in other groups of 10 nonexposed subjects and 10 formaldehyde-exposed workers with bronchial asthma, and "caused sneezing, itching and congestion in all subjects" (Krakowiak et al. 1998). Pulmonary functions were also measured in each of these studies, but no exposure-related effects were found in any of the groups (see below). An acute inhalation MRL of 0.04 ppm was calculated as described in the footnote in Table 2-1 and in Appendix A based on the LOAEL (0.4 ppm) from the study by Pazdrak et al. (1993).

Formaldehyde-induced effects on human pulmonary function variables including forced vital capacity (FVC), forced expiratory volume in 1.0 seconds ($FEV_{1.0}$), peak expiratory flow rate (PEFR), and forced expiratory flowrate between 25 and 75% FVC ($FEFR_{25–75}$), have not been found as consistently as symptoms of eye and nose irritation at acute exposure levels in the range of 0.4–3 ppm. In controlled exposure studies, no statistically significant exposure-related effects on lung function measurements were found in 10 healthy subjects exposed to up to 2 ppm for 3 hours (Kulle et al. 1987; Kulle 1993), 15 healthy subjects exposed to 0 or 2 ppm for 40 minutes with or without exercise (Schachter et al. 1986; Witek et al. 1986), 15 formaldehyde-exposed laboratory workers exposed to 0 or 2 ppm for 40 minutes with or without exercise (Schachter et al. 1987), 15 asthmatic volunteers exposed to 0 or 2 ppm for 40 minutes with or without exercise (Witek et al. 1986, 1987), 18 subjects, 9 of whom had complaints of health effects from exposure to urea-formaldehyde foam insulation in their homes, exposed to 1 ppm for 90 minutes (Day et al. 1984), 16 healthy student volunteers exposed to up to 1.7 ppm for 4 hours (Andersen and Molhave 1983), 13 subjects with allergic dermal sensitivity to formaldehyde and 5 healthy subjects exposed to 0.4 ppm for 2 hours (Gorski et al. 1992), 10 formaldehyde-exposed textile or shoe manufacturing workers with purported bronchial asthma and 10 nonexposed healthy subjects exposed to 0.4 ppm for 2 hours (Krakowiak et al. 1998), 13 formaldehyde-exposed subjects, who previously reported symptoms of chest tightness, coughing, or wheezing, exposed to placebo or up to 3 ppm for 20 minutes (Reed and Frigas 1984), or 15 patients with documented severe bronchial

hyperresponsiveness (to histamine) exposed to room air and up to 0.7 ppm for 90 minutes (Harving et al. 1986, 1990).

A few controlled exposure studies have found only subtle or infrequent effects of acute exposure to low concentrations of formaldehyde on pulmonary function variables (Green et al. 1987; Nordman et al. 1985; Sauder et al. 1986). Nordman et al. (1985) measured PEFR, FVC, and FEV_1 during and after a 30-minute "challenge" exposure to placebo, 1 or 2 ppm in a group of 230 patients who had been occupationally exposed to formaldehyde and had reported respiratory symptoms consistent with asthma during a 6-year period. Patients were first challenged with 1 ppm; if no response was found, a second challenge of 2 ppm was given. Exposure-related drops in PEFR of 15% or greater in response to 2 ppm formaldehyde were found in 12/230 of the patients; one of these 12 subjects showed a response to 1 ppm. Formaldehyde concentrations were not measured during each test, but periodic checks of exposure concentrations indicated that challenge concentrations ranged from 0.8 to 0.9 ppm for the 1 ppm target and 1.7–2.0 ppm for the 2 ppm target. Nordman et al. (1985) concluded that pulmonary function sensitivity to formaldehyde, at concentrations of 1 to 2 ppm, is rare. Sauder et al. (1986) measured small, but statistically significant, decreases in FEV_1 (2% decrease) and $FEFR_{25–75}$ (7% decrease) after 30 minutes of exposure to 3 ppm, but not after 1 or 3 hours of exposure, in a group of nine healthy subjects who performed intermittent exercise during exposure and who served as their own controls. Green et al. (1987) measured statistically significant, but small, average deficits (2–3%) in FEV_1, FVC, and FEV_3 (but no change in $FEFR_{25–75}$) in a group of 22 exercising healthy subjects during and after 1 hour of exposure to 3 ppm, but found no significant deficits in a group of 16 asthmatic subjects similarly exposed. Among the 38 subjects in this study, five (13%; 2 normal and 3 asthmatic) displayed exposure-related percentage deficits in FEV_1 greater than 10%, but generally less than 15%.

Acute Occupational Exposure Human Studies. Numerous assessments of pulmonary function variables in formaldehyde-exposed workers during workday shifts have found, similar to findings from controlled exposure studies, either no effects or only small and subtle effects from formaldehyde exposure during a work period. Bracken et al. (1985) measured no significant changes in pulmonary function variables (FVC, FEV_1, and $FEFR_{25–75}$) during a workshift in which 10 laboratory technicians were exposed to estimated average formaldehyde concentrations ranging from 0.106±0.02 to 0.269±0.05 ppm. No significant differences in changes in pulmonary function variables across a workshift were found in groups of 22 embalmers exposed to an estimated mean concentration of 0.36±0.61 ppm (range 0.08–0.81 ppm) during a 2- to 3-hour embalming procedure compared with a nonexposed group of

13 subjects (Holness and Nethercott 1989) or in groups of 55 plywood workers exposed to estimated concentrations ranging from 0.22 to 3.48 ppm compared with a nonexposed group of 50 subjects (Malaka and Kodama 1990). Kilburn et al. (1985a) reported that decreases in FVC, FEV_1, and $FEFR_{25–75}$ occurred during a workshift in a group of fiberglass batt workers and not in a group of nonexposed hospital workers, but workplace air concentrations of formaldehyde were not assessed for the batt workers. Alexandersson and Hedenstierna (1989) reported that small, but statistically significant, declines in FEV_1/FVC and $FEFR_{25–75}$ occurred during a workshift in a group of 11 nonsmoking woodworkers, but not in 10 smokers, who were exposed to an estimated mean TWA formaldehyde concentration of 0.4±0.1 ppm. Alexandersson and Hedenstierna (1989) did not compare workshift changes in the exposed group to changes in a control group. Horvath et al. (1988) measured small, but statistically significant, average declines in $FEFR_{50}$, $FEFR_{75}$, and $FEFR_{25–75}$ during a workshift in a group of 109 particle board workers exposed to estimated TWA formaldehyde concentrations ranging from 0.17 to 2.93 ppm (mean 0.69 ppm), but no significant workshift change in these variables in a group of 254 nonexposed, food-processing workers. Median concentrations of airborne nuisance particulates (i.e., wood dust) in the particle board plant were 0.38 and 0.11 mg/m^3 for total and respirable particulates, respectively. Akbar-Khanzadeh et al. (1994) found no statistically significant differences in workshift changes in pulmonary function variables (FVC, FEV_1, FEV_3, and $FEFR_{25–75}$) in a group of 34 students exposed for 2- to 3-hour periods to an estimated TWA concentration of 1.24±0.61 ppm (range 0.07–2.94 ppm) in a gross anatomy laboratory compared with a nonexposed group of 12 subjects, except that the exposed group showed an average 1.2% decline in FEV_3 during exposure compared with a 1.3% increase in FEV_3 for the controls during a comparable period. In another group of 50 students exposed to formaldehyde-containing embalming fluid in a 3-hour gross anatomy laboratory and a control group of 36 nonexposed students in a 3-hour physiotherapy laboratory, pulmonary function variables increased during the 3-hour periods, but the average increases in FEV_1 and $FEFR_{25–75}$ for the exposed group (2.7% and 2.2%, respectively) were statistically significantly less than the average increases (5.2% and 9.3%, respectively) for the control group (Akbar-Khanzadeh and Mlynek 1997). Estimates of breathing zone formaldehyde concentrations in the anatomy laboratory ranged from 0.3 to 4.45 ppm with a mean of 1.88±0.96 ppm. In both studies by Akbar-Khanzadeh and colleagues, eye and nose irritation were reported by more than 70% of exposed subjects.

Repeated-Exposure Human Studies. Studies of formaldehyde-exposed humans with repeated exposure under occupational or residential conditions provide confirmatory evidence that formaldehyde can be irritating to the upper respiratory tract (Boysen et al. 1990; Edling et al. 1988; Garry et al. 1980;

Holmstrom et al. 1989c; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987), but only limited evidence that pulmonary functions may be adversely affected by repeated exposure to formaldehyde (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Krzyzanowski et al. 1990; Malaka and Kodama 1990).

Garry et al. (1980) surveyed 275 possible cases of formaldehyde exposure for which health complaints were registered during a 5-month period (February through June) in 1979 with the Minnesota Department of Health and measured formaldehyde air levels in living rooms and bedrooms of the subjects' residences. Formaldehyde concentrations ranged from approximately 0.1 to 3 ppm; approximate mean values for the 5 months were 0.65, 0.4, 0.2, 0.6, and 1.0 ppm. Eye, nose, and throat irritation was reported in about 75% of adults (age $18 years, n=102), 60% of children (age 3–12 years, n=30), and 60% of infants (n=36). Cough and wheeze reporting percentages were about 35% in adults, 70% in children, and 60% in infants. This study provided no information on the duration of exposure.

Ritchie and Lehnen (1987) surveyed approximately 2,000 people living in conventional and mobile homes and measured formaldehyde concentrations in air samples taken from two rooms in each residence. Subjects were selected from requests made to the Minnesota Department of Health for formaldehyde testing. Reporting percentages of subjects with eye irritation, nose/throat irritation, headaches, and skin rash were recorded for homes with formaldehyde concentrations classified as "low" (<0.1 ppm), "medium" (0.1 ppm– <0.3 ppm), or "high" (>0.3 ppm). In both conventional and mobile homes with air concentrations >0.3 ppm, more than 60% of subjects reported eye irritation, nose/throat irritation, or headache; with air concentrations between 0.1 and 0.3 ppm, respective reporting percentages ranged approximately from 10 to 20%, 15 to 20%, and 20 to 25%, depending on home type. Reporting percentages for homes with concentrations <0.1 ppm were less than 10% for each of these three symptoms. A major limitation associated with this study is that the participants, in order to be eligible for the study, complained about symptoms and were therefore a self-selected group with a potential bias.

Holness and Nethercott (1989) surveyed 84 funeral directors and apprentices exposed to an estimated mean concentration of 0.36±0.19 ppm (range 0.08–0.81 ppm) for an average of 8.2 years and 38 nonexposed control subjects. Embalmers reported that symptoms of irritation of the eyes, upper respiratory tract, and skin occurred during work more frequently than controls: chronic bronchitis

(20 versus 3%), shortness of breath (20 versus 3%), and nasal irritation (44 versus 16%) were among the most common respiratory complaints.

Horvath et al. (1988) surveyed 109 workers in a particle board and molded plastics plant for symptoms of respiratory tract irritation. The duration of exposure among exposed workers ranged from <1 year to 20 years, with a mean and median of 10.3 and 10 years, respectively. Estimates of formaldehyde air concentrations ranged from 0.17 to 2.93 ppm with a mean of 0.69 ppm. Nuisance particles (predominantly softwood dust) were also detected in the particle board area. The percentages of particle board workers reporting a number of symptoms of respiratory irritation over a workshift were statistically significantly greater than workshift reporting percentages for a nonexposed group of 264 food-processing workers: cough (34.9 versus 18.9%), chest pains (9.2 versus 2%), phlegm production (26.6 versus 9.8%), burning nose (28.4 versus 2%), stuffy nose (33.9 versus 14.2%), burning or watering eyes (39.5 versus 9.1%), itchy nose (21.1 versus 7.9%), and sore/burning throat (22 versus 3.9%).

Several studies have histologically examined nasal biopsy specimens in formaldehyde-exposed workers and observed epithelial lesions that are consistent with the irritant and reactive properties of formaldehyde (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c).

Edling et al. (1988) found histological evidence of epithelial damage in biopsied specimens from the nasal mucosa of 75 workers from two particle board processing plants and a laminate plant. From air measurements occasionally made during an 8-year period before the study, estimates of TWA concentrations were calculated ranging from 0.08 to 0.9 ppm. (A mean TWA concentration was not reported, but the midpoint of this range is 0.49 ppm). Peaks of up to 4.07 ppm were measured during the 8-year period. Air concentrations were qualitatively assessed as being “somewhat higher” during earlier periods. Wood dust air concentrations in the particle board plants ranged from 0.6 to 1.1 mg/m^3; air in the laminate plant was reported to be without wood dust. Employment durations ranged from 1 to 39 years with a mean of 10.5 years. Runny nose, nasal crusting, and runny eyes when at work were reported by 60 and 75% of the exposed subjects, respectively, but frequencies were not compared in the report with frequencies of symptoms for a control group of 25 nonexposed subjects. Little information was given about the selection of the control group, except that they were “selected with regard to age and smoking habits”, however, 35% of exposed versus 48% of controls were smokers. Gross clinical examination showed that 25% of exposed workers had either swollen nasal mucosa or dry nasal mucosa; prevalence of this condition in the control group was not reported. Nasal mucosal biopsy sections were

assigned a score as follows: 0 - normal respiratory epithelium; 1 - loss of ciliated epithelium cells; 2 - mixed cuboid/squamous epithelium, metaplasia; 3 - stratified squamous epithelium; 4 - keratosis; 5 - keratosis with budding of epithelium; 6 - mild or moderate dysplasia; 7 - severe dysplasia; and 8 - carcinoma. Normal ciliated epithelium was found only in 3/75 exposed subjects; whereas a loss of ciliated cells and goblet cell hyperplasia was noted in 59/75 subjects, and 6/75 exposed subjects showed mild dysplasia. No subjects displayed severe dysplasia or carcinoma. Edling et al. (1988) did not report incidences of nasal lesions found in the control group, but did report that the average histological score for the exposed group (2.8) was statistically significantly greater than the control score (1.8). Histological scores did not increase with increasing employment duration in the exposed group. The authors reported that there was no difference in average histological scores between the exposed workers from the particle board plants, where confounding exposure to wood dust occurred, and those from the laminate plant without wood dust exposure. This observation supports the hypothesis that the observed nasal epithelial lesions were caused by formaldehyde and not by an interaction between formaldehyde and wood dust.

Holmstrom et al. (1989c) examined histological changes in nasal tissue specimens from a group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper, a group of 100 furniture factory workers working with particle board and glue components, and a nonexposed, control group of 36 office workers in the same village as the furniture factories. Mean durations of employment in the groups were 10.4 years (sd 7.3, range 1–36 years) for the chemical workers and 9.0 years (sd 6.3, range 1–30 years) for the furniture workers. Estimates of personal breathing zone air concentrations ranged from 0.04 to 0.4 ppm (median 0.24±0.13 ppm) for the chemical workers, from 0.16 to 0.4 ppm (median 0.20±0.04 ppm) for the furniture workers, and from 0.07 to 0.13 ppm in the late summer for the office workers with a year-round office worker median reported as 0.07 ppm with no standard deviation. The mean wood dust concentration in the furniture factory was reported to have been between 1 and 2 mg/m^3. Nasal mucosa specimens were taken from the medial or inferior aspect of the middle turbinate. Histology scores were assigned to each specimen based on a 0–8 scale, identical to the scale used by Edling et al. (1988; described previously). Nasal histology scores ranged from 0 to 4 (mean 2.16, n=62) for the chemical workers, from 0 to 6 (mean 2.07, n=89) for the furniture workers, and from 0 to 4 (mean 1.46, n=32) for the office workers. The mean histological score for the chemical workers, but not the furniture workers, was significantly different from the control score, thus supporting the hypothesis that the development of the nasal lesions is formaldehyde-related and not obligatorily related to a possible interaction between formaldehyde and wood dust. The most

severe epithelial change found (light or moderate epithelial dysplasia) was found in two furniture workers. Among the chemical workers (not exposed to wood dust), loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently than in the control group of office workers. Within both groups of formaldehyde-exposed workers, no evidence was found for associations between histological score and duration of exposure, index of accumulated dose, or smoking habit. A chronic inhalation MRL of 0.008 ppm was calculated as described in Table 2-1 and in Appendix A based on the minimal LOAEL of 0.24 ppm for mild nasal lesions in chemical factory workers in this study using an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability).

Boysen et al. (1990) histologically examined biopsy specimens from the nasal mucosa of 37 workers in a chemical plant that produced formaldehyde and formaldehyde resin and 37 age-matched, nonexposed controls. Exposed workers had been employed in the plant for more than 5 years (range 3–36 years, mean 20 years), had volunteered for the study, and represented about half of the workers in the plant. Controls were selected from office staff of two chemical plants, laboratory personnel from a hospital, and outpatients at an eye, ear, and nose clinic. Workers were classified into five exposure level groups based on "knowledge of the production process, recent measurements, and previous and present subjective sensations experienced by the workers". Exposure measurement data were not reported, but the exposure levels during the 1950s and 1960s were reported to have been "high". Workers in exposure level 1 (containing zero exposed workers) were defined as having occasional exposure (not daily) up to the level of olfactory detection. Twelve exposed workers reported frequent, but not daily, exposure that was irritating to the eyes or upper respiratory tract (exposure level 2), 17 workers reported daily exposure up to a level of olfactory detection (level 3), 5 reported daily exposure above the level of irritation (level 4), and 3 reported daily exposure inducing discomfort (level 5). The investigators surmised that concentrations between 0.5 and 2 ppm were associated with exposure levels 1–3, and that levels 4 and 5 were associated with concentrations >2 ppm. Biopsy samples were taken from the anterior curvature of the middle turbinate of the nasal cavity judged to have the best air flow. Specimen sections were assigned histology scores for the following findings: 1 for stratified cuboidal epithelium, 2 for mixed stratified cuboidal/stratified squamous epithelium, 3 for nonkeratinizing stratified squamous epithelium, 4 for keratinizing stratified squamous epithelium, and 5 for dysplasia. Numbers of subjects in the exposed group assigned histological scores ranging from 0 to 5 were: 3, 16, 5, 9, 1, and 3; respective numbers of subjects for the control group were: 5, 17, 10, 5, 0, and 0. The mean histological score for the exposed group (1.9) was statistically significantly greater than the mean for the controls (1.4). Much

of the difference in histological score between the exposed and control groups can be accounted for by three cases of dysplasia and one case of keratinizing stratified squamous epithelium in the exposed group; these lesions were not found in the nonexposed group. The workers with dysplasia were purported to have been exposed to concentrations in the range of 0.5–2.0 ppm and not to concentrations higher than 2 ppm.

Ballarin et al. (1992) examined smears of nasal respiratory mucosa cells sampled from the inner turbinate of 15 nonsmokers who were exposed to formaldehyde released from a urea-formaldehyde glue used in a plywood factory and 15 age- and sex-matched nonexposed clerks from outside of the factory. Estimates of formaldehyde air concentrations ranged from: 0.21 to 0.60 ppm (mean 0.39±0.20 ppm) in the warehouse where seven subjects worked, 0.08 to 0.14 ppm (mean 0.1±0.02 ppm) in the shearing press where six subjects worked, and 0.09 ppm (only one sample taken) in the sawmill area where two subjects worked. Mean wood dust concentrations for the three areas were 0.23±0.1 mg/m^3, 0.41±0.21 mg/m^3, and 0.73 mg/m^3, respectively. Exposed subjects worked at the factory for 2–19 years (mean 6.8±5.0 years). Nasal mucosal slides were scored as follows: normal cellularity, 1; number of mucus-secreting cells greater than ciliated cells, 1.5; hyperplasia, 2; squamous metaplasia, 2.5; mild dysplasia, 3; moderate dysplasia, 4; severe dysplasia, 5; and malignant cells, 6. In the exposed group, all subjects had a greater number of nonciliated than ciliated cells, 40% had hyperplasia, 67% had squamous metaplasia, and 6% slight dysplasia. In controls, 26% had normal cytology, 67% had more ciliated than nonciliated cells, 33% had hyperplasia, and 6% had squamous metaplasia. The mean cytology score for the exposed group (2.3±0.5) was reported to be statistically significantly greater than the control score (1.6±0.5). Also found in this study was a statistically significantly higher percentage of micronucleated mucosal cells in the exposed group compared with the control group (0.91%±0.47 versus 0.25%±0.22).

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

estimated to have been exposed to formaldehyde concentrations ranging from 0.08 to 0.81 ppm (mean 0.36±0.19 ppm) (Holness and Nethercott 1989).

Other studies have presented evidence for generally small or subtle formaldehyde-induced changes in pulmonary function variables with repeated occupational exposure (Alexandersson and Hedenstierna 1988, 1989; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990).

Using American Thoracic Society Criteria, Malaka and Kodama (1990) reported that the percentages of subjects with abnormal values for a number of pulmonary function variables (e.g., FEV_1 and $FEFR_{25–75}$) were significantly higher in a group of 93 plywood workers compared with a group of 93 nonexposed subjects. The plywood workers were employed for a mean of 6.2±2.4 years in workplaces with estimated formaldehyde air concentrations ranging from 0.22 to 3.48 ppm. The mean product of employment duration times workplace air formaldehyde concentration was 6.2 ppm/year (sd 2.72 ppm/year) for the exposed group of workers; division of this value by the average duration of employment (6.2 years) arrives at an estimated average exposure concentration of 1 ppm formaldehyde. Reported average respirable and total wood-dust concentrations in workplace air were 0.60 and 1.35 mg/m^3, respectively. Mean values of baseline FEV_1 and $FEFR_{25–75}$, after adjustment for dust exposure, were reportedly statistically significantly lower in the exposed group of workers compared with the nonexposed group (FEV_1 2.78 L [sd 0.41] versus 2.82 L [sd 0.3]; and $FEF_{25–75}$ 3.14 L/second [sd 0.76] versus 3.44 L/second [sd 0.78]). Malaka and Kodama (1990) noted that although the small differences were statistically significant, their clinical significance was unclear.

Mean baseline measures of FVC and FEV_1 were significantly lower (by <10%) than reference values in a group of 21 woodworkers employed for an average of 11 years, but mean values of these variables did not decline significantly when measured 5 years later (Alexandersson and Hedenstierna 1989). Estimates of workplace air concentrations were 0.3±0.2 ppm at the beginning and 0.4±0.1 ppm at the end of the 5-year period.

Mean values for FVC and FEV_1 were significantly lower than reference values in a group of 38 workers exposed to formaldehyde and other solvents used in lacquer applications, but the difference was small (<5–10% change from reference values) (Alexandersson and Hedenstierna 1988). The workers in the lacquer-applying workplace were employed for an average of 7.8 years; estimates of formaldehyde concentrations in workplace air ranged from 0.2 to 2.1 ppm with a TWA mean of 0.3 ppm.

Mean values of FVC, FEV_1/FVC, and maximum mid-expiratory flow rate were significantly lower in a group of 37 anatomy and histopathology workers compared with values for a control group of 37 nonexposed workers from the same college (FVC 2.18 L versus 2.63 L; FEV_1/FVC 0.607 versus 0.787; flow rate 1.55 L/second versus 2.71 L/second) (Khamgaonkar and Fulare 1991). Employment durations were not reported in this study, but estimated formaldehyde air concentrations ranged from 0.036 to 2.27 ppm (mean 1.0±0.55 ppm) in the anatomy and histopathology workplaces compared with 0 to 0.52 ppm (mean 0.1±0.11 ppm) in the control workplaces. The study authors suggested that the apparent bronchoconstrictor effect of formaldehyde was due either to a direct effect of formaldehyde or a reflex response caused by irritation of the nose and throat.

Mean baseline PEFR declined by about 2% over a 10-week period in a group of 24 physical therapy students who dissected cadavers for 3-hour periods per week (Kriebel et al. 1993). Estimates of breathing zone formaldehyde concentrations ranged from 0.49 to 0.93 ppm (geometric mean 0.73±1.22 ppm). PEFR, the only pulmonary function variable measured in this study, was measured before and after each exposure period. Postexposure PEFR means were 1–3% lower than preexposure PEFR means during the first 4 weeks, but this difference was not apparent during the last 6 weeks. Fourteen weeks after the end of the 10-week period, the mean PEFR for the group returned to the preexposure baseline value.

Effect levels associated with formaldehyde-induced changes in pulmonary function variables in workers exposed to airborne formaldehyde concentrations generally less than 1 ppm are not included in Table 2-1 because the observed differences: are not of sufficient magnitude to be of obvious clinical significance, have not been observed consistently across studies, and may be confounded, in some cases, by the presence of wood dust particulates which may facilitate transport of adsorbed formaldehyde to deeper regions of the respiratory tract compared with low-level exposure to formaldehyde alone. In contrast, mild nasal epithelial lesions observed in formaldehyde-exposed workers: have been observed consistently across four studies (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c), do not appear to be confounded by exposure to wood dust (see Edling et al. 1988; Holmstrom et al. 1989c), and are consistent with results from animal toxicity, pharmacokinetic, and anatomical airflow studies indicating that, at concentrations #1 ppm, inhaled formaldehyde gas does not reach lower regions of the respiratory tract (see following review of animal inhalation toxicity studies and Sections 2.3 and 2.4).

A single study was located providing suggestive, but to date uncorroborated, evidence that elevated levels of formaldehyde in residential air may change pulmonary function variables in children, but not adults. Krzyzanowski et al. (1990) reported that children who lived in households with formaldehyde air concentrations greater than 0.06 ppm had greater prevalence rates of physician-diagnosed bronchitis or asthma compared with children who lived in households with concentrations less than 0.06 ppm. A statistically significant trend for increasing prevalence rate with increasing formaldehyde air concentration was found for households with environmental tobacco smoke, but the trend was not significant in households without tobacco smoke. A statistically significant trend was also found for decreasing PEFR values in children with increasing household formaldehyde air concentration. The clinical significance of these findings is uncertain (see Section 2.6 for more discussion).

Acute Inhalation Animal Studies. Studies in animals confirm that the upper respiratory tract is a critical target for inhaled formaldehyde and describe exposure-response relationships for upper respiratory tract irritation and epithelial damage in several species. Acute inhalation animal studies show that inhaled formaldehyde, at appropriate exposure concentrations, damages epithelial tissue in specific regions of the upper respiratory tract in rats, mice, and monkeys (Chang et al. 1983; Monticello et al. 1989, 1991; Morgan et al. 1986a, 1986c), that formaldehyde is a more potent sensory irritant in mice (Chang et al. 1981, 1983; Kane and Alarie 1977) than in rats (Chang et al. 1981, 1983), that lung damage from inhaled formaldehyde occurs at higher concentrations than those only affecting the upper respiratory tract (Kamata et al. 1996a, 1996b; Swiecichowski et al. 1993), that mice are less susceptible to formaldehyde-induced upper respiratory tract epithelial damage than rats (Chang et al. 1983), that rats and monkeys may be equally susceptible to epithelial damage from formaldehyde but display similar epithelial lesions in different regions of the upper respiratory tract (Monticello et al. 1989, 1991), and that formaldehyde induces bronchoconstriction and airway hyperreactivity in guinea pigs (Amdur 1960; Swiecichowski et al. 1993).

Formaldehyde-induced epithelial damage in the nasal cavity of rats (e.g., squamous metaplasia and hyperplasia) displays regional specificity (anterior regions of the nasal epithelium, posterior to the vestibule at the lowest effective concentrations) and occurs with acute exposures to concentrations generally greater than 2–6 ppm. Monticello et al. (1991) found no evidence for histological nasal epithelial damage in F344 rats exposed to 0.7 or 2 ppm, 6 hours/day for 1, 4, or 9 days, but damage was observed at 6, 10, and 15 ppm. Regions of epithelium showing histological lesions also showed increased rates of cellular proliferation at concentrations greater than 6 ppm (Monticello et al. 1991).

Site-specific damage to nasal epithelial cells after acute exposure (6 hours/day for 1 to 3 weeks) of F344 rats to formaldehyde was correlated with inhibition of mucociliary function (i.e., mucostasis) at concentrations of 2, 6, and 15 ppm, but no effects on these end points were found at 0.5 ppm (Morgan et al. 1986a, 1986c). Morgan et al. (1986c) reported that mucus flow was stopped after only 1 hour of exposure to 15 ppm in regions of the nasal epithelium that later developed lesions, and that this effect was still apparent 18 hours after exposure ceased. Other acute inhalation studies with rats (Bhalla et al. 1991; Cassee and Feron 1994; Monteiro-Riviere and Popp 1986; Wilmer et al. 1987) provide supporting evidence that short-term exposure to concentrations in excess of 2 ppm can damage nasal epithelial tissues in this species (see Table 2-1).

Upper respiratory tract epithelial lesions similar to those observed in rats have been observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, 5 days/week for 1 week; the regional distribution of these lesions was not restricted to the nasal cavity, as they were in rats exposed to 6 ppm (Monticello et al. 1991), but extended to the trachea and major bronchi (Monticello et al. 1989). Lesions were most severe in the nasal passages and were minimal in the lower airways (larynx, trachea, and carina). Regions of epithelium with lesions corresponded with regions in which high rates of cellular proliferation were measured. No evidence for lesions or changes in cell proliferation rates were found in the maxillary sinuses. Studies describing exposure-response relationships for upper respiratory tract epithelial damage in monkeys acutely exposed to inhaled formaldehyde were not located.

Inhaled formaldehyde is a more effective sensory irritant (i.e., stimulates trigeminal nerve endings and inhibits respiration rate and tidal volume) in mice than in rats (Chang et al. 1981; Kane and Alarie 1977), whereas nasal effects such as rhinitis and degeneration of respiratory epithelial cells are more severe in rats than in mice, and increased indices of cell proliferation in nasal epithelium are more frequent in rats than mice, after exposure to 15 ppm, 6 hours/day for 1 or 5 days (Chang et al. 1983). Measured RD_{50} values for mice (2.2–5.9 ppm; concentrations associated with a 50% decrease in respiratory rate) were much lower than RD_{50} values for rats (22.7–31.7 ppm) (Chang et al. 1981). Kane and Alarie (1977) reported a similar RD_{50} value, 3.1 ppm, for formaldehyde in mice. These results suggest that the lesser sensitivity of mice to formaldehyde-induced nasal tissue damage may be due, at least in part, to the mouse's ability to maintain decreased respiration rates and decreased tidal volumes in the presence of airborne formaldehyde, whereas the rat does not have this ability and thus sustains a greater degree of tissue damage.

Acute inhalation exposure to formaldehyde has been associated with tissue damage in the lungs only at much higher exposure concentrations than those affecting the nasal region alone. Histological and ultrastructural examination of lung tissue from rats exposed to 10 ppm, 6 hours/day for 4 days found no evidence for tissue injury, although these rats showed clinical signs of eye and nose irritations (Dinsdale et al. 1993). In addition, activities of alkaline phosphatase and γ-glutamyl transpeptidase in bronchoalveolar lavage fluid and lung tissue concentrations of cytochrome P-450 were not significantly elevated in exposed rats compared with control rats. These results indicate that very limited amounts of formaldehyde reach the lungs with exposure to 10 ppm. In contrast, Kamata et al. (1996a) reported that single 6-hour exposures of male F344 rats to 150 ppm formaldehyde induced histological changes throughout the nasal turbinates (including hyperkeratosis of the squamous epithelium in the vestibule, desquamation of the respiratory epithelium), the trachea (increased secretion and desquamation of mucosal cells), and the lung (hyperplasia of the alveolar wall and plasma-like secretions in the lung), whereas similar exposure to 15 ppm produced only slight hypersecretion of the nasal and tracheal mucosal epithelium. Kamata et al. (1996b) also noted that F344 rats exposed to 128 or 295 ppm formaldehyde for 6 hours showed bloody nasal discharge and pulmonary edema, indicating that, at these very high concentrations, formaldehyde can reach and damage lung tissue as well as nasal tissue.

Experiments with guinea pigs provide evidence that acute exposure to inhaled formaldehyde can influence lower airway resistance and hyperreactivity of the lungs (Amdur 1960; Swiecichowski et al. 1993). Amdur (1960) measured significantly increased airway resistance in guinea pigs exposed for 1 hour to formaldehyde concentrations as low as 0.3 ppm; the average increase in resistance was about 14, 29, and 43% over control values at 0.3, 1.2, and 3.6 ppm, respectively. Amdur suggested that the changes in resistance were due to bronchoconstriction. More recently, Swiecichowski et al. (1993) reported that pulmonary resistance was significantly increased in guinea pigs exposed to 9.4 ppm for 2 hours, but not in guinea pigs exposed to 3.4 ppm or lower for 2 hours. Longer duration exposure (8 hours) changed the exposure-response relationship; concentrations as low as 0.3 ppm produced significantly increased pulmonary resistance. Pulmonary sensitivity to acetylcholine was significantly increased by 2-hour exposures to concentrations $9.4 ppm and by 8-hour exposures to $0.3 ppm. No exposure-related epithelial damage or inflammatory response was detected by histological examinations of portions of the midtrachea.

Intermediate Inhalation Animal Studies. Results from intermediate-duration inhalation studies with rats (Appelman et al. 1988; Feron et al. 1988; Monticello et al. 1991; Rusch et al. 1983; Woutersen et al. 1987; Zwart et al. 1988), Rhesus monkeys (Monticello et al. 1989), Cynomolgus monkeys (Rusch et al. 1983), mice (Maronpot et al. 1986), and hamsters (Rusch et al. 1983) indicate that the nasal epithelium is the most sensitive target of inhaled formaldehyde. The studies support the hypothesis that mice and hamsters are less sensitive than rats and monkeys to formaldehyde-induced nasal damage (Maronpot et al. 1986; Rusch et al. 1983), show that formaldehyde-induced damage to the upper respiratory tract epithelium (hyperplasia and squamous cell metaplasia) has a wider regional distribution in Rhesus monkeys than in rats (Monticello et al. 1989, 1991), show that site-specific nasal lesions in both monkeys and rats corresponded to regions with high rates of cellular proliferation (Casanova et al. 1994; Monticello et al. 1989, 1991), indicate that damage to the respiratory epithelium is more concentration-dependent than duration-dependent (Wilmer et al. 1987, 1989), and show that concentrations of DNA-protein cross links are correlated with regional sites of formaldehyde-induced epithelial damage in the nose of rats (Casanova et al. 1994).

In a study designed to detect potential effects on tissues and organs distant from the nose and to describe exposure-response relationships for nasal lesions in rats exposed to between 1 and 20 ppm formaldehyde for intermediate durations, Woutersen et al. (1987) exposed groups of 10 male and 10 female Wistar rats to 0, 1, 10, or 20 ppm 6 hours/day, 5 days/week for 13 weeks. Sections of the lungs, trachea, larynx, and nose were microscopically examined in all rats; all other major organs and tissues were also examined microscopically in control and high-exposure groups. Exposure to 20 ppm produced severe and extensive keratinized squamous metaplasia of the nasal respiratory epithelium, focal degeneration and squamous metaplasia of the olfactory epithelium, and squamous metaplasia of the laryngeal epithelium (males only). No exposure-related lesions were found in other tissues or organs. Respiratory effects at 10 ppm were restricted to moderate squamous metaplasia of the nasal respiratory epithelium. Effects noted in the 1-ppm group were restricted to minimal focal hyperplasia and squamous metaplasia of the nasal respiratory epithelium found in three rats.

Zwart et al. (1988) exposed groups of male and female Wistar rats to formaldehyde at concentrations of 0, 0.3, 1, or 3 ppm, 6 hours/day, 5 days a week for 13 weeks to study details of formaldehyde-induced nasal tissue damage. Exposure-related nasal tissue histological changes were restricted to a small area of the anterior region of the nose normally covered with respiratory epithelium and were found only in the high-exposure group. Lesions were described as ranging from epithelial disarrangement to epithelial

hyperplasia and squamous metaplasia. After 3 days of exposure, increased rates of cellular proliferation, compared with controls, were found in the 1- and 3-ppm groups in epithelial regions where lesions were found after 13 weeks in the 3-ppm group. After 13 weeks of exposure, cellular proliferation rates were not increased in the lesion-laden regions of exposed rats, but were increased in more posterior regions of the nasal epithelium, most notably in rats exposed to 3 ppm. These results are consistent with the hypothesis that the change of mucus-covered respiratory epithelial cells to squamous epithelial cells is adaptive.

Appelman et al. (1988) exposed groups of male SPF Wistar rats to 0, 0.1, 1, or 10 ppm formaldehyde 6 hours/day, 5 days/week for 13 or 52 weeks. Within each exposure group, half of the animals had their nasal mucosa damaged by acute electrocoagulation prior to formaldehyde exposure. In groups without predamaged nasal mucosa, exposure-related effects were restricted to rhinitis and hyperplasia and metaplasia of the nasal respiratory epithelium in the 10-ppm group. Comprehensive histological examination of major tissues and organs in the control and 10-ppm groups revealed no other exposure-related lesions. Microscopic examination of nose sections from the 1- and 0.1-ppm groups without electrocoagulation revealed no exposure-related effects. Rats with predamaged nasal mucosa were more susceptible to the cytotoxic action of formaldehyde; at 52 weeks, focal squamous metaplasia of the nasal respiratory epithelium was found in rats exposed to 0.1 or 1 ppm formaldehyde.

Monticello et al. (1991) exposed groups of 36 male F344 rats to 0, 0.7, 2, 6, 10, or 15 ppm, 6 hours/day, 5 days/week for up to 6 weeks and labeled with tritiated thymidine prior to scheduled termination to determine rates of cellular proliferation in specific regions of the nasal epithelium. After 6 weeks of exposure to 10 or 15 ppm, epithelial hyperplasia and squamous metaplasia of the respiratory epithelium were located primarily in the nasoturbinates, just posterior to the nasal vestibule, with milder lesions extending into more posterior regions including the nasopharynx. Exposure to 6 ppm produced mild epithelial hyperplasia and squamous metaplasia that was restricted to the most anterior regions of the respiratory epithelium in the nasoturbinates. Statistically significant increases in cellular proliferation rates were measured in the groups exposed to 6 ppm or higher. Exposure-related effects on nasal epithelium were not found in the 2- or 0.7-ppm groups. Sites of cellular injury were well-correlated with sites of increased rates of cellular proliferation.

Casanova et al. (1994) exposed groups of male F344 rats to 0, 0.7, 2, 6, or 15 ppm 6 hours/day, 5 days/week for 81 days to examine the effect of preexposure to formaldehyde on the concentrations of

DNA-protein cross links formed in specific regions of nasal cavity epithelium in response to acute exposure to radiolabeled formaldehyde. DNA-protein cross link concentrations were approximately 6-fold higher in the mucosal lining of the lateral meatus (where formaldehyde-induced lesions develop) than in the mucosal lining of the medial and posterior meatus (where lesion development is less strong). Preexposure to formaldehyde at concentrations #2 ppm did not affect the formation of DNA-protein cross links, but at higher concentrations, pre-exposed rats showed decreased acute formation of DNA-protein cross links compared with rats without prior exposure to formaldehyde.

Monticello et al. (1989) exposed groups of three male Rhesus monkeys to 0 or 6 ppm formaldehyde, 6 hours/day, 5 days/week to compare respiratory responses to formaldehyde in primates with those in rodents. Comprehensive histological examination of respiratory tract tissues (and also extra-respiratory tissues) was conducted. Exposure-related lesions were confined to the epithelium of the upper respiratory tract and were described as mild hyperplasia and squamous metaplasia confined to particular regions of the transitional and respiratory epithelium of the nasal passages and the respiratory epithelium of the trachea and carina. Cellular proliferation rates were significantly elevated in damaged regions of the nasal epithelium. Nasal lesions seen in monkeys were similar to those reported in rats exposed to 6 ppm by a similar exposure protocol and duration in a companion study (Monticello et al. 1991) except that the lesions extended into the trachea in the monkeys. The lesions in the larynx, trachea, and carina of the formaldehyde-exposed primates included multifocal loss of cilia and goblet cells, mild epithelial hyperplasia, and early squamous metaplasia. Cell proliferation rates in the trachea and carina were increased as well. In both species, regions where lesions were found were well-correlated with regions in which high rates of cellular proliferation were measured (Monticello et al. 1989, 1991). The investigators suggested that the difference in the location of the lesions was due to different breathing patterns in the rat and monkey and differences in the anatomic structure of their respective nasal passages.

Rusch et al. (1983) histologically examined the lungs, trachea, and nasal turbinates of groups of 6 or 12 male Cynomolgus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Golden Syrian hamsters exposed to 0, 0.2, 0.98, or 2.95 ppm for 22 hours/day, 7 days/week for 26 weeks. Examination of other organs and tissues at necropsy for gross lesions revealed no exposure-related effects, but these tissues were not microscopically examined. Monkeys exposed to 2.95 ppm showed an increased incidence of hoarseness, congestion, and nasal discharge. Monkeys in the lower exposure groups showed a greater incidence of nasal discharge than control monkeys, but the discharge was “only a

minimal grade" and was noted sporadically throughout the study. The study authors judged that the nasal discharge at the two lowest exposure levels was not of biological significance. Body weights of exposed monkeys were not significantly different from body weights of controls. Monkeys and rats exposed to 2.95 ppm, but not the lower concentrations, showed a significantly increased incidence of squamous metaplasia and/or basal cell hyperplasia of the nasal cavity epithelium; the response was reported to be most clearly seen in both species in the mid-region of the nasoturbinates. No lesions were found in the most anterior sections of the nose or in the ethmoturbinates. Incidences of monkeys with squamous metaplasia/hyperplasia in nasal turbinate epithelium were 0/12, 0/6, 1/6, or 6/6 at 0, 0.2, 0.98, and 2.95 ppm, respectively. Respective incidences of rats with squamous metaplasia/hyperplasia were 5/77, 1/38, 3/36, and 23/37. The investigators made no mention of any difference in the regional distribution of the nasal lesions in rats and monkeys or of any histological changes in the trachea or lungs of the exposed monkeys or rats. Ultrastructural examinations were made of the nasal turbinates, trachea, and lungs from rats in the control and 0.98-ppm group; no exposure-related changes were found. No histological changes were found in the nasoturbinates, trachea, or lungs of the exposed hamsters compared with controls. An intermediate inhalation MRL of 0.03 ppm was calculated as described in Table 2-1 and in Appendix A based on the NOAEL of 0.98 ppm for nasopharyngeal irritation in Cynomolgus monkeys using an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Wilmer et al. (1987) investigated whether varying the exposure to formaldehyde (i.e., continuous versus intermittent) affected formaldehyde cytotoxicity to upper respiratory tract epithelium. Groups of male albino Wistar rats were exposed to 0, 5, or 10 ppm formaldehyde, 8 hours/day continuously, or to 10 or 20 ppm formaldehyde, 8 hours/day intermittently (30-minute exposure periods separated by 30-minute periods of nonexposure). Eighteen hours after the third day or fourth week of exposure, three rats from each group were injected with ^{3}H-thymidine, sacrificed, and their nasal cavities were processed and examined for cell turnover. After 4 weeks of exposure, cell turnover rates in nasal epithelium were significantly elevated in the rats exposed to 10 and 20 ppm intermittently, but not in rats exposed to 5 and 10 ppm continuously. The majority of cell labeling occurred in the naso- and maxillary turbinates. Focal thinning and disarrangement of the respiratory epithelium lining were noted in some of the 10-ppm and all of the 20-ppm rats. Squamous metaplasia with cellular hyperplasia was noted in some of the rats exposed to 5 ppm and in most of the rats exposed to 10 or 20 ppm. Minimum to moderate rhinitis was seen in each of the treatment groups. In a similar study, Wilmer et al. (1989) studied the same toxicological end points in male albino Wistar rats using lower concentrations of 0, 1, or 2 ppm

formaldehyde, 8 hours/day continuously, or 2 or 4 ppm formaldehyde, 8 hours/day intermittently (30-minute exposure periods separated by 30-minute periods of nonexposure), all groups were treated for 5 days/week for 13 weeks. After 13 weeks of exposure, there were no statistically significant differences between the 1 and 2 ppm (continuously dosed), the 2 ppm (intermittently dosed) groups, and the controls in cell turnover rates, however, the mean cell turnover rate after 13 weeks of exposure in the 4-ppm rats was 2.9-fold greater than that of control rats. Treatment-related histological changes were noted only in the 4-ppm intermittent exposure group. The changes consisted of increased disarrangement, hyperplasia, and squamous metaplasia with or without keratinization of the respiratory epithelium lining of the septum and nasoturbinates. The group continuously exposed to 2 ppm formaldehyde (i.e., the same total daily exposure as the 4-ppm intermittent group) did not exhibit an increased incidence of these lesions. These data suggest that the concentration of formaldehyde is more important in determining epithelial damage than the duration of exposure.

Maronpot et al. (1986) exposed groups of 10 male and 10 female B6C3F1 mice to formaldehyde 6 hours/day, 5 days/week for 13 weeks at concentrations of 0, 2, 4, 10, 20, or 40 ppm. Comprehensive histological examinations of major tissues and organs were conducted. Significant mortality and severe weight loss occurred in the 40-ppm group. Exposure-related lesions were restricted to the respiratory tract, except for hypoplasia of the uterus and ovaries in the 40-ppm group which were interpreted to be due to severe body weight loss. In the 40-ppm groups, squamous metaplasia, keratinization, suppurative inflammatory exudate, serous exudate, and mild degeneration of the epithelium were noted in nasal sections. Similar lesions were noted in the 20- and 10-ppm groups, although the severity declined with decreasing concentrations. Similar lesions were seen in only one male mouse at 4 ppm, and in none of the 4-ppm females; no such lesions were noted in either sex at exposures of 2 ppm. Squamous metaplasia, suppurative inflammation, and fibrosis was also noted in the trachea and larynx of most mice in the 40-ppm group; similar, though less severe, lesions were noted in the 20-ppm group. Lung lesions consisting of epithelial hyperplasia, suppurative inflammation, squamous metaplasia, and fibrosis were seen in some of the mice exposed to 40 ppm, but were not found in mice exposed to lesser concentrations.

Studies of pulmonary function variables in rats after intermediate-duration exposure to inhaled formaldehyde have not found marked, exposure-related effects (Dallas et al. 1985, 1986; Saldiva et al. 1985). Dallas and colleagues measured the change in minute volume produced by acute challenges with formaldehyde administered either intratracheally (Dallas et al. 1986) or by nosepiece (Dallas et al. 1985)

in rats exposed to 0, 0.5, 3 (nose-piece experiment only), or 15 ppm formaldehyde, 6 hours/day 5 days/week for 8 or 16 weeks. Responses to the acute challenge were compared with responses in age-matched, nonexposed rats. A slightly diminished minute volume response to the formaldehyde challenge was observed in the exposed rats (from the 15-ppm groups only) compared with the response in nonexposed rats with both types of challenge administration, but this was statistically significant only with nosepiece administration. Saldiva et al. (1985) found no statistically significant differences between a group of rats exposed to 5.7 ppm formaldehyde, 8 hours/day, 5 days/week for 5 weeks and a group of nonexposed rats in mean values for numerous pulmonary function variables including FEV in 1/4 second and several measures of forced expiratory flow rates.

Chronic Inhalation Animal Studies. Chronic-duration exposures to inhaled formaldehyde have also been studied in rats, mice, and hamsters. In rats exposed to concentrations #15 ppm, formaldehyde-induced effects were restricted to nonneoplastic and neoplastic lesions found primarily in anterior regions of the nasal epithelium, posterior to the vestibule (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Swenberg et al. 1980; Woutersen et al. 1989). Nonneoplastic damage to rat nasal epithelium occurred at concentrations as low as 2 ppm, 6 hours/day, 5 days/week (Kamata et al. 1997), whereas significantly increased incidences of neoplastic lesions (squamous cell carcinomas, squamous cell papillomas or polyploid adenomas) were found in rats generally at concentrations greater than 6 ppm (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Nonneoplastic damage to upper respiratory tract epithelium has also been observed in mice exposed to $5.6 ppm, 6 hours/day, 5 days/week for 2 years (Kerns et al. 1983b) and in hamsters exposed to 10 ppm, 5 hours/day, 5 days/week for life (Dalbey 1982). Nasal tumors similar to those found in formaldehyde-exposed rats were found in mice exposed to 14.3 ppm for 2 years (Kerns et al. 1983b), but were not found in formaldehyde-exposed hamsters (Dalbey 1982). See Section 2.2.1.8 for more details of neoplastic findings from these studies.

Male and female Fischer 344 rats were exposed to 0, 2, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b; Swenberg et al. 1980). The exposure period was followed by a 6-month observation period. Interim sacrifices were performed at 6, 12, 18, 24, 27 (3 months postexposure), and 30 months (6 months postexposure). In the 14.3-ppm treatment group, early mortalities occurred, rats tended to be dyspneic and emaciated, and many had facial swellings which were subsequently determined to be nasal cavity carcinomas. Microscopic lesions were limited to the nasal cavity and trachea, however, lesions were initially seen only in the ventral portion of the nasal

septum. As the study progressed, the lesions spread and became progressively more severe. In the low- and mid-dose groups, rhinitis, epithelial dysplasia, and squamous metaplasia developed over the course of the study. Occasionally, animals in the high-dose group exhibited minimal-to-mild epithelial hyperplasia or dysplasia or squamous metaplasia of the tracheal mucosa; these effects were not seen in the lower-dose groups and disappeared in the high-dose group during the postexposure periods. Malignant nasal tumors were found in 5.6- and 14.3-ppm rats (see Section 2.2.1.8). Neoplastic lesions were not found in other regions of the respiratory tract or in other organ systems.

Woutersen et al. (1989) investigated the effects of damage to the nasal mucosa on the induction of non-neoplastic tissue changes and tumors from long-term exposure to formaldehyde. Male and female Wistar rats were used, with 67% of all rats undergoing electrocoagulation of the nasal mucosa. Half of the animals were exposed to formaldehyde for 28 months and the other half for 3 months, all at doses of 0, 0.1, 1, or 10 ppm for 6 hours/day, 5 days/week. In undamaged noses in the 28-month study, histopathological changes were not seen in the 0.1 or 1 ppm groups; exposure to 10 ppm resulted in an increased incidence of squamous metaplasia and basal cell/pseudoepithelial hyperplasia of the respiratory epithelium, thinning and disarrangement of the olfactory epithelium, and rhinitis. In damaged nasal mucosa in the long-term study, exposure to all levels of formaldehyde resulted in squamous metaplasia. Rats exposed to formaldehyde vapors for 3 months (without electrocoagulation pretreatment) were sacrificed following a 25-month recovery period. Non-neoplastic nasal lesions with statistically significant increased incidences, compared with controls, were found only in the most anterior regions of the nasal cavity in 10-ppm rats: squamous metaplasia of the respiratory epithelium (17/26 compared with 3/26 in controls; $p<0.01$, Fisher exact test performed by Syracuse Research Corporation), and rhinitis (13/26 compared with 5/26; $p<0.05$, Fisher exact test performed by Syracuse Research Corporation). Nasal tumors were found only in the 10-ppm, 3-month-exposure group; one rat had a squamous cell carcinoma and one had a polypoid adenoma (see Section 2.2.1.8 for more details on neoplastic responses in this study).

Monticello et al. (1996) assessed the role of regional increases in nasal epithelial cell proliferation in the formation of formaldehyde-induced nasal neoplastic and non-neoplastic tissue damage in male Fischer 344 rats. Rats were exposed to 0, 0.7, 2, 6, 10, or 15 ppm formaldehyde, 6 hours/day, 5 days/week for 24 months. During the last 5 days of exposure prior to each interim sacrifice period (3, 6, 12, and 18 months), 6 rats per dose group were labeled with ^{3}H-thymidine via osmotic pumps to measure regional rates of cell proliferation in nasal cavity epithelium. No formaldehyde-induced non-

neoplastic lesions were found in the nasal cavities of rats from the 0.7- or 2-ppm groups. Non-neoplastic lesions in the 6-ppm group were limited to focal squamous metaplasia in the anterior region of the nasal cavity. In the 10- and 15-ppm groups, lesions seen included epithelial hypertrophy and hyperplasia, squamous metaplasia, inflammatory cell infiltration, nasal turbinate adhesions, and olfactory degeneration. These lesions occurred more frequently and with greatest severity in the 15-ppm group. Cell proliferation in nasal epithelium was not affected by formaldehyde exposures of 6 ppm or less; increases in the cell labeling index were significant at the 10- and 15-ppm exposure levels. Nasal tumors were found in the 6-, 10-, and 15-ppm groups (see Section 2.1.1.8).

Kamata et al. (1997) exposed groups of 32 male F344 rats by inhalation to formaldehyde concentrations of 0.3, 2, or 15 ppm, 6 hours/day, 5 days/week for up to 28 months. Two control groups of 32 rats were included: an inhalation chamber group ("0 ppm") inhaling 4.2 ppm methanol and a "room control, no-exposure group". Significantly increased mortality (after 9 months) and decreased body weights (after 4 months) were restricted to the 15-ppm group compared with the control groups. No exposure-related effects on hematological parameters were found. Comprehensive autopsies and histological examination of the pituitary, thyroid, nasal region, trachea, esophagus, stomach, intestine, prostate gland, spinal cord, and mesenteric lymph nodes found exposure-related effects only in the nasal cavities. Epithelial cell hyperplasia, hyperkeratosis, and squamous metaplasia were apparent in all exposure groups and were predominately restricted to the respiratory epithelium of nasal turbinates and maxilloturbinates, just posterior to the nasal vestibule. Incidences for epithelial cell hyperplasia with squamous cell metaplasia were 0/32, 0/32, 4/32, 7/32, and 29/32 in the 0-, room control-, 0.3-, 2-, and 15-ppm groups respectively; incidences for squamous cell metaplasia without epithelial cell hyperplasia were 0/32, 0/32, 1/32, and 5/32, respectively (this combination of lesions did not occur in the 15-ppm group). Nasal tumors squamous cell carcinomas and papillomas were found only in the 15-ppm group (see Section 2.2.1.8). Kamata et al. (1997) concluded that the study did not identify a NOAEL for nonneoplastic nasal lesions due to the finding of epithelial cell hyperplasia with squamous cell metaplasia in the 0.3-ppm group, but the incidences for nonneoplastic nasal lesions in the 0.3-ppm group were not statistically significantly different compared with the controls. In Table 2-1, 0.3 ppm is noted as a NOAEL for non-neoplastic lesions in the nasal epithelium.

Kerns et al. (1983b) exposed male and female B6C3F1 mice to 0, 2, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months, followed by a 6-month observation period. Interim sacrifices were performed at 6, 12, 18, 24, 27, and 30 months. Major tissues from each organ system in control and

high-exposure mice were examined histologically. Non-neoplastic nasal lesions were found in the 5.6- and 14.3-ppm groups of mice, most notably inflammatory, dysplastic, and squamous metaplastic changes in the respiratory epithelium. Minimal to moderate hyperplasia of the squamous epithelium lining the nasolacrimal duct and atrophy of the olfactory epithelium of the ethmoturbinates also were observed in the 5.6- and 14.3-ppm groups. At the end of exposure (24 months), nasal lesions were found in >90% of 14.3-ppm mice and "in a few" 5.6-ppm mice (incidence was not specified). Mice sacrificed 3 months postexposure showed regression of the formaldehyde-induced nasal epithelial lesions. At 24 months, mice in the 2-ppm group were "free of significant nasal lesions", but a few mice had serous rhinitis and minimal hyperplasia of the squamous epithelium lining the nasolacrimal duct. Two male mice in the 14.3-ppm group sacrificed at 24 months displayed squamous cell carcinomas in the nasal cavity similar to those found in rats. The number of mice sacrificed at 24 months was not specified in the published report, but the incidence was indicated to be significantly increased compared with controls. No other tumors were reported in exposed or control mice.

Dalbey (1982) exposed groups of male Golden Syrian hamsters to 0 (n=132) or 10 (n=88) ppm formaldehyde, 5 hours/day, 5 days/week for life (up to about 110 weeks). Exposed hamsters showed reduced survival time compared with controls. End points in this study were restricted to histopathological examinations of respiratory tract tissues. There was no evidence of rhinitis in treated animals, and no tumors were found in the respiratory tract of treated or control animals. Hyperplastic and metaplastic areas were seen in the nasal epithelium of 5% of the treated hamsters but were not seen in controls. Dalbey (1982) also exposed groups of 50 male hamsters to 0 or 30 ppm formaldehyde, 5 hours/day, 1 day/week for life. No respiratory tract tumors were reported to have been found in control or exposed animals, but Dalbey (1982) did not mention if the nasal epithelium was examined for non-neoplastic changes in these two groups of hamsters.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to formaldehyde.

No histological evidence for formaldehyde effects on cardiovascular tissues was found in intermediate-duration inhalation studies, using a 6 hour/day, 5 day/week exposure protocol, with mice exposed to up to 40 ppm for 13 weeks (Maronpot et al. 1986), Rhesus monkeys exposed to 6 ppm for 6 weeks (Monticello et al. 1989), rats exposed to up to 20 ppm for 13 weeks (Woutersen et al. 1987), or rats exposed to up to 10 ppm for 13 or 52 weeks (Appelman et al. 1988). Similarly, no evidence for

formaldehyde effects on cardiovascular tissues were found in chronic inhalation studies with rats or mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for 2 years (Kerns et al. 1983b). The only study located that examined cardiovascular function in animals exposed to airborne formaldehyde was a report that concluded that blood pressure and heart rate were not affected in anesthetized rats exposed for 1 minute to 1,628 ppm formaldehyde (Egle and Hudgins 1974).

Gastrointestinal Effects. Few studies regarding gastrointestinal effects after inhalation exposure were located. In humans, Kilburn (1994) describes vague gastrointestinal effects in four patients who had been occupationally exposed to formaldehyde for 14–30 years. Three of the patients were anatomists and were exposed to formalin; the fourth was a railroad worker who worked next to a wood-products factory that used large quantities of phenol-formaldehyde resins. Intestinal cramps with flatus and bloody stools was one of many nonspecific effects noted in this small population.

No histological evidence for formaldehyde effects on the gastrointestinal tract was found in intermediate-duration inhalation studies using a 6 hour/day, 5 days/week exposure protocol with mice exposed to up to 40 ppm for 13 weeks (Maronpot et al. 1986), Rhesus monkeys exposed to 6 ppm for 6 weeks (Monticello et al. 1989), rats exposed to up to 20 ppm for 13 weeks (Woutersen et al. 1987), or rats exposed to up to 10 ppm for 13 or 52 weeks (Appelman et al. 1988). Similarly, no evidence for formaldehyde effects on gastrointestinal tissues were found in chronic inhalation studies with rats exposed to up to 15 ppm, 6 hours/day, 5 days/week for 2 years or more (Kamata et al. 1997; Kerns et al. 1983b), or in mice exposed similarly (Kerns et al. 1983b).

Hematological Effects. Pross et al. (1987) evaluated the immunologic response of asthmatic subjects exposed to urea-formaldehyde foam insulation (UFFI) off-gas products. Subjects consisted of 23 individuals with a history of asthmatic symptoms attributed to UFFI and 4 individuals (controls) with asthma unrelated to UFFI by-products. Subjects were exposed to one of the following: room air (placebo) for 30 minutes; 1 ppm formaldehyde gas for 3 hours; UFFI particles (4 μm, 0.5 particles/mL) for 3 hours, commencing 48 hours after formaldehyde gas exposure; and UFFI off-gas products for 3 hours, commencing 48 hours after UFFI particle exposure. There were no significant alterations in any of the white blood cell populations when the four unexposed controls were compared to the subjects (who also lived in a home where UFFI is present) before or after being exposed to UFFI in the chamber. However, there was a significant increase in the percentage and absolute number of eosinophils and

basophils in the subjects (who also lived in UFFI-homes) after exposure to UFFI in the exposure chamber when compared to the white blood cell values obtained before chamber exposure to UFFI.

No exposure-related effects on hematological variables were found in rats exposed to up to 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), in rats exposed to up to 10 ppm, 6 hours/day, 5 days/week for up to 52 weeks (Appelman et al. 1988), in rats or mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for up to 24 months (Kerns et al. 1983b), or rats exposed to up to 15 ppm for 28 months (Kamata et al. 1997). Dean et al. (1984) reported that female mice exposed to up to 15 ppm for 6 hours/day, 5 days/week for 3 weeks showed a statistically significant decrease in absolute number of monocytes compared with control values, but no other hematological variable was affected by exposure in this study.

Musculoskeletal Effects. Few studies were located that described musculoskeletal effects of formaldehyde after inhalation exposure. Holness and Nethercott (1989) reported that muscle or joint stiffness was reported more frequently by a surveyed group of funeral directors and embalmers than in a referent nonexposed group (23 versus 5%), but reporting of similar symptoms has not been frequently encountered in other health surveys of formaldehyde-exposed groups of workers.

With 6-hours/day, 5-days/week exposure protocols, no formaldehyde-induced histological changes in muscle or skeletal tissue were found in mice exposed to up to 40 ppm for 13 weeks (Maronpot et al. 1986), in monkeys (bone marrow of sternum) exposed to 6 ppm for 6 weeks (Monticello et al. 1989), in rats (femur and muscle tissue) exposed to up to 15 ppm for 28 months (Kamata et al. 1997), or in rats or mice exposed to up to 14.3 ppm for 24 months (Kerns et al. 1983b).

Hepatic Effects. No studies were located that reported hepatic effects in humans following exposure to airborne formaldehyde.

Murphy et al. (1964) found increased activities of alkaline phosphatase in livers of rats exposed to 35 ppm formaldehyde for 18 hours and suggested that formaldehyde may be hepatotoxic. More recent animal studies, however, have found no consistent evidence for formaldehyde-induced hepatotoxicity. Woutersen et al. (1987) found statistically significant increased levels of aspartate amino transferase, alanine amino transferase, and alkaline phosphatase in plasma of rats exposed to 20 ppm, (but not to 10 or 1 ppm) 6 hours/day, 5 days/week for 13 weeks, but found no exposure-related microscopic lesions

in the livers of these rats. In another experiment from the same laboratory, Appelman et al. (1988) found no exposure-related changes in serum aspartate amino transferase, alanine amino transferase, or alkaline phosphatase in plasma, no changes in liver concentrations of total protein or reduced glutathione, and no hepatic histological changes in rats exposed to up to 10 ppm by the same protocol for 13 or 52 weeks. Kamata et al. (1997) also reported that no exposure-related changes were found, at several sampling dates, in activities of serum alkaline phosphatase, aspartate amino transferase, or alanine amino transferase in rats exposed to up to 15 ppm, 6 hours/day, 5 days/week for up to 28 months. In 15-ppm rats, absolute, but not relative, liver weights were statistically significantly decreased compared with controls. This effect appears to have been a secondary effect from decreased food consumption at this exposure level rather than a direct effect of formaldehyde on the liver. No histological liver changes were found in Rhesus monkeys exposed to 6 ppm formaldehyde, 6 hours/day, 5 days/week for 6 weeks (Monticello et al. 1989), in mice exposed to up to 40 ppm by a similar protocol for 13 weeks (Maronpot et al. 1986), or in rats or mice exposed to up to 14.3 ppm for 24 months (Kerns et al. 1983b). The weight of available evidence suggests that airborne formaldehyde may produce toxic effects on the liver only at high concentrations that may exceed metabolic and binding capacities in the respiratory tract.

Renal Effects. In the only report located regarding renal effects in humans after inhalation exposure to formaldehyde, Freestone and Bentley (1989) noted that renal failure occurred in a 68-year-old man who inhaled and/or ingested an undetermined amount of formaldehyde. He stated that he had inhaled formaldehyde for a sore throat, however, the medical staff believed that he may have gargled with the formaldehyde as well. Dopamine was administered until renal function improved and the man was released.

No evidence from histological examinations or blood chemistry monitoring for formaldehyde-induced kidney effects has been found in intermediate-duration inhalation studies with rats, Rhesus monkeys, or mice (Appelman et al. 1988; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987), or in chronic inhalation studies with rats and mice (Kamata et al. 1997; Kerns et al. 1983b). Appelman et al. (1988) noted that rats exposed to 10 ppm, 6 hours/day, 5 days/week for 52 weeks had “frequent oliguria”. Kerns et al. (1983b) also measured urinalytic variables in rats and mice exposed to up to 14.3 ppm by a similar protocol for 24 months, but did not report a similar finding.

Endocrine Effects. No studies were located regarding endocrine effects in humans exposed to inhaled formaldehyde. No evidence from histological examinations or organ weight measurements for formaldehyde-induced effects on endocrine organs (e.g., pancreas, pituitary, adrenals, thyroid) has been found in intermediate-duration inhalation studies with rats, mice or Rhesus monkeys (Appelman et al. 1988; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987), or in chronic inhalation studies with rats or mice (Kamata et al. 1997; Kerns et al. 1983b).

Dermal Effects. Occupational exposures to formaldehyde have been associated with dermal irritation and the diagnosis of allergic contact dermatitis by patch testing. Reported historical percentages of subjects with skin problems showing positive responses to formaldehyde in patch tests performed by dermatologists using aqueous solutions with 1 or 2% formaldehyde include 7.8% in North America between 1992 and 1994 (Marks et al. 1995), 1.6% in a 1983–1984 Swedish study (Meding and Swanbeck 1990), 2.6% in a 1988–1989 European study (Menné et al. 1991), and 3.7% in a 1990–1994 Polish study (Kiec-Swierczynska 1996). Lack of case-specific exposure information for these patients precludes the determination of the degree to which sensitization may have been caused by direct dermal contact to formaldehyde in liquids or by contact with formaldehyde gas in air, but the widespread use of formaldehyde or formaldehyde-releasing chemicals in cosmetics and cleaning agents (Flyvholm 1991; Rastogi 1992) suggest that the dermal route of exposure may be the more important sensitizing route. Dermal effects in humans from exposure to formaldehyde are further discussed in Sections 2.2.3.2 and 2.2.3.3.

Acute controlled exposure studies of volunteers exposed to airborne formaldehyde at concentrations ranging from 0.4 to 3 ppm have not found increased reporting of skin irritation symptoms (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Weber-Tschopp et al. 1977). Eberlein-Konig et al. (1998), however, found subtle skin effects in seven subjects described as having formaldehyde atopic eczema compared with seven nonsensitized subjects. Exposure to 0.08 ppm formaldehyde for 4 hours in an exposure chamber induced increased transepidermal water loss, but not skin roughness, on the uncovered lower arms of subjects with atopic eczema; neither transepidermal water loss nor skin roughness were increased by similar exposure in a group of seven subjects without atopic eczema. Serum levels of eosinophil cationic protein and soluble interleukin-2 receptor were not increased by exposure in either group.

No evidence for formaldehyde-induced effects on the skin has been reported in intermediate-duration inhalation studies with rats, hamsters, Rhesus monkeys, or mice (Appelman et al. 1988; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987), or in chronic inhalation studies with rats or mice (Kamata et al. 1997; Kerns et al. 1983b), except that the highest concentration used in these studies (40 ppm used in the 13-week mouse study by Maronpot et al. 1986) produced severe clinical signs of toxicity in mice including mouth breathing, ataxia, and "loss of skin elasticity".

Ocular Effects. From occupational exposure experience and results in controlled acute inhalation exposure studies in humans, airborne formaldehyde is well-known as an eye irritant. Because formaldehyde-induced eye irritation and upper respiratory tract irritation have often been noted at similar exposure concentrations, results from survey studies of occupationally-exposed workers and controlled acute exposure studies in which subjects reported symptoms of eye irritation were discussed earlier in the Respiratory Effects part of this section.

Studies of animals exposed to airborne formaldehyde for intermediate and chronic durations have not found increased incidences of histological changes in the eyes of mice exposed to up to 40 ppm (Kerns et al. 1983b; Maronpot et al. 1986), rats exposed to up to 20 ppm (Appelman et al. 1988; Kerns et al. 1983b; Swenberg et al. 1980; Woutersen et al. 1987), or monkeys exposed to 6 ppm (Monticello et al. 1989). Kerns et al. (1983b) reported that ophthalmoscopic examinations revealed no exposure-related changes in rats or mice examined at several intervals during a 2-year period of exposure to concentrations as high as 14.3 ppm. Clinical signs of eye irritation during exposure, however, have been reported in monkeys ("mild lacrimation and conjunctival hyperemia") exposed to 6 ppm for up to 6 weeks (Monticello et al. 1989), in rats exposed to 10 ppm for up to 4 days (Dinsdale et al. 1993), and in rats ("ocular discharge") exposed to 2 to 15 ppm, but not to 0.5 ppm, for up to 3 weeks (Morgan et al. 1986c). Swenberg et al. (1980) described the development of a "unilateral ocular discharge" that was associated with the subsequent development of nasal tumors in rats exposed to 14.3 ppm; this discharge is likely distinct from the clinical signs of eye irritation noted in the other animal studies and in the human studies.

Body Weight Effects. Body weight effects have not been associated with formaldehdye exposure in humans, but exposure-response relationships have been described in animal studies.

Body weight decreases $10% of control values were observed in male rats exposed to 10 ppm, but not to 1 ppm, 6 hours/day, 5 days/week for 13 or 52 weeks (Appelman et al. 1988); in male rats exposed to 2.95 ppm, but not to 0.98 ppm, 22 hours/day, 7 days/week for 26 weeks (Rusch et al. 1983); in male rats exposed to 20 ppm, but not to 10 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987); in male mice exposed to $20 ppm, and female mice exposed to 40 ppm, 6 hours/day, 5 days/week for 13 weeks (Maronpot et al. 1986); in male and female rats exposed to 14.3 ppm, but not to 5.6 ppm, 6 hours/day, 5 days/week for 2 years (Kerns et al. 1983b); in male rats exposed to 15 ppm, but not to 2 ppm, 6 hours, 5 days/week for 4 to 28 months (Kamata et al. 1997); and in male rats exposed to 10 ppm, but not to 1 ppm, 6 hours/day, 5 days/week for 28 months (Woutersen et al. 1989).

No body weight effects were observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, for 5 days or 5 days/week for 6 weeks (Monticello et al. 1989), in female rats, Cynomolgus monkeys, or hamsters exposed to up to 2.95 ppm, 22 hours/day, 7 days/week for 26 weeks (Rusch et al. 1983), in female rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), or in mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b).

2.2.1.3 Immunological and Lymphoreticular Effects

As discussed previously in Section 2.2.1.2 (dermal effects from inhalation exposure), formaldehyde is commonly diagnosed as a dermal allergen worldwide. Lack of case-specific exposure information precludes determining the degree to which sensitization may have been caused by direct dermal contact to formaldehyde in liquids or by contact with formaldehyde gas in air, but the widespread use of formaldehyde or formaldehyde-releasing chemicals in cosmetics and cleaning agents (Flyvholm 1991; Rastogi 1992) suggest that the dermal route of exposure may be the more important sensitizing route. Dermal effects in humans from exposure to formaldehyde, including formaldehyde allergic contact dermatitis, are further discussed in Section 2.2.3.2 and 2.2.3.3.

Investigations into the possibility of immunologically-mediated respiratory responses in formaldehyde-exposed individuals reporting respiratory problems such as bronchial asthma have provided very limited positive evidence.

There are only a few available case reports of bronchial asthma suggestive of respiratory tract sensitization to formaldehyde gas including two renal dialysis nurses (Hendrick and Lane 1975, 1977;

Hendrick et al. 1982), a plastic moulder (Burge et al. 1985), a printer (Burge et al. 1985), a worker in a phenol formaldehyde manufacturing plant (Burge et al. 1985), and a carpenter (Lemiere et al. 1995). These cases of formaldehyde-exposed workers all displayed marked changes in FEV_1 or airflow rates in response to acute challenges with formaldehyde gas at exposure levels <3 ppm. Nordman et al. (1985) provided acute formaldehyde (2 ppm) challenges to 230 patients who had been occupationally exposed to formaldehyde and who had reported respiratory symptoms consistent with asthma, but found challenge-induced decreases in PEFR >15% in only 12 subjects. Although an immunologic-mediated response may be consistent with the observed airway responses, the mechanism of sensitization in these subjects is uncertain. Challenge-induced deficits in FEV_1 or airflow rates indicative of lower airway sensitization were not found in studies of: 9 subjects complaining of respiratory problems from urea-formaldehyde foam insulation in their homes who were challenged with 1–1.2 ppm formaldehyde for 90 minutes (Day et al. 1984); 10 formaldehyde-exposed textile or shoe manufacturing workers with purported bronchial asthma who were challenged with 0.41 ppm for 2 hours (Krakowiak et al. 1998); and 13 formaldehyde-exposed subjects who had previously reported asthma-like symptoms who were challenged with 0.1, 1, or 3 ppm for 20 minutes (Reed and Frigas 1984).

Several studies have examined serum for formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed humans (Dykewicz et al. 1991; Grammar et al. 1990; Kramps et al. 1989; Wantke et al. 1996a, 1996b). In general, the studies do not provide consistent evidence for a formaldehyde-induced allergic respiratory syndrome, but provide suggestive evidence that children may have an increased tendency to develop specific antibodies after exposure to low levels of formaldehyde in indoor air (Wantke et al. 1996a).

Formaldehyde-specific IgE antibodies could be detected in only 1/86 serum samples from four groups of formaldehyde-exposed subjects (Kramps et al. 1989). The groups included 28 subjects living or working in places with formaldehyde-containing construction materials (e.g., chipboard) and estimated formaldehyde concentrations ranging from 0.08 to 0.37 ppm, 18 occupationally exposed subjects from an anatomy laboratory and in other unspecified industries where air concentrations were not measured, 12 hospital attendants who worked with formaldehyde-sterilized hemodialysis equipment, and 28 hemodialysis patients treated with formaldehyde-sterilized equipment. Variable symptoms such as headache, eye irritation, and respiratory complaints were reported by 24/28 subjects in the construction-material group. The group of 18 occupationally exposed subjects reported nonspecific irritation of eyes and airways associated with their work; the subject with detected formaldehyde-specific IgE displayed no

allergic symptoms. The hospital attendants and hemodialysis patients reported no exposure-related symptoms. Durations of exposure or employment were not reported for the subjects in this study.

Grammer et al. (1990) studied the immunologic nature of formaldehyde sensitivity in 37 workers who complained of formaldehyde-related illness and were examined by a group of physicians. Blood samples were collected and assayed for IgE and IgG activity against formaldehyde and formaldehyde-human serum albumin (f-HSA). Fourteen workers had symptoms consistent with an irritant syndrome, another 14 had symptoms consistent with a possible irritant, and 9 had no work-related symptoms. Four workers also had symptoms consistent with formaldehyde allergy. None of the workers had IgG activity against formaldehyde. Five workers had antiformaldehyde IgE activity, but further testing revealed that the IgE lacked formaldehyde specificity. The authors concluded that in this group of workers, there was no evidence of an immunologically mediated response to formaldehyde.

Dykewicz et al. (1991) sought to determine whether IgE or IgG antibodies to formaldehyde were related to formaldehyde exposure or respiratory symptoms arising from such an exposure. The authors studied 55 hospital histology technicians, internal medicine residents, pathology residents, current smokers, subjects with known workplace exposure to formaldehyde, and controls with no history of formaldehyde exposure. Reported workplace formaldehyde concentrations were 0.2–0.64 ppm for pathology residents, 0.64 ppm for histology technicians, and 0.6–11 ppm for miscellaneous formaldehyde exposure scenarios. No workplace air concentrations were measured for the other occupations. Average years of occupational exposure to formaldehyde were 12.45 years for histology technicians, 0.38 years for medical residents, 3.21 years for pathology residents, and 18.34 years for 5 subjects exposed to miscellaneous workplaces with formaldehyde. Each subject was evaluated by questionnaire for the presence of upper- and lower-respiratory tract and ocular symptoms and formaldehyde-related illnesses. Blood samples were drawn from each subject and were analyzed for IgE and IgG reactivity with f-HSA. Three subjects had IgE against f-HSA; these three and two others had low levels of anti-f-HSA IgG. The presence of IgG and IgE antibodies to formaldehyde was not clearly related to formaldehyde exposure or pack-years of smoking. One subject had both IgE and IgG antibodies and also suffered from eye and respiratory symptoms when exposed to formaldehyde at his workplace. The authors concluded that they could not establish a relationship of IgE and IgG to formaldehyde exposure. They further concluded that if immunologically mediated rhinitis or conjunctivitis existed, it must occur at extremely low frequencies. Several limitations of this study should be noted. First, the investigators recruited volunteers who may have systematically differed from the general populations from which they were

sampled. One of the exposure groups comprised cigarette smokers, who have exposures to many chemicals in addition to their formaldehyde exposures. Although the study focuses on formaldehyde antibodies, which would be unaffected by the other chemicals, respiratory symptoms among smokers would reflect exposures to the other smoke constituents.

Wantke et al. (1996a) measured elevated levels of formaldehyde-specific IgE in 24/62 8-year-old children who were students in three particle board-paneled classrooms with estimated formaldehyde air concentrations of 0.075, 0.069, and 0.043 ppm. In a health survey, the children reported headaches (29/62), fatigue (21/62), dry nasal mucosa (9/62), rhinitis (23/62), cough (15/62), and nosebleeds (14/62). Sums of numbers of children with each of nine symptoms for each classroom decreased with decreasing formaldehyde concentration (49, 47, and 24, respectively, for the 0.075-, 0.069-, and 0.043-ppm classrooms), but the investigators reported that elevated levels of specific IgE did not correlate with the number and severity of symptoms. The children were moved to a new school without particle board paneling and were evaluated again, 3 months after moving. Estimated formaldehyde concentrations in the new classrooms were 0.029, 0.023, and 0.026 ppm. The numbers of children reporting symptoms decreased significantly compared with premoving reporting figures, and mean serum levels of formaldehyde-specific IgE, measured in 20 of the children, declined significantly compared with premoving mean levels.

Formaldehyde-specific IgE was not detected in a group of 45 medical students, before or after the students attended a 4-week anatomy dissecting course (Wantke et al. 1996b). Estimates of laboratory air concentrations of formaldehyde ranged from 0.059 to 0.219 ppm (mean 0.124±0.05 ppm). Surveys revealed frequencies of irritation symptoms consistent with other studies (e.g., itching of the skin in 33/45 students, headache in 15/45, and burning eyes in 13/45).

Thrasher et al. (1987) assessed the effects of formaldehyde exposure on cellular immunity and antibody formation in eight symptomatic and eight unexposed individuals. The exposed group was comprised of three males and five females. Seven of the exposed individuals resided in mobile homes for periods ranging from 2 to 7 years; the eighth exposed subject was a laboratory worker who resided in a newly decorated, energy-efficient apartment. Air monitoring in four of the homes revealed formaldehyde vapor concentrations ranging from 0.07 to 0.55 ppm. Venous blood samples were collected from all subjects and lymphocytes were used for T- and B-cell enumeration and blastogenesis; serum samples were used to determine IgG and IgE antibodies to formaldehyde. IgE antibodies to formaldehyde were not detected in

exposed or control subjects; IgG antibodies in exposed subjects ranged from 1:8 to 1:256, but were undetected (1:4) in 7 of the controls. T- and B-cell numbers were significantly lower ($p<0.05$) in mobile home residents (48 and 12.6%, respectively) compared to control subjects (65.9 and 14.75%, respectively). Phytohemagglutinin-stimulated T- and B-cell blastogenesis was significantly depressed ($p<0.01$) in mobile home residents compared to control subjects (17,882 versus 28,576 counts per minute, respectively).

In a later study, Thrasher et al. (1990) evaluated four groups of patients with varying levels and durations of formaldehyde exposure. The groups consisted of asymptomatic chiropractic students exposed during anatomy classes (controls), mobile home residents, office workers, patients with multiple symptoms who had been removed from the source of formaldehyde for at least a year, and occupationally exposed patients. All groups were assessed for immunologic function via white cell, lymphocyte and T-cell counts, T-helper/suppressor ratios, B cell counts, and production of antibodies against f-HSA. When compared to controls (students), the patient groups had significant elevations in formaldehyde antibody titers and B-cell titers. The level of autoantibodies was also significantly elevated in patients exposed long-term to formaldehyde.

Gorski et al. (1992) investigated the correlation between formaldehyde-induced contact dermatitis and granulocyte chemiluminescence resulting from free-radical release in healthy and formaldehyde-sensitive patients. Thirteen patients with contact dermatitis who were occupationally exposed to formaldehyde and five healthy volunteers participated in the study. All subjects underwent skin-prick tests for common allergens as well as a histamine inhalation provocation test. Subjects were exposed to 0.5 mg/m^3 (0.41 ppm) formaldehyde for 2 hours, and peak expiratory flow was measured immediately before exposure, at 60 and 120 minutes of exposure, and at 6 and 21 hours after completion of exposure. In formaldehyde-sensitive patients, skin-prick tests and total serum IgE were normal; no antiformaldehyde IgE was detected. In formaldehyde-sensitive patients, peripheral blood granulocyte chemiluminescence significantly increased within 30 minutes of exposure commencement, and remained elevated 24 hours later, compared to initial values. Granulocyte chemiluminescence did not increase in healthy patients.

Pross et al. (1987) evaluated the immunologic response of asthmatic subjects exposed to UFFI off-gas products. Subjects consisted of 23 individuals with a history of asthmatic symptoms attributed to UFFI and 4 individuals with asthma unrelated to UFFI byproducts. All subjects were exposed to the following in an environmental chamber: room air (placebo) for 30 minutes; 1 ppm formaldehyde gas for 3 hours;

UFFI particles (4 μm, 0.5 particles/mL) for 3 hours, commencing 48 hours after formaldehyde gas exposure; and UFFI off-gas products for 3 hours, commencing 48 hours after UFFI particle exposure. There was a significant increase in the percentage and absolute number of eosinophils and basophils in the subjects that lived in UFFI-homes. There were no differences between exposure groups with respect to lymphocyte subpopulations either before or after UFFI exposure. However, when T8 suppressor cell count control values for the UFFI-exposed group were compared to T8 (suppressor) cell count values collected after UFFI chamber exposure, a small but statistically significant ($p<0.01$) increase in T8 cell count was observed. The significance of this change in T8 cell count is not known. Phytohemagglutin- and formalin-treated-red-blood-cell-stimulation studies revealed no differences between treatment groups in nonspecific or specific lymphocyte reactivity in response to UFFI exposure. Likewise, UFFI exposure had no effect on humoral immunity. Natural killer function was also unaffected by in-home or chamber exposure to UFFI, as was the interferon-boosted (IFN) natural killer cell response. Approximately half of the subjects from each group were classified as atopic based on skin-prick tests, but there was little correlation with NK function. The authors concluded that short-term exposure to formaldehyde was not immunosuppressive and did not result in systemic immune reactivity.

No histopathological effects on lymphoreticular tissues (e.g., spleen, thymus, lymph nodes) were observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, 5 days/week for 6 weeks (Monticello et al. 1989); in rats exposed to up to 10 ppm, 6 hours/day, 5 days/week for 13 or 52 weeks (Appelman et al. 1988); in rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987); in mice exposed to 40 ppm, 6 hours/day, 5 days/week for 13 weeks (Maronpot et al. 1986); in rats and mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b); or in rats exposed to up to 15 ppm, 6 hours/day, 5 days/week for 28 months (Kamata et al. 1997).

In a study by Adams et al. (1987), the effects of exposure to formaldehyde on the maturation of the mononuclear phagocyte system in female B6C3F1 mice were investigated. Mice were exposed to a target concentration of 15 ppm formaldehyde 6 hours/day, 5 days/week for 3 weeks. Exposure to formaldehyde for 3 weeks did not affect lymphoid organ weights or the number of resident or activated macrophages. Formaldehyde exposure resulted in lower peritoneal macrophage leucine aminopeptidase concentrations, but did not appear to induce maturation of resident macrophages. Formaldehyde treatment did not alter the ability of induced macrophages to bind and lyse tumor cells. In macrophages elicited by pyran copolymer MVE-2, the ability to release reactive oxygen intermediates (H_2O_2) was increased almost 2-fold as a result of formaldehyde exposure. The authors concluded that formaldehyde

exposure did not disturb the systemic development of tumoricidal macrophages, but did enhance the release of reactive oxygen intermediates.

Dean et al. (1984) studied immune function in female B6C3F1 mice 6–8 weeks of age. Mice were exposed by inhalation to 15 ppm formaldehyde for 6 hours/day, 5 days/week for 3 weeks. Several tests that evaluated immune function were used: (1) tumor challenge procedure consisting of a subcutaneous injection of PYB6 sarcoma cells, (2) tumor resistance assessment consisting of an intravenous injection of B16F10 melanoma cells, and (3) an intravenous challenge using *Listeria monocytogenes* bacteria. Other tests that evaluated immune function were cell-mediated immunity (consisting of monitoring the delayed hypersensitivity response to keyhole limpet hemocyanin); lymphoproliferative responses to T-cell mitogens (phytohemagglutinin) and B-cell mitogens (*Escherichia coli lipopolysaccharide*); spontaneous cytotoxicity (natural killer cell); macrophage function (elicitation, activation, phagocytic); plaque-forming cell activity; and spleen and bone marrow cellularity. Thymus and spleen weights were unaffected by formaldehyde exposure. A significant decrease in the absolute number of monocytes was observed in the formaldehyde-treated mice ($4/mm^3$ versus $43/mm^3$ in controls; $p<0.05$); all other hematological parameters in treated mice were similar to those of controls. Spleen and bone marrow cellularity were similar in treated and control groups. Formaldehyde-treated animals experienced lower mortality (30%) than controls (70%) in response to challenge with *Listeria monocytogenes*. Formaldehyde-treated mice were also less susceptible to tumor transfer or formation compared to controls. No differences were noted in treated and control mice for the following parameters: delayed hypersensitivity reaction; natural killer cell-mediated tumor cytotoxicity; lymphocyte proliferation; lymphocyte surface markers; macrophage function; and plaque-forming cell response. The authors concluded that exposure to 15 ppm formaldehyde for 3 weeks was not immunotoxic; they hypothesized that this was due to the highly reactive nature of the compound which prevents penetration into the deep lung and tissue penetration in general.

Holmstrom et al. (1989b) evaluated the long-term inhalation effects of formaldehyde exposure to immune function in female Sprague-Dawley rats exposed to 12.6 ppm formaldehyde for 6 hours/day, 5 days/week for 22 months. After 22 months of formaldehyde exposure, the rats were inoculated subcutaneously with Pneumovax (Merck Sharpe and Dohme) and antitetanus vaccine (National Bacteriological Laboratory). Animals were sacrificed at 21–25 days after vaccination. Blood samples were collected from each animal before vaccination and just prior to sacrifice. The blood was analyzed for response to Pneumovax and tetanus vaccination using an enzyme-linked immunosorbant assay technique. The results indicated that

there were no differences between exposed and control animals in IgM production in response to Pneumovax. Mean overall IgG production in response to Pneumovax was similar between exposed and control rats; however, a 2-fold increase in IgG production in response to the 19F pneumococcal antigen was seen in 4 of 8 exposed rats compared to 1 of 6 control rats. The IgM response to tetanus immunization was similar in the exposed and control groups; levels increased at least 2-fold in a majority of animals in both groups. Likewise, IgG levels increased significantly in response to tetanus toxoid, but the response did not differ between treatment groups. The authors concluded that there was no evidence of immunosuppression in response to long-term exposure to near-maximal levels of formaldehyde in rats.

Whereas other animal experiments have not found convincing evidence that repeated inhalation exposure to formaldehyde has direct effects on the immune system, there is suggestive evidence that it may have an indirect effect by facilitating sensitization of nasal tissue to high-molecular weight allergens in mice (Tarkowski and Gorski 1995). The ability of intranasal administration of 25 μg of ovalbumin (once a week for 7 weeks) to increase the titer of serum IgE antibodies to ovalbumin (IgE anti-OVA) was examined in groups of 10 Balb/c mice preexposed to 0 or 1.6 ppm formaldehyde 6 hours/day for 10 days, or to 0 or 1.6 ppm, 6 hours/day once a week for 7 weeks. In a second experiment, groups of mice were preexposed to 0 or 1.6 ppm, 6 hours/day for 10 days, injected with up to 4 doses of 1 μg ovalbumin in the peritoneum, and examined for serum IgE antiOVA titers. Serum titers of IgE antiOVA were significantly higher (after four intranasal doses of OVA) in mice preexposed to formaldehyde 6 hours/day for 10 days compared with control titers; mean IgE antiOVA titer at 7 weeks in 10-day preexposed mice was >60 units compared with about 15 units for controls. No significant difference in IgE-OVA was found between controls and the group preexposed to formaldehyde once a week for 7 weeks. With intraperitoneal administration of ovalbumin, preexposure to formaldehyde for 10 consecutive days had no effect on serum IgE-OVA titers compared with controls.

In a similar experiment with guinea pigs, Riedel et al. (1996) observed a greater percentage of allergic responses to inhaled ovalbumin in a group of guinea pigs pre-exposed to 0.25 ppm formaldehyde, 8 hours/day for 5 days than in a control group without preexposure to formaldehyde (10/12 versus 3/12) (Riedel et al. 1996).

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Bach et al. (1990) sought to determine whether humans reacted acutely to formaldehyde exposure, and if previous chronic-duration exposure to formaldehyde altered the responses noted in acute exposure. Thirty-two men with at least 5 years of occupational exposure to formaldehyde and 29 matched controls were exposed to formaldehyde at concentrations of 0, 0.12, 0.32, or 0.98 ppm for 5.5 hours. During the exposure period, subjects underwent a battery of performance tests designed to estimate the subject's distractibility, short-term memory, and capability to understand and perform certain tasks. Controls tended to suffer from headaches, "heavy head", and physical tiredness more than the exposed workers. In both occupationally exposed subjects and nonexposed subjects, decreased performances in several tests were statistically significantly correlated with increasing acute concentration of formaldehyde. Occupationally exposed subjects showed significantly decreased performance, compared with nonexposed subjects, only in a digit span test, but not in variables for a graphic continuous line test, an addition test, or a digit symbol test. The authors noted that the typical dose-related symptoms of respiratory irritation were not seen in this study.

Kilburn and colleagues have presented evidence for neurological impairments in several studies of formaldehyde-exposed histology technicians, but confounding exposure to other neurotoxic solvents prevents drawing definitive conclusions concerning the neurotoxicity of formaldehyde from these studies (Kilburn 1994; Kilburn and Warshaw 1992; Kilburn et al. 1985b, 1987). Kilburn et al. (1985b) reported that a group of 76 female histology technicians reported statistically significantly greater frequencies of neurobehavioral symptoms such as lack of concentration and loss of memory, disturbed sleep, impaired balance, variations in mood, and irritability than did a referent group of 56 non-exposed female clerical workers. The technicians had been employed from 2 to 37 years (mean 12.8 years). Analysis of workplace air samples indicated concentrations for several solvents ranging from 0.2 to 1.9 ppm for formaldehyde, 3.2 to 102 ppm for xylene, 2 to 19.1 ppm for chloroform, and 8.9 to 12.6 ppm for toluene. Subsequently, Kilburn et al. (1987) administered a battery of 10 tests that assessed memory, balance, coordination, dexterity, motor speed, and aspects of cognitive function to 305 female histology technicians and analyzed the results by regression analysis with age, years of smoking, hours per day of exposure to formaldehyde and other solvents as explanatory variables. Increased daily hours of exposure to formaldehyde were significantly correlated with decreased performance in several tests, whereas hours of daily exposure to other solvents were only correlated with decreased perfomance in a single test. However, in a later prospective study of performance by 318-494 histology technicians in a battery of

neurobehavioral tests, no statistically significant cumulative effects due to occupational exposure to formaldehyde (or other solvents) or of aging were found over a 4-year period (Kilburn and Warshaw 1992). Kilburn (1994) further reported that three anatomists and one railroad worker, who were occupationally exposed to airborne formaldehyde for 14-30 years and who were disabled, each showed impaired performance on several neurobehavioral tests (e.g., choice reaction time, abnormal balance, digit symbol, and tests of perceptual motor speed).

In laboratory animals, Morgan et al. (1986a) studied male Fischer 344 rats exposed to 15 ppm formaldehyde for 10, 20, 45, or 90 minutes, or 6 hours. Some additional rats were also exposed to 2 ppm formaldehyde for 90 minutes or 6 hours to establish whether this level was a no-effect concentration. The rats exposed to 15 ppm formaldehyde exhibited restless behavior for the first 10–15 minutes of exposure.

Boja et al. (1985) investigated the effects of low-level formaldehyde exposure on behavior and neurochemistry in male Sprague-Dawley rats. Animals were exposed to either air or formaldehyde at concentrations of 5, 10, or 20 ppm for 3 hours. The following day the rats were exposed to either the same treatment or the opposite treatment (i.e., treatment groups of air-air, air-formaldehyde, formaldehyde-air, or formaldehyde-formaldehyde). Behavioral activity was periodically monitored. After the second day of exposure, rats were sacrificed, their brains were removed, and samples of striatum, nucleus accumbens, frontal cortex, lateral septum, amygdala, hypothalamus, and hippocampus were collected and analyzed for norepinephrine, dopamine, and 5-hydroxytryptamine and their major metabolites. Exposure to 5 ppm formaldehyde resulted in statistically significant decreased motor activity within 15 minutes. At the beginning of day 2, all of the rats exposed to formaldehyde on day 1 displayed lower activity levels. Similar effects on motor activity were seen at the 10 ppm formaldehyde exposure level, whereas effects seen after 20 ppm exposure were reported to be “not readily interpretable” and were not shown. Exposure to 5 ppm formaldehyde statistically significantly increased concentrations of 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenylacetic acid, and dopamine in the hypothalamus, but did not affect the concentrations of norepinephrine or 5-hydroxytryptamine. Data for other brain regions or exposure concentrations were not reported (Boja et al. 1985).

Wood and Coleman (1995) assessed the behavioral response to formaldehyde exposure in male Swiss mice. Eight mice were trained to terminate exposure to noxious gases, using 1,000 ppm ammonia. All animals learned to terminate 100% of the ammonia exposures. After mice consistently terminated

ammonia exposures, they were exposed to a series of formaldehyde exposures at concentrations of 0, 1, 1.8, 3, 5.6, and 10 ppm. Beginning at the lowest formaldehyde concentration (1 ppm), mice terminated significantly more exposures compared to air ($p<0.0005$). The number of terminations increased and the time to termination decreased as the concentration of formaldehyde increased. Exposure durations in the second series were significantly shorter ($p=0.0012$) than those experienced in the first series, indicating an increased sensitivity to formaldehyde. Wood and Coleman (1995) suggested that a conditioned response may have developed in the mice rather than a change in the sensitivity of the sensory epithelium.

In studies of intermediate-duration exposure, Maronpot et al. (1986) studied the effects of formaldehyde exposure in male and female B6C3F1 mice. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for 13 weeks at target concentrations of 0, 2, 4, 10, 20, or 40 ppm. No obvious gross signs of neurotoxicity were seen in mice treated with 2, 4, or 10 ppm formaldehyde, but mice in the 20-ppm group exhibited dyspnea, listlessness, and hunched posture. These symptoms were also noted in the 40-ppm groups with greater severity; in addition, mice in this group exhibited ataxia.

Appelman et al. (1988) examined the effects of preexisting nasal damage and formaldehyde exposure in male SPF Wistar rats. Groups of 40 rats each were exposed to 0, 0.1, 1, and 10 ppm formaldehyde. Within each dose group, half of the animals had their nasal mucosa damaged by electrocoagulation. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for either 13 or 52 weeks ($n=10$ per dose/nasal damage subgroup). Behavior and appearance were not affected by formaldehyde exposure; brain weights and histopathology in all of the formaldehyde-treatment groups were not significantly different from the control animals.

Woutersen et al. (1987) examined the effects of inhalation exposure to formaldehyde in male and female Wistar rats. Groups of 10 animals per sex were exposed to target concentrations of 1, 10, or 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. Uncoordinated movement and wall-climbing were noted during the first 30 minutes of each exposure period in the 20-ppm group; the rats in the lower-dose groups did not exhibit abnormal behavior. In the 20-ppm males, relative organ weights were higher in 6 of the 11 animals examined (no further data supplied), and in the females of this dose group, only relative brain weights were significantly greater than those of controls. No treatment-related gross or histopathological lesions of the brain were noted in any sex or dose-group at necropsy.

Kerns et al. (1983b) studied the effects of long-term formaldehyde exposure on 120 male and female Fischer 344 rats and B6C3F1 mice exposed to 0, 2, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months. The dosing period was followed by a 6-month observation period. Interim sacrifices were performed at 6, 12, 18, 24, 27, and 30 months. No dose-related neurofunctional effects were noted at any dose or interim sacrifice time-point in either sex or species.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Ward et al. (1984) investigated whether formaldehyde exposure resulted in altered sperm numbers or morphology in male pathologists. Exposed subjects consisted of 11 men; 10 were employed for 1–11 months (average 4.3 months) and the other was employed for several years. All subjects provided three semen samples collected at 2–3 month intervals. Sperm samples were analyzed for sperm count, morphology, and F-body frequency. Time-weighted average air concentrations in workplaces ranged from 0.61 to 1.32 ppm (midpoint of range 0.97 ppm). The mean sperm count for exposed workers was lower than that of controls ($62.9x10^6$/mL versus $87.4x10^6$/mL); however, the difference was not statistically significant. The frequency of abnormal sperm was not greater in exposed subjects. The frequency of sperm containing 1F- or 2F-bodies was similar between exposed and control subjects. The small number of subjects in this study limited its detection power.

Garry et al. (1980) investigated the health effects associated with formaldehyde exposure in Minnesota residents. A total of 275 cases of possible formaldehyde exposure were investigated between February and June 1979. Medical histories of the patient and all family members were recorded, and 30-minute air samples were collected from the living room and bedroom of each residence. Environmental information (age, type of home, type of insulation, type of heat) was also collected. Formaldehyde levels ranged from 0.1 to 3 ppm. The rate of miscarriages in exposed women in this study (11.6%) did not differ from the rate of miscarriages seen in other studies of non-exposed women. There is no information on the duration of exposure; therefore, chronic-duration exposure is assumed.

The possible teratogenic effects of inhaled formaldehyde were investigated in groups of 25 female rats exposed to airborne formaldehyde at levels of 0, 2, 5, and 10 ppm, 6 hours/day on gestation days 6–15.

No maternal or fetal deaths occurred, and pregnancy parameters (numbers of corpora lutea, implantation sites, pre-implantation losses) were not affected by formaldehyde exposure (Martin 1990).

Although maternal toxicity, expressed as a statistically significant decrease in bodyweight gain, was observed in pregnant Sprague Dawley rats exposed to 40 ppm, but not 20 ppm, 6 hours/day on gestation days 6–20 (Saillenfait et al. 1989), other statistically significant changes in reproductive variables (e.g., number of implantation sites and number of resorptions), however, were not found.

Woutersen et al. (1987) examined the effects of inhalation exposure to formaldehyde in male and female Wistar rats. Groups of 10 animals per sex were exposed to target concentrations of 1, 10, and 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. No treatment-related gross lesions were noted for the ovaries and testes at necropsy.

Appelman et al. (1988) provided data on the reproductive organs of rats exposed to formaldehyde. Male SPF Wistar rats were exposed to 0, 0.1, 1, and 10 ppm formaldehyde. Within each dose group, half of the animals (n=20) had their nasal mucosa damaged by electrocoagulation. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for either 13 or 52 weeks. No significant changes in testicle weights of treated rats were noted when compared to controls.

Maronpot et al. (1986) examined the effects of formaldehyde exposure on reproductive organs in male and female B6C3F1 mice. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for 13 weeks at concentrations of 2, 4, 10, 20, and 40 ppm. Gross and histopathological examination showed ovarian and uterine hypoplasia characterized by decreased prominence of endometrial glands and stroma and an associated lack of ovarian luteal tissue in 40-ppm females. Ovarian and uterine hypoplasia were not observed in the lower exposure groups. No histopathological effects were noted in male reproductive organs. Maronpot et al. (1986) ascribed to the belief that the ovarian and uterine effects reflected “the general debility and weight loss rather than a direct target organ effect of formaldehyde”.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects for the intermediate duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

Studies regarding the developmental toxicity of airborne formaldehyde in humans are limited to a population-based case-control study of 244 mothers with "low-birth weight" newborns in Lithuania compared with 4,089 control mothers with "normal weight" newborns (Grañulevi…iene et al. 1998). Questionnaire information was collected from cases and controls for risk factors including place of residence. Based on air monitoring data, residential districts were grouped into low (mean concentration 1.6 ppb), moderate (2.8 ppb), or high (3.8 ppb) formaldehyde-exposure districts. After adjustment for other risk factors such as age, occupation, last pregnancy outcome, and smoking habit, the odds ratio (OR) for low-birth weight incidence was elevated in those with formaldehyde exposure >2.8 ppb compared with those with exposure <2.8 ppb, but not to a statistically significant degree (OR=1.37, 95% confidence interval [CI] 0.90–2.09).

Martin (1990) exposed groups of 25 pregnant Sprague-Dawley rats to 0, 2, 5, or 10 ppm in an inhalation chamber, 6 hours/day from gestation days 6 to 15. Another nonexposed group of 25 pregnant rats was housed outside of the inhalation chamber ("room control"). Dams were sacrificed on day 20 and uterine contents were evaluated. Statistically significant decreased food consumption and weight gain occurred in the 10-ppm dams. No statistically significant effects from exposure were found on the following variables: numbers of corpora lutea, implantation sites, live fetuses, dead fetuses and resorptions, fetal weights, fetal sex ratios, and pre- and postimplantation losses. Likewise, no exposure-related effects were reported on the incidences of litters and fetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies. The only statistically significant finding reported was for increased incidences of reduced ossification of the pubic and ischial bones in the 5- and 10-ppm groups, compared with the 0-ppm groups but not the "room control" group. Martin (1990) did not consider these findings to be biologically significant, noting that they were considered to be related to the "slightly lower" fetal weights and "slightly larger" litter sizes in the 5- and 10-ppm groups. The published report, however, did not provide more details on the quantitative data collected, making assignment of fetal effect levels in this study uncertain.

Saillenfait et al. (1989) assessed the effects of maternal formaldehyde inhalation on embryonic and fetal development in Sprague-Dawley rats. Groups of 25 mated females were exposed to 0, 5, 10, 20, and 40 ppm formaldehyde on gestation days 6–20. The dams were weighed on gestation days 0, 6, and 21. All dams survived the experiment. On gestation day 21, the dams were sacrificed and their uteri were

exposed and examined. The following parameters were assessed: maternal weight gain, percentage pregnant, litter sex ratio, fetal mortality, fetal weight, cleft palate malformations, and alterations of soft and skeletal tissues. Exposure to 40 ppm formaldehyde resulted in a 51% reduction in weight gain in dams compared to controls ($p<0.01$). There were no significant differences between treatment groups in the incidences of pregnancies; number of implantations or resorptions; numbers of dead or live fetuses; fetal sex ratios; or the incidences of external, visceral, or skeletal abnormalities. Fetal weights were significantly lower in male offspring from dams exposed to 20 ppm formaldehyde ($p<0.05$) and in male and female offspring from dams exposed to 40 ppm formaldehyde ($p<0.01$); the decreases seen in the 20 ppm group were <5% of control values. At 40 ppm, the differences in weights averaged 21%. The authors concluded that maternal exposure to formaldehyde during gestation days 6–20 was not teratogenic at levels #40 ppm, but was slightly fetotoxic at 20 ppm.

The highest NOAEL value and less serious and serious LOAEL values from the Saillenfait (1989) study for developmental effects in rats are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

Several studies were identified that described the genotoxic effects of formaldehyde after inhalation exposure. In one study, peripheral lymphocytes from eight anatomy students exposed to formaldehyde-embalming solution over a 10-week course were examined for sister chromatid exchange (SCE). Results were compared with preexposure values for each student. Breathing-zone monitoring revealed mean exposure of 1.2 ppm (range 0.73–1.95 ppm). A small average increase in the incidence of SCE was observed in the lymphocytes of the students after exposure (7.2/cell) when compared to values obtained before exposure (6.39/cell) (Yager et al. 1986). Conversely, Vasudeva and Anand (1996) examined the effects of formaldehyde exposure on the incidence of chromosomal aberrations in peripheral blood lymphocytes of 30 medical students exposed to formaldehyde vapors at concentrations of <1 ppm for 15 months. Questionnaires established that the participants were healthy and had insignificant medical histories. There was no difference in the incidences of chromosomal aberrations among the exposed and control groups. The mean frequencies of aberrant metaphases in the exposed and control groups were 1.2 and 0.9%, respectively. There was no correlation between reported irritant effects of formaldehyde and the number of aberrant metaphases, and the authors concluded that exposure to formaldehyde at concentrations seen in this study does not lead to chromosomal aberrations.

Fleig et al. (1982) performed chromosome analyses on 15 exposed and 15 non-exposed employees from formaldehyde manufacturing facilities. Exposed workers had an average duration of exposure of 28 years (range 23–35 years). Average exposure concentrations did not exceed 5 ppm prior to 1971 and 1 ppm after 1971. The formaldehyde exposures of individual workers were classified into one of the three following categories: Category 1: exposure #25% of the maximum workplace concentration (MAK); Category 2: exposure up to a maximum of 60% MAK; and Category 3: exposure up to 100% of the MAK. Peripheral blood samples were collected from each worker and lymphocytes were separated and cultured for 70–72 hours at 37 EC. Cells were subsequently fixed and examined for chromatid- and chromosome-type aberrations. There were no differences between exposed and control groups in the incidence of chromosomal aberrations. The mean frequency of aberrant metaphases among formaldehyde-exposed persons was 3.07 versus 3.33% in controls. No correlation was found between formaldehyde exposure levels and the number of aberrant metaphases.

Shaham et al. (1996a) measured the formation of DNA-protein cross links in peripheral white blood cells of occupationally exposed workers (n=12) and unexposed controls (n=8). The average length of occupational exposure was 13 years. All subjects completed a questionnaire regarding demographics, occupational and medical background, and smoking and hygiene habits. Venous blood samples were collected from each worker and were processed to isolate DNA-protein cross links. Personal and room concentrations of formaldehyde were collected at various periods during the working day among the exposed subjects, with formaldehyde room concentrations ranging from 1.38 to 1.6 ppm. Personal monitoring devices indicated formaldehyde concentrations of 2.8–3.1 ppm during peak work and an average concentration of 1.46 ppm at times when work was usually completed. Exposure to formaldehyde resulted in a significant increase in the incidence of DNA-protein cross links. Mean (±sd) incidences in exposed and nonexposed workers were 28±6 and 22±6%, respectively. Within the exposed workers group, technicians had significantly greater levels of DNA-protein cross links than physicians (32.3±4.3 and 26.3±4.4%, respectively). A linear relationship between years of exposure and DNA-protein cross links formation was also detected. When the data were analyzed considering worker smoking habits, DNA-protein cross links was consistently elevated among formaldehyde-exposed versus corresponding controls (p=0.03). The authors concluded that DNA-protein cross links can be used as a biomarker of exposure; however, the assay measures DNA-protein cross links in general, not those specific to formaldehyde cross link formation.

Chebotarev et al. (1986) examined the lymphocytes sister chromatic exchanges (SCEs) of 40 wood-working employees and 22 control workers for chromosomal aberrations, SCEs, and unscheduled DNA repair or synthesis. The level of chromosomal aberrations in formaldehyde-exposed workers was 2.76%, which was significantly elevated compared to spontaneous chromosomal aberrations in controls (1.64%, $p<0.05$). The incidence of chromosomal breakage in exposed workers (2.95%) was significantly greater than the frequency of spontaneous breakage (1.64%, $p<0.05$). No differences between exposed and control subjects were seen for SCEs either at baseline (8.01 versus 8.24 exchanges per cell) or after induction with the genotoxin thiotepa (23.32 versus 25.78 exchanges per cell). There were no differences between formaldehyde-exposed and control samples in unscheduled DNA repair rates at baseline (335.2 versus 341.9) or after treatment with hydroxyurea (179.8 versus 194.2). However, when treated with thiotepa, unscheduled DNA repair rates in lymphocytes from formaldehyde-exposed workers were lower than those from control workers (217.2 versus 270.4, $p<0.05$). Using another measure of mutagenicity, Ballarin et al. (1992) evaluated 15 nonsmoking workers (8 males, 7 females) who worked in a plywood factory for cytopathologic changes in nasal mucosal cells, and compared the results to matched controls. Mean levels of exposure to formaldehyde ranged from 0.07 to 0.08 ppm in the sawmill and shearing press departments to 0.32 ppm in the warehouse. The total range of exposure in all areas containing formaldehyde vapors was 0.06–0.49 ppm. Workers were also exposed to wood dust. Nasal mucosal cells from exposed workers exhibited significantly increased incidence of micronuclei (0.9 versus 0.25 for controls), chronic inflammation, and a significantly higher frequency of squamous metaplasia cells (histological score: 2.3 versus 1.6) than cells from control workers. Micronuclei were found mainly in the ciliated cells.

In another study, Connor et al. (1985b) tested urine obtained from hospital autopsy service workers exposed to formaldehyde and from matched control workers for cellular mutagenicity. Exposed workers had worked in the hospital for at least 6 months. Actual exposure to formaldehyde was determined to be from 0.1 to 5.8 ppm, using personal breathing zone monitoring; the TWA exposures to formaldehyde in work areas were estimated to be 0.61–1.32 ppm. Mutagenicity tests using *Salmonella typhimurium (S. typhimurium)* TA 100 and TA 98 were conducted, with or without rat S9 (microsomes containing cytochrome P-450) suspension. No increase was seen in mutagenicity using urine of exposed workers, compared to control urine. Addition of S9 had no significant effect on the genotoxicity of the urine.

Studies in laboratory animals have also demonstrated that formaldehyde can be genotoxic in some cells after inhalation exposure. Dallas et al. (1992) exposed male Sprague-Dawley rats to formaldehyde

concentrations of 0, 0.5, 3, and 15 ppm, by inhalation for 6 hours/day for 5 days. The rats were sacrificed, and their pulmonary macrophages and bone marrow cells were harvested and analyzed by flow cytrometry and cytogenetic analysis. Cell division was arrested using colchicine treatment (1 mg/kg) 2 hours prior to sacrifice. Five days after the beginning of exposure, formaldehyde-exposed groups exhibited no more than 4% chromosomal aberrations in the bone marrow cells, which was not significantly different from control values. There were no differences with respect to dose group. Chromatid breaks, chromosome breaks, and centric fusions were observed in bone marrow cells, but were not considered to be associated with formaldehyde exposure. An increase in chromosomal abnormalities in pulmonary macrophages, predominantly chromatid breaks, was observed in the 15 ppm group (7.5 versus 3.4% for controls) after 5 days of exposure. Small increases were also seen in the 0.5 and 3 ppm groups, but these were not statistically significant. No chromosome breaks or centric fusions were observed in control cells obtained by pulmonary lavage.

Dallas et al. (1992) also extended the exposure treatment time to 1 or 8 weeks. The rats were sacrificed after 1 or 8 weeks of exposure, and pulmonary macrophages and bone marrow cells were harvested and analyzed by flow cytrometry and cytogenetic analysis. Formaldehyde-exposed groups exhibited no more than 4% chromosomal aberrations in the bone marrow cells, which was not significantly different from control values. Chromatid breaks, chromosome breaks, and centric fusions were observed in bone marrow cells, and again, were not associated with formaldehyde exposure. With respect to pulmonary macrophages, an increase in chromosomal abnormalities was observed in the 15 ppm group (9.2 versus 4.8% for controls) after 5 days of exposure. Small increases were also seen in the 0.5 and 3 ppm group, but these were not statistically significant. The predominant cytogenetic damage was chromatid breaks, observed in both control and treated cells. No chromosome breaks or centric fusions were observed in control cells obtained by pulmonary lavage. In formaldehyde-treated animals, chromosome breaks and centric fusions were noted, but were not dose-related.

Lam et al. (1985) studied the effects of inhalational co-exposure to acrolein and formaldehyde in male Fischer 344 rats. Rats were exposed for 6 hours to room air (controls), 2 ppm acrolein, 6 ppm formaldehyde, or a combination of 2 ppm acrolein and 6 ppm formaldehyde. The animals were sacrificed immediately after completion of exposure, and their nasal tissues were harvested. The DNA was isolated and the aqueous and interfacial portions were collected separately. Exposure to formaldehyde significantly increased the percentage of interfacial DNA (12.5%), the specific portion of the DNA which contains the DNA cross linked to proteins, compared to rats exposed to room air only

(8.1%, $p<0.05$). Co-exposure to acrolein resulted in a further increase in the percentage of interfacial DNA (18.6%) which was significantly greater than the effect of formaldehyde alone ($p<0.05$). The authors concluded that simultaneous exposure to acrolein enhanced formaldehyde-induced DNA-protein cross linking.

Other genotoxicity studies are discussed in Section 2.5. More extensive evaluation of the genotoxic potential of formaldehyde is available (IARC 1995; WHO 1989).

2.2.1.8 Cancer

Human Studies Overview. The finding of nasal tumors in rodents exposed to high levels of airborne formaldehyde in the early 1980s (Albert et al. 1982; Kerns et al. 1983b; Swenberg et al. 1980) led to a concern for cancer effects in occupationally exposed workers. There are now more than 40 epidemiology studies examining the potential for occupational formaldehyde exposure to cause cancer in humans. The studies include cohort mortality studies of formaldehyde-exposed industrial workers, cohort mortality studies of formaldehyde-exposed professionals or medical specialists, and case-control studies that looked for associations between occupational exposure to formaldehyde and cancers of the nose, pharynx, or lung. Published reviews and evaluations of the epidemiology studies include early reviews by IARC (1987), Purchase and Paddle (1989), and an *ad hoc* panel convened by Universities Associated for Research and Education in Pathology (1988). More recent reviews have been published by Conaway et al. (1996), ECETOC (1995), IARC (1995), and McLaughlin (1994). In addition, three meta-analyses of the data have been published (Blair et al. 1990a; Collins et al. 1997; Partanen 1993). Although some of the epidemiological studies have found some scattered evidence for extra-respiratory site cancers in groups of formaldehyde-exposed workers, the data are not consistent across studies and adjustment for potential confounding cancer risk factors has not often been possible. Most, if not all reviewers, have agreed that cancer of the respiratory tract, particularly the upper respiratory tract, is more biologically plausible than formaldehyde-induced cancer at distant sites given the reactivity of formaldehyde, the capacity of tissues to metabolize formaldehyde, and the results from chronic rodent inhalation studies showing that formaldehyde-induced nonneoplastic and neoplastic effects are restricted to the upper respiratory tract with exposures to concentrations below 5–10 ppm. Accordingly, the meta-analyses of the human data have focused on the findings for respiratory cancer deaths in occupationally exposed humans.

Six mortality studies of the following cohorts of formaldehyde-exposed industrial workers are included in recent reviews and the meta-analyses: 26,561 U.S. workers involved in formaldehyde production, resin making, and several other activities using formaldehyde (Blair et al. 1986, 1990a); 7,660 workers in six British plants using formaldehyde (Acheson et al. 1984a; Gardner et al. 1993); 11,030 workers in three U.S. garment facilities (Stayner et al. 1988); 1332 Italian workers involved in resin making (Bertazzi et al. 1986, 1989); 3929 foundry workers exposed to formaldehyde (Andjelkovich et al. 1994b, 1995a); and 6,039 workers in a Conneticut chemical plant that included some of the workers from the Blair et al. study (Marsh et al. 1994, 1996). Data from the Blair et al. (1986) study have been independently analyzed by Sterling and Weinkam (1989, 1995).

In the industrial worker cohort studies, the range of standardized mortality ratios (SMR; see Table 2-2 for definitions of selected epidemiological terms) relevant to exposure to airborne formaldehyde were (a zero reflects a finding of no deaths from the subject cancer):

- for *lung cancer* - 0.9 to 1.4 (lung cancer deaths were reported in each cohort);
- for *nasopharyngeal cancer* - 0 to 3.0 (only the Blair et al. [1986, 1990a] study had nasopharyngeal cancer deaths: 6 observed versus 2 expected);
- for *nasal cancer* - 0 to 0.6 (Andjelkovich et al. 1994b, 1995a; Bertazzi et al. 1986, 1989; Marsh et al. 1994, 1996; and Stayner et al. 1988, however, did not report nasal cancer deaths); and
- for *buccal cavity and/or pharynx cancer* - 1.1 to 1.69 (only Bertazzi et al. 1986, 1989 did not report buccal cavity and/or pharynx cancer).

Small excess relative risks for buccal cavity and/or pharynx cancer and lung cancer were most consistently observed across these studies. The increases in risk were generally not of statistical significance with the exception of the Blair et al. (1986) report of an SMR of 3.0 (95% CI, 1.3–6.6) for nasopharyngeal cancer.

Nine mortality studies of the following cohorts of formaldehyde-exposed professionals or medical specialists are included in recent reviews and the meta-analyses: 2,079 British pathologists and 12,944 medical specialists (Harrington and Shannon 1975); 1,263 deceased New York embalmers (Walrath and Fraumeni 1983); 1,109 deceased California embalmers (Walrath and Fraumeni 1984); 1,477 Ontario funeral workers (Levine et al. 1984a); 2,317 U.S. anatomists (Stroup et al. 1986); 5,810 U.S. pathologists (Matanoski 1991); 5,585 U.S. pathologists (Logue et al. 1986); 4,046 deceased

Table 2-2. Definitions of Selected Epidemiology Terms

Standardized mortality ratio (SMR)	is the ratio of a cause-specific mortality rate in an exposed cohort during a given period to the mortality rate of an unexposed cohort; mortality rates are often adjusted for age or other confounding variables.
Proportionate mortality ratio (PMR)	is the ratio of a cause-specific mortality proportion in an exposed group to the mortality proportion in an unexposed group; mortality proportions may be adjusted for confounding variables such as age. Cause-specific mortality proportions can be calculated when the cohort (the population at risk) cannot be defined due to inadequate records, but the number of deaths and the causes of deaths are known.
Standardized proportionate incidence ratio (SPIR)	is similar to a PMR in that it is a ratio of a proportion of a specific disease in an exposed group compared with the proportion in an unexposed group.
Odds Ratio(OR) and Relative Risk (RR)	are risks expressed as ratios of the incidence of diseased subjects exposed to a particular risk factor to the incidence of diseased subjects in a nonexposed referent group.

members of U.S. funeral directors' organizations (Hayes et al. 1990); and 4,512 British pathologists (Hall et al. 1991).

In the professional worker cohort studies, the range of SMRs or proportionate mortality ratios (PMRs) for respiratory or buccal cavity sites were:

- for *lung cancer* - 0.1 to 1.1 (the group of New York State embalmers [Walreth and Fraumeni 1983] was the only cohort that showed an excess: 72 observed versus 66.8 expected);
- for *nasopharyngeal cancer* - 2.1 (the group of deceased U.S. funeral directors was the only professional cohort reporting this type: 4 observed versus 1.85 expected [Hayes et al. 1990]);
- *nasal cancer* deaths were either reported as zero or not reported among the nine professional cohorts;
- for *buccal cavity and/or pharynx cancer* - 0.2 to 1.3 (at least one buccal cavity and/or pharyngeal cancer death was noted in each of the professional cohorts).

Case-control studies examining potential associations between occupational exposure to formaldehyde and specific types of cancer include those of:

- *lung cancer* (Bond et al. 1986; Chiazze et al. 1993; Coggon et al. 1984; Gerin et al. 1989; Jensen and Andersen 1982; Partanen et al. 1985, 1990) with relative risks ranging from 0.6 to 1.1;
- *nasal cancer* (Brinton et al. 1984, 1985; Hayes et al. 1986; Hernberg et al. 1983a, 1983b; Luce et al. 1993b; Olsen et al. 1984; Rousch et al. 1987; Vaughan et al. 1986a, 1986b) with relative risks ranging from 0 to 12.6; and
- *nasopharyngeal cancer* (Olsen et al. 1984; Rousch et al. 1987; Vaughan et al. 1986a, 1986b; West et al. 1993) with relative risks ranging from 0.6 to 5.5.

The first two meta-analyses of the epidemiology studies (Blair et al. 1990a; Partanen 1993) took similar approaches to analyzing the same data, except that Partanen included three case-control studies not included in the earlier analysis. Both analyses calculated summary or aggregate relative risks for lung cancer, cancer of the nose and nasal sinuses, and nasopharyngeal cancer, and analyzed data from a subset of the available studies that were classified into "low/medium" or "substantial" exposure categories based on exposure level and/or duration of exposure information. Although different methods to calculate aggregate relative risks across studies were used in the two studies, similar results were obtained and conclusions reached.

In both analyses, aggregate relative risks for lung cancer deaths calculated for formaldehyde-exposed medical and nonmedical professionals were at or below those expected. Aggregate relative risks for lung cancer in industrial worker studies showed a small excess relative risk (1.1) in both analyses, but no evidence for an exposure-related increase in relative risk comparing the "low/medium" relative risks (1.2) with those of the "substantial" exposure class (1.0 or 1.1). Small excess aggregate relative risks for occupationally-exposed workers in all of the studies existed for cancer of the nose and nasal sinuses (1.1 [95% CI, 0.8–1.4] - Blair et al. 1990a; 1.1 [95% CI, 0.8–1.5] - Partanen 1993), and cancer of the nasopharynx (1.2 [95% CI, 0.8–1.7] - Blair et al. 1990a) and 2.0 [95% CI, 1.4–2.90] - Partanen 1993). Relative risks for both types of cancer increased with increasing exposure intensity in Table 2-3.

Both Blair et al. (1990a) and Partanen (1993) concluded that a causal role for formaldehyde in the induction of the observed cancers of the nasopharynx and nasal cavities was supported by their evidence for exposure-response relationships, the portal-of-entry site of these cancers, and the consistency of these findings with results from animal studies.

A third meta-analysis by Collins et al. (1997) arrived at the conflicting conclusion that the available studies do not support a causal relationship between formaldehyde exposure and nasopharyngeal cancer. This study analyzed data from essentially the same case-control studies, but included a few cohort mortality studies that were not available or included in the earlier meta-analyses (e.g., Andjelkovich et al. 1994b, 1995a; Gardner et al. 1993). Collins et al. (1997) noted that nasopharyngeal cancer rates were elevated in a minority of the available studies, that most studies did not find any nasopharyngeal cancers, and that many studies did not report on nasopharyngeal cancer. Unlike the calculational techniques used in the previous meta-analyses, a calculational technique was used to adjust for underreporting of expected mortality rates in the calculation of "weighted meta relative risks". Meta relative risks (with 95% CIs) for nasopharyngeal cancer were 1.0 (0.5–1.8) for the 14 cohort studies included in the analysis, 1.2 (0.4–2.5) for the six industrial worker cohort studies, and 1.3 (0.9–2.1) for the seven case-control studies. Collins et al. (1997) concluded from their review of the available studies that exposure estimates for the case-control studies were both lower and less certain than exposures in the industrial worker cohort studies, and that their analysis does not support an exposure-response relationship between formaldehyde and nasopharyngeal cancer.

Recent reviews of the available epidemiology studies arrive at differing conclusions. NTP (1998) notes that formaldehyde is reasonably anticipated to be a human carcinogen. IARC (1995) concluded, "Taken

Table 2-3. Meta-analysis of Epidemiology Studies of Cancer of the Nose and Nasal Sinuses and Nasopharyngeal Cancer

Cancer site	Level or duration of exposure to formaldehyde							
	Low/medium				Substantial			
	O/E[a]	RR[b]	O/E	RR	O/E	RR	O/E	RR
	Blair et al. 1990a		Partanen 1993		Blair et al. 1990a		Partanen 1993	
Nose and nasal sinuses	38/46	0.8 (0.6–1.1)	33/30	1.1 (0.7–1.8)	30/28	1.1 (0.7–1.5)	36/21	1.7 (1.0–2.8)
Nasopharynx	30/27	1.1 (0.7–1.6)	23/16	1.6 (1.0–2.7)	13/6	2.1 (1.1–3.5)	11/4	2.7 (1.4–5.6)

[a] Observed/Expected cancer deaths
[b] Relative risk (with 95% CI); CIs for the Blair et al. 1990a entries were calculated by Partanen (1993).

together, the epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases in the cohort studies". IARC's overall evaluation that formaldehyde is probably carcinogenic to humans (Group 2A) was based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals. EPA (1991a) classified formaldehyde in Group B1 - probable human carcinogen, based on an evaluation of limited human evidence and sufficient laboratory animal evidence. More recently, in a collaborative review and evaluation of the formaldehyde epidemiology studies, EPA and CIIT (CIIT 1998) concluded, "It appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out." Adopting another view, McLaughlin (1994) concluded, "Clearly, the causal criteria used by epidemiologists to evaluate an association, such as strength of the association, consistency, specificity, dose-response, plausibility, and coherence, are not satisfied by the epidemiologic studies in the formaldehyde-cancer research domain". ECETOC (1995) similarly concluded, "After a careful review of the cytologic, cytogenic and epidemiological studies there is an absence of evidence to support the judgement of an etiologic relationship between formaldehyde and human cancer risk."

Selected Cohort Mortality Studies. Blair et al. (1986) performed a historical cohort study to evaluate the mortality experience of 26,561 workers in 10 formaldehyde-producing or -using workplaces. TWA exposures to formaldehyde were estimated to range from trace amounts to >2 ppm. The mortality experience of workers exposed to workplace air concentrations $0.1 ppm was compared with that of "nonexposed" workers in the cohort exposed to concentrations <0.1 ppm. Using national rates of mortality as reference, greater than expected mortalities for a number of cancer types were noted in the exposed group, but the elevated rates of mortality were not statistically significantly different than national rates. Types of cancers with elevated SMRs included: Hodgkin's disease (SMR=1.42); and cancers of the liver (SMR=1.02); larynx (SMR=1.42); lung (SMR=1.11); bone (SMR=1.23); prostate (SMR=1.15); and kidney (SMR=1.23). The nonexposed group generally showed less than expected deaths from these cancers, (i.e., SMRs<1.00) Mortality from selected cancers were also compared among several subgroups of the cohort with varying exposure-concentration experiences. Among the aforementioned cancers, only deaths due to Hodgkin's disease exhibited a dose response. No individual exposure category SMR, however, was significantly elevated, and comparisons of the SMRs across different exposure categories is inappropriate for this indirectly adjusted measure. No unusual cancer patterns were noted among white women or black men. Among subsites of the buccal cavity, the nasopharynx had a significantly greater than expected incidence (7 cases observed versus 2.2 cases

expected) of cancer. This study demonstrated that there was insufficient evidence to firmly associate occupational formaldehyde exposure with the observed cancers, even when considering that the SMRs for the unexposed workers were small. No consistent correlation was noted between cumulative exposure and the risk of any cancer. This study used a cohort study design with a large study population. Additional strengths of this study included the fact that experienced nosologists assigned the cause of death and in addition to the SMR analysis based on vital statistics data, the study also included analyses using internal comparison groups. Industrial hygienists made estimates of the intensity of formaldehyde exposures using all available sources of information (most similar studies estimated only the duration). Overall, the analysis was very thorough and allowed for different exposure intensity levels and different possible "latency" periods between exposure and death. The investigators attempt to rule out confounding factors from socioeconomic status, and the follow up was good overall (95%), although it was only 83% for women. Weaknesses included the fact that death certificate data can often be inaccurate, so some cancers of interest could have been missed. Also, no information about tobacco use or other nonoccupational exposures was available.

In a later study by Blair et al. (1990b), the risk of lung cancer was assessed among 20,714 white male workers exposed to formaldehyde in 10 production plants. The estimated average levels of exposure were 0.1–1.9 ppm formaldehyde. The overall risk of lung cancer did not appear to be correlated with average formaldehyde levels in each plant. Among the exposed sample, the SMRs did not increase consistently with any measure of exposure. The SMR for those with cumulative exposures of <0.5 ppm-year was 1.3, while the SMR for those with >5.5 ppm-year was 1.7. The risk of lung cancer did not increase with the time from last exposure; however, the risk did increase based upon the year of entry into the industry. Among the >20-year latency group, those beginning employment prior to 1958 had a greater risk of cancer than did those beginning work in 1958 or later (SMR=1.4). Those exposed to formaldehyde at or after the age of 35 were more likely to have lung cancer than those exposed prior to age 35 (SMR=1.3). The interaction of formaldehyde with other noxious substances was investigated and the results suggested that those exposed to formaldehyde were not at risk of cancer unless exposed to another substance. The authors concluded that no clear exposure-response trends could be identified from the data. Strengths and weaknesses of this study were basically the same as those described in the Blair et al. (1986) study.

Data from the Blair et al. (1986) study were reanalyzed by Sterling and Weinkam (1989, 1995) to account for the healthy worker effect. The cohort was composed of all workers employed in 10 selected

plants. For lung cancer mortalities, mortality risk increased with cumulative exposure, approaching statistical significance in all workers with cumulative exposures of >2 ppm-years. The authors concluded that, when comparing workers with high formaldehyde exposures to those with little or no exposure, there is an increased risk of lung cancer associated with exposure to formaldehyde.

Harrington and Shannon (1975) examined a population of 2,079 British pathologists and 12,944 medical laboratory technicians or pathologists between January 1, 1955 and December 31, 1973. During that period, 154 technologists and 156 pathologists died, and copies of all death entries were obtained. The SMR was 60 for pathologists and 67 for medical technologists. Excess deaths from lymphatic and hematopoietic neoplasms were noted in male pathologists (observed 8, expected 3.3, $p<0.01$). No other neoplastic diseases were noted as causing excess mortality in either occupational group. It should be noted that the study group was too small for any firm conclusions to be drawn about the carcinogenicity of formaldehyde exposure in humans. No records were available and no adjustment was made for smoking or other possible confounding factors.

Levine et al. (1984a) studied the mortality patterns of 1,477 male undertakers licensed from 1928 to 1957 (dose not specified). The numbers of deaths due to malignant neoplasms (SMR=0.87) and specific cancers (SMR=0.52–1.24) were not significantly elevated. Mortality due to nonmalignant diseases was slightly elevated, but could not be clearly related to the inhalation of formaldehyde. Strengths of this study include the following: a cohort design with a high rate of success for ascertaining vital status (96%), death certificates obtained for most decedents, and underlying cause of death coded by a trained nosologist. Several apparent weaknesses should be noted, including the sample size, which was small for detecting rare outcomes of disease. Exposure levels to formaldehyde were low, and the undertakers did not necessarily engage in embalming work, so the exposures may have been too low to cause mortality excesses. Death certificate data are often inaccurate, so some cancers of interest could have been missed. Exposure began in the late 1920s, but the 40 deaths that occurred before 1950 (13% of all deaths) were excluded from the analysis. These earlier decedents could have had higher exposure levels than those who were still alive in 1950, so a potentially important source of information was unavailable due to data constraints for the reference population.

Harrington and Oakes (1984) established a population of 2,307 men and 413 women to study the incidence of cancer induction due to formaldehyde exposure in humans. During the study period, 126 of these pathologists died; death certificates were obtained for 121 of them. Observed and expected deaths

from all causes and from certain specific causes were reported as well as the corresponding SMR for observed deaths as a percentage of expected deaths. Excess deaths from brain tumors were found (observed 6, expected <2, $p<0.02$), but no nasal cancers were found. Strengths of this study included the use of a cohort design and a very low rate of follow up loss (0.6% for pathologists and 1.5% for medical laboratory technicians). The study also achieved some adjustment for possible confounding effects of socioeconomic status for one of the analyses by comparing the study cohort mortality experience with that of other medical groups, although that analysis could only examine broad categories of death. Weaknesses of this study included the fact that specific exposures or their possible levels were not identified for the two cohorts (there is no mention of formaldehyde exposure). The follow up period (19 years maximum for pathologists and only 11 years for the technicians) was somewhat short, but it is unclear whether exposures may have occurred before the beginning of the follow up period. Moreover, the modest number of pathologists (n=2,079) results in low statistical power for detecting any excesses of rare outcomes. It was also noted that for the primary analysis, there presumably were substantial socioeconomic differences between the cohort members and the reference population, so confounding could have occurred. Because the SMR is an indirectly standardized measure (i.e., it uses internal weights), the comparison of SMRs across occupational groups was considered to be inappropriate.

Walrath and Fraumeni (1984) performed a proportionate mortality study of 1,007 white male embalmers in California from 1916 to 1978 who were known to have died between 1925 and 1980. Total cancer mortality was significantly elevated, with PMR of 1.21. Deaths from cancers of the brain and the nervous system (PMR=1.94), colon (PMR=1.87), prostate (PMR=1.75), and leukemia (PMR=1.75) were significantly higher than expected. The reported types of brain cancer were for glioblastoma (2), astrocytoma (3), adenocarcinoma (1), and unspecified cancers (3). No increase in mortality for cancers of the respiratory tract, including the nasal passages was noted in this study. A parallel mortality study of embalmers from New York State (Walrath and Fraumeni 1983) showed similar findings with significant excess of deaths from cancers of the brain and nervous system (PMR=1.56), colon (PMR=1.43), ischemic heart disease (PMR=1.12), and nonsignificant excess of cirrhosis of the liver (PMR=1.33), and leukemia (PMR=1.40). PMRs were significantly elevated for cancers of the skin, kidney, and brain among those who were licensed only as embalmers. Even with these findings, the authors suggested that a more thorough investigation was needed to quantify the risks of cancer and other chronic diseases in relation to formaldehyde exposure. Strengths and weaknesses for both of these studies are similar. Strengths included the fact that formaldehyde was probably the primary chemical exposure for this PMR analysis of embalmers, although embalming fluid does include smaller amounts of other chemicals

(methanol, diethylene glycol, propylene glycol, phenol, benzoic acid, fragrances, etc.). Exposure durations and follow up periods were probably long enough for the study to detect any cancer excesses associated with formaldehyde exposure, although details about individual decedents were unavailable. For the final analysis, death certificates were available for a large percentage (92%) of the identified decedents. A trained nosologist coded the underlying cause of death for all death certificate using the coding rules in effect at the time of each death. Therefore, the assignment of the cause of death should have been comparable to that used for standard (comparison) population. The analysis controlled for potential confounding effects from age, race, sex, and calendar year. Several weaknesses of this study were also noted. In general, PMR studies have a relatively weak design compared to other types of studies. The analysis included only those deaths reported to the Bureau of Funeral Directing and Embalming, and the completeness of this reporting is not known. The authors indicate that deaths at ages >65 years were substantially under reported. Consequently, the causes of death in the analysis could have differed systematically from the causes found in the total population of deceased embalmers (e.g., for chronic conditions that led to death at older ages). The total U.S. population was used as the external comparison population, even though rates from New York state would probably be stable enough to provide expected values. Possible regional differences in cancer incidence (rather than occupational exposures) could have affected the observed pattern of mortality excesses and deficits. Study weaknesses included that cancer deaths are often reported inaccurately on death certificates. Exposure levels for formaldehyde were unknown, no analyses that combine the white and black decedents (with appropriate adjustment) were presented, even though there were similarities in the pattern of excess deaths. A combined analysis presumably would have greater statistical power. Lastly, the expected number of deaths for nasal cancer, an end point of particular interest, was only 0.7, so the study had low statistical power to detect an excess of this cancer.

Stroup et al. (1986) evaluated the risk of death due to cancers and other causes in 2,317 anatomists in a retrospective cohort study. Of the 2,317 in the study population, 33% (n=738) were known to have died. SMRs for deaths due to various cancers in anatomists was variable; the only condition with a significantly elevated SMR (SMR=2.7, $p<2.25$) was brain cancer. All of the anatomists that died of brain cancer were in either gross anatomy, microanatomy, or a combination of the two, indicating relatively high exposures to formaldehyde. The authors concluded that there was a substantial risk of brain cancer among anatomists, but since these anatomists were also exposed to a large number of biological stains and solvents, in addition to formalin and formaldehyde, the etiologic agent responsible for these results was not certain. This study has several strengths and weaknesses. The study of the anatomists used a

classic retrospective cohort design with a well defined denominator; follow up was at least 10 years for all cohort members. Follow up and death certificate acquisition was good and a trained nosologist coded the underlying cause of death for all cohort members. In addition to using national disease rates for the SMR analysis, the authors also used mortality rates from a cohort of psychiatrists, who presumably have similar demographic and socioeconomic characteristics compared with the anatomists. Subgroups of anatomists were studied in an attempt to separate possible effects of formaldehyde from those of other occupational chemical exposures. Among the study weaknesses was the fact that exposure levels for formaldehyde were unknown and occupational exposures to chemicals other than formaldehyde (or to viruses) could have been responsible for the observed cancer excesses. Diagnoses from death certificates are unreliable, but the use of the psychiatrist comparison group helps eliminate the possibility of differential disease misclassification (i.e., detection bias). The low expected number of deaths (0.5) for cancer of the nasal cavity and sinus indicates that the study had low statistical power for detecting an excess of nasal cancer.

Stayner et al. (1985a, 1985b, 1988) evaluated the carcinogenicity of formaldehyde in garment workers by performing a proportionate mortality study of 256 deaths reported from three shirt-manufacturing plants. All three plants had processed formaldehyde-treated fabrics since 1958 and the duration of employment for the study group averaged 9.4 years. Air monitoring in two of the plants revealed that virtually all employees were exposed to 0.1–1 ppm formaldehyde. Statistically significant excesses in mortality were detected for cancers of the buccal cavity (PMR=7.50), biliary passages and liver (PMR=3.13), and other lymphatic and hematopoietic sites (PMR=4.00). The number of deaths in each organ category was low; hence, the degree of confidence in PMRs and in the conclusion that cancers are associated with formaldehyde exposure must also be low. Stayner concluded that, based upon factors such as the long latency period and lack of exposure to other known carcinogens, the excesses in mortality in garment workers due to cancers of the buccal cavity, biliary passages and liver, and other lymphatic and hematopoietic sites were likely associated with formaldehyde exposure. There was no attempt to adjust the cancer rate for smoking or other confounding factors, and no air sampling records were evaluated. Later, Stayner et al. (1988) examined the relationship between formaldehyde exposure and the development of upper respiratory cancers in garment factory workers. A total of 2,008 men and 9,022 women from three garment factories had a formaldehyde concentration exposure geometric mean value of 0.15 ppm (range 0.14–0.17 ppm). Across all workers, mortality from all causes was less than expected, as was mortality from all malignant neoplasms. However, significantly ($p<0.05$) greater than expected mortalities were detected for the buccal cavity (SMR=3.43) and connective tissue (SMR=3.64).

Nonsignificant elevations were also noted for the trachea/bronchus/lung (SMR=1.14), pharynx (SMR=1.13), bladder (SMR=1.12), leukemia and aleukemia (SMR=1.14), and other lymphopoietic neoplasms (SMR=1.70). When stratified by sex and race, white females had significant excesses of buccal cavity cancer (SMR=4.85). When stratified by latency period, cancers of the buccal cavity (SMR=7.05) and leukemia (SMR=3.10) were significantly elevated for workers with latencies of 20 years or more, while cancers of the trachea/bronchus/lung (SMR=1.71) were significantly elevated among workers with latencies of >10 years. When stratified by duration of exposure, mortalities due to cancers of the buccal cavity (SMR=7.57) and other lymphopoietic neoplasms (SMR=3.81) were significantly elevated for workers with exposure durations of 10 years or more, while mortalities due to connective tissue cancers were significantly elevated in workers exposed for 4–9 years (SMR=6.19). Mortalities due to cancer of the trachea/bronchus/lung appeared to be inversely related to duration of exposure. In their discussion, the authors stressed that, while no excesses in nasal cancer were seen, the power of the study was too low to detect an effect for this rare cancer. Also, the authors noted that the patterns seen in trachea/bronchus/lung cancers (most prevalent in short duration/latency groups) were inconsistent with normal dose-response patterns; this was also attributed to a lack of statistical power. A strength of this study is that the cohort study design is more powerful than the PMR design used in the earlier study (Stayner et al. 1985a, 1985b) that included some of the same workers. As in the earlier study, confounding factors from other occupational exposures were unlikely. Vital status was ascertained for a very high proportion of the cohort members (96%). The authors also used various sources to verify the employment histories and vital status of the workers and the analyses of mortality by duration of exposure add credibility to the observed cancer excesses (i.e., the risk was positively associated with duration of exposure). Some of the weaknesses were the same as in the authors' earlier PMR study: exposures that may have been too low to cause a detectable increased risk of mortality and historical exposures that may have been higher, but with unknown levels. Because of the small study population, the study had only modest statistical power to detect possible excesses of rare outcomes. Death certificate data are often inaccurate, so some cancers of interest could have been missed. The authors attempted to rule out possible nonoccupational confounding factors with mixed results. For example, at least two of the four who died from buccal cancer had a history of tobacco use (one had used snuff, a fairly strong risk factor for buccal cancer). The authors concluded that the results of the study should be viewed with caution, due to limited statistical power and latency periods and the possibility of other confounding factors.

Bertazzi et al. (1986) attempted to correlate occupational exposure to formaldehyde with cancer rates in male resin workers using SMR analysis. Based on job descriptions, workers were divided into three groups: "exposed to formaldehyde", "exposed to other chemicals", or "exposure unknown". An analysis of the death rates revealed a significantly ($p<0.05$) elevated rate of deaths from all cancers when compared to the national rates (SMR=1.54); however, significance declined when the cohort was compared to the local population trends (SMR=1.06). Among individual cancer types, significantly elevated SMRs were detected for lung cancer against the national and local trends (SMRs=2.36 and 1.86, respectively). Deaths from hematologic neoplasms were elevated (SMRs=1.54 and 2.01), but not significantly. When the cohort was divided by chemical exposure, the group exposed to formaldehyde tended to have elevated SMR values; however, the trends were not significant. The authors concluded that, in addition to the significantly elevated lung cancer mortality rate among all workers, the mortality rates among formaldehyde-exposed workers for all cancers, and cancers of the alimentary tract, lung and blood system were noteworthy, although nonsignificant. Study strengths included a cohort design with high rate of follow up (98.6%); formaldehyde exposure levels that were apparently high (although not well characterized); and past exposures that were not measured but were presumably higher. It appears that most workers with formaldehyde exposure had not been exposed to other chemicals in the plant (although this point was not made completely clear by the authors). Subanalyses looked at SMRs with regard to duration of employment and by formaldehyde exposure status. Some apparent weaknesses of this study were that the cohort was too small (1,332 persons) to detect increases in rare diseases and that the follow up period after formaldehyde exposure was somewhat short (as noted by the authors), so that exposure-related cancers with long latency periods might not have had time to appear during the course of this study. Environmental measurement data were very sparse and detailed work history records were unavailable for most cohort members, so “reconstructions” were obtained through interviews of past workers and others (few details were provided). No exposure levels were provided for 18% of workers. Data for individuals with regard to potential confounding variables were unavailable, and no information was provided on the assignment of the cause of death codes used in the SMR analyses.

Gardner et al. (1993) assessed the risk of disease and cancers among British male chemical workers exposed to formaldehyde. The cohort for the study consisted of 7,660 men who began employment prior to 1965 and 6,357 men who began employment after 1964. Formaldehyde exposure ranged from <0.1 to >2 ppm. There was one death from nasal cancer and no deaths from nasopharyngeal cancer, nor were any nonfatal cases of nasopharyngeal reported. Among lung cancer cases, there was no association of cancer with formaldehyde exposure. Among men classified as exposed to the higher end of possible

exposure levels of formaldehyde, there was no indication of a relationship between cancer and duration of employment, and no association between cancer and cumulative dose. In those employed prior to 1965, there was a significant excess of lung cancer, with the authors stating that the increase was probably due to smoking and other environmental pollution. This appears to be related to one factory in which more men were exposed to high levels of formaldehyde. The determination of exposure levels in this study was crude and the information on co-exposure to other chemicals was not analyzed. The possibility of dermal exposure cannot be ruled out in many of these workers. Strengths of this study included the cohort design, with careful checks of member eligibility and systematic assignment of estimated exposure levels. SMR analyses use disease rates from local populations to help avoid potential biases due to regional differences in disease rates and the long follow up period allows time for the manifestation of any exposure-related cancers. Weaknesses of this study included the observation that no actual measurements of formaldehyde exposure levels occurred, but the investigators did undertake a detailed estimation procedure for classifying expected exposure levels. There were also potential confounding factors from other occupational exposures. In addition, the procedure for assigning the underlying cause of death for cohort members was not explicitly described, and comparisons of the SMRs across different exposure categories is inappropriate for this indirectly adjusted measure. The authors presumably could have used a regression modeling approach to explore possible dose-response associations without the need for an external referent population. A pronounced "healthy worker effect" is typically expected in this type of cohort study for all-causes mortality, but only one of the six factory populations showed an SMR <0.95, even for workers who were hired relatively recently. The authors may have overlooked this indirect evidence of a health hazard in the factories.

Andjelkovich et al. (1990) examined mortality in a cohort of 8,147 foundry workers who worked in an automobile manufacturing plant for at least 6 months between 1950 and 1979. For the observation period of 1950 through 1984, a significant excess was found for lung cancer mortality, but most of the excess of lung cancer deaths was accounted for by smoking habits. In a subsequent nested case control study of this cohort that examined risk factors for 220 cases of lung cancer mortality that occurred between 1950 and 1989 compared with 2,200 age- and race-matched controls without lung cancer, cigarette smoking was a strong predictor of lung cancer mortality, but exposure to formaldehyde was not significantly associated with lung cancer (Andjelkovich et al. 1994b). In a final phase of these studies, Andjelkovich et al. (1995a) studied the mortality experience (for the period between 1960 and 1989) of a subset of 3,929 members of the cohort who were exposed to formaldehyde in the foundry during the period of January 1960 through 1987, and compared it to the experience of a referent, nonexposed

population of 2,032 men who worked at the foundry, but not in formaldehyde-exposed jobs. The year 1960 was chosen as the starting point of the study because it was the year that formaldehyde was introduced into the operations used in the foundry. Exposure to formaldehyde was assessed via work histories and was ranked as high, medium, low, or none (but exposure concentration ranges were not reported). In the exposed group, elevated SMRs (calculated using national rates for comparison) were found for deaths from several cancer types, but the elevation was not statistically significant for any cancer type. Cancer types with elevated SMRs were (with SMRs noted in parentheses): buccal cavity and pharynx (1.31); stomach (1.64); rectum (1.17); trachea, bronchus, and lung (1.20); and urinary organs (1.13). Similar SMRs were found for the nonexposed control group. Because of the findings from animal studies of formaldehyde-induced nasal tumors, special attention was given to malignant and non-malignant diseases of the respiratory system (cancers of the buccal cavity and pharynx, larynx, or trachea, bronchus, and lung, and emphysema), but comparison of the cause-specific mortality between the exposed and nonexposed groups showed no statistically significant difference, except for a significantly elevated SMR for emphysema in the nonexposed group.

Strengths of the Andjelkovich et al. (1990, 1994b, 1995a) studies included the nested case-control design, which provided a high degree of efficiency while ensuring that the controls were selected from the same population that gave rise to the cases. Incidence density sampling of controls leads to an unbiased estimate of the mortality rate ratio. The use of conditional logistic regression analysis enabled appropriate adjustments for covariates and attempts to control for effects of cigarette smoking appeared to be fairly successful, although the response rate for collecting the smoking information was less than ideal (about 70%). In addition, the follow up duration was long enough for exposure-related lung cancer excesses to appear, and the data analysis allowed for "latency" periods of different duration. Industrial hygienists estimated the exposure levels for formaldehyde as well as for silica, a potential confounder of the formaldehyde-cancer association. There was no opportunity for "recall bias" (except for the smoking information, which was collected from cohort members or their families). Study weaknesses were related to lung cancer information, which came almost exclusively from death certificates, which can be inaccurate. Tumor histology information was unavailable. It seemed apparent that no actual measurements of formaldehyde exposure levels were available, although some silica measurements were available. The study authors point out that a only a modest proportion of the cohort was exposed to formaldehyde, so the statistical power of the study was somewhat low. However, the estimated odds ratios indicate a lack of association that would presumably be unaffected by an increase in the study's sample size.

Selected Case-Control Studies. Luce et al. (1993b) attempted to determine whether occupational exposure to formaldehyde was associated with an increased risk of sinonasal cancer in humans. Case subjects were patients with primary malignancies of the nasal and paranasal sinuses. Odds ratios for squamous cell carcinomas in formaldehyde-exposed workers, when adjusted for wood dust and glue exposure, were not significantly elevated. The odds ratio for adenocarcinomas was confounded by the frequent co-exposure to wood dust, a known carcinogen. However, in those exposed to wood dust, an increased odds ratio was noted in those also exposed to formaldehyde. The authors concluded that the data did not support an increased risk of nasal cancers due to formaldehyde alone.

Partanen et al. (1985), in a case-referent study, attempted to determine whether respiratory cancer was associated with formaldehyde exposure in woodworkers. Anatomic sites classified as "respiratory cancers" included the tongue, mouth, pharynx, nose, sinuses, larynx, epiglottis, lung, trachea, and "other". Fifty-seven male production workers diagnosed with respiratory cancers were selected, with the average level of formaldehyde exposure being 1 ppm and the average duration of exposure being 10 years. The odds ratios for respiratory cancers due to formaldehyde, adjusted for latency periods, peak exposures, or co-exposures, were statistically significant. The authors concluded that a positive relationship between respiratory cancers and formaldehyde exposure could not be substantiated, because 87% of the workers exposed to formaldehyde were also exposed to wood dust, a known nasal carcinogen. The strengths of this study were that cases and controls were sampled from a large cohort, so the population at risk is well defined. Exposure status was determined from a review of work histories (blinded with regard to disease status), so recall bias was avoided. Some air measurements were available for assessing exposure levels. The investigators used a fairly elaborate exposure matrix approach to classify cases and controls with regard to exposure status, and at least some control for potential confounding effects from other occupational exposures and cigarette smoking was possible. Study weaknesses included the notation that the cohort was too small for studying nasal cancer; there were no reported cases, and the expected number of cases in the total cohort was <1. In addition, smoking information was missing for a large proportion of cases and controls, and there was high correlation between formaldehyde and wood dust exposures, so it was difficult to separate their respective effects. The breaking of the matched case-control pairs in the analysis can lead to inflation of the odds ratio even if the analysis stratifies by levels of the matching variables.

In a later study, Partanen et al. (1990) performed a retrospective study that attempted to determine the association of respiratory cancer (136 cases, 408 controls) with formaldehyde exposure; this case control

study was nested in a total cohort of 7,307 woodworkers having had a minimum level of 0.1 ppm and a minimum cumulative exposure of 3 ppm months to formaldehyde. The odds ratio for respiratory cancers in exposed versus unexposed workers, when corrected for vital status, smoking, and a latency period of 10 years, was not statistically significant. The strengths were that the study population was an expansion of that used in the authors' earlier study (Partanen et al. 1985). Additional industries were added and the follow up period was extended, so the number of workers with respiratory cancers was considerably larger. The strengths and weaknesses were essentially the same as those in the earlier study. However, there were improvements over the initial study. First, the study's statistical power was greater due to the larger sample size. Second, the authors conducted a more proper analysis by using conditional logistic regression modeling that preserved the matched sets of cases and controls (the earlier analysis broke the matched sets). Lastly, the authors presented some separate analyses for lung cancer cases and upper respiratory cancer cases, so that more homogeneous groups of respiratory cancers that might have different etiologies were analyzed separately.

In a study by Roush et al. (1987), the potential for mortality from nasopharyngeal cancer and sinonasal cancer associated with occupational exposure to formaldehyde was investigated. Cases of nasopharyngeal and sinonasal cancer were identified through the Connecticut Tumor Registry; the list was restricted to males with these cancers who died in Connecticut during the period 1935–1975. Controls were obtained from men dying in Connecticut during the same time period. Information on the death certificate was used to search for information on the subjects' work history. The work history information was used by an industrial hygienist to classify each subject into formaldehyde exposure categories based on likelihood and level of exposure. For those with probable exposure at some point at least 20 years before death, the odds ratio for nasopharyngeal cancer was 2.3. The odds ratio increased to 4 in the same group when narrowed to those dying at the age of $68. When frequencies of cancers were analyzed by occupation, the odds ratio for developing either cancer in the rubber industry was elevated (2.2), but not significantly. All four printers developed cancer. The authors concluded that there is an increased risk of nasopharyngeal cancer associated with probable exposure to formaldehyde; further, they concluded that the association is latency- and age-dependent. The authors suggest that the cause of sinonasal cancer in printers may be due to the presence of mineral oil mist, which has previously been associated with sinonasal cancer in the metals industry. Strengths of this study included a fairly large number of cases and a clinical review of medical records conducted for 75% of cases to confirm the diagnosis. Weaknesses included the fact that all cases and controls were deceased, and the possibility that risk factors for nasopharyngeal or sinonasal cancer that also increase the risk of death from other

causes (e.g., cigarette smoking) could be over represented in the control groups (a conservative bias would disguise exposure-disease associations for nasal cancer). Occupational information was ascertained from death certificates and city directories, so substantial exposure misclassification was likely. Information about possible occupational or nonoccupational confounders was lacking, as persons with formaldehyde exposures may also have had other carcinogenic exposures. The low prevalence of substantial formaldehyde exposures among study participants leads to low statistical power for detecting exposure-disease associations. This study is also limited because it was dependent on indirect information in creating the exposure index, nonoccupational exposures to formaldehyde were not addressed, and exposure to other potentially causal agents was not addressed.

Hayes et al. (1986) attempted to determine the environmental factors associated with nasal cancers in males from the Netherlands. A total of 91 case and 195 control subjects were included in the study. Patients or, if already deceased, close relatives completed interviews concerning work, smoking, and drinking histories. Based on these interviews, subjects were classified based on probability and level of formaldehyde exposure. The relative risk (measured as the odds ratio) of adenocarcinomas of the nasal cavity and sinuses was elevated (11.3) for those working in the wood and paper industries; the relative risk for all other cancers was not elevated. The relative risk for squamous cell carcinomas associated with formaldehyde exposure was significantly elevated ($p<0.05$) when the data were adjusted for wood dust exposure. Adjustments for smoking did not perceptibly change the relative risk. The authors concluded that formaldehyde may be a human carcinogen, but conceded that the study's limitations (questionable exposure conditions) prevented conclusive statements. Although the authors describe this case-control study as having low statistical power, they included a substantial number of persons with nasal cancer (n=116) given the rarity of this tumor. The study included incident (rather than prevalent) cases. Tumor histology information was available and trained industrial hygienists, who were unaware of each participant's case/control status, estimated the potential for formaldehyde and wood dust exposure for each reported job. The study collected fairly extensive information about exposures and potential confounders. Regarding study weaknesses, no actual exposure measurements were available for cases or controls. The disagreements between the two industrial hygienists demonstrate the inherent inaccuracy of the exposure assessment (the exposure misclassification presumably caused a conservative bias). Because the study relied on interview data for assessing exposures, possible "recall bias" could have led to over reporting of exposures by cases (or their next-of-kin) compared to controls. Although industrial hygienists estimated the potential for formaldehyde exposure based on reported jobs, the cases compared to controls may have been more likely to remember and report jobs that involved chemical

exposure. In addition, next-of-kin interviews were necessary for a substantial number of cases. Response rates were fairly low (64%) for next-of-kin interviews for cases as well as controls, and those who chose to participate (especially among families of deceased cases) compared to nonparticipants may have been those who tended to be aware of jobs held by the decedent that involved chemical exposures.

Hansen and Olsen (1995) investigated the risk of cancer due to occupational exposure to formaldehyde in Danish male workers. A total of 126,347 men born between 1897 and 1964 and diagnosed with cancer during the period of 1970–1984 were identified from the Danish Cancer Registry. The risk of cancer at a specific site was estimated from the standardized proportionate incidence ratio (SPIR), which was the proportion of cases of a specific cancer among workers from formaldehyde-associated industries versus the number of cases of the same cancer among all Danish workers. Of the 91,182 subjects with a full employment history, 2,041 had their longest length of employment at least 10 years prior to their cancer diagnosis. Among these 2,041 subjects, there were significant increases in the relative risk of cancers of the sinonasal cavity (SPIR=2.3), kidney (SPIR=1.3), and colon (SPIR=1.2). When analyzed by intensity of formaldehyde exposure and co-exposure to wood dust, there was a significant elevation in sinonasal cancers among workers exposed to formaldehyde and wood dust (SPIR=5.0) and workers moderately exposed to formaldehyde and probably not exposed to wood dust (SPIR=3.0). Workers with a low exposure to formaldehyde had a SPIR close to unity. The authors concluded that the increased incidences of kidney and colon cancers were biologically irrelevant due to the rapid metabolism of formaldehyde. Strengths of this study included the observation that this population-based proportionate morbidity ratio study used the entire adult white male population of Denmark as the population at risk. The determination of exposure status required at least a 10-year interval between first potential exposure to formaldehyde and the diagnosis of cancer (although a longer interval may have been more appropriate) and, because the study used cancer incidence (rather than mortality) based on cancer registry records, disease misclassification was probably low. Several weaknesses were also noted in this study. First, the exposure classification was crude and was based on having worked in a company that used or manufactured at least one kilogram of formaldehyde per worker (no exposure measurements were available), and it was based solely on the longest job held. Exposure misclassification is therefore likely. In the extreme case, some workers classified as “exposed” could have had shorter exposure durations than some who were classified as unexposed. The study authors point out that the study excludes exposures that occurred before April 1964, so nondifferential exposure misclassification probably occurred. They correctly state that any nondifferential misclassification should cause a conservative bias (i.e., the SPIR would underestimate the true magnitude of the association). In addition, use of the

"longest job held" approach for classifying exposure status could lead to confounding if, for example, the longest job was associated with formaldehyde exposures and other shorter jobs were associated with wood dust exposure. However, there is no reason to believe that such confounding actually occurred. Exposure intensity was based on white collar/blue collar status, which presumably is also a surrogate for socioeconomic status. Confounding by socioeconomic status (e.g., from nutrition differences) could have occurred between the lower and higher exposure categories.

Gerin et al. (1989) investigated the cancer risk involved with occupational exposure to <1 ppm formaldehyde in a study which included 3,726 subjects. From the data collected, the OR between formaldehyde exposure and each type of cancer was estimated. The only cancer with a slightly elevated OR was adenocarcinoma of the lung in the long-duration/high-exposure group (OR=2.3). The 95% CI was 0.9–6 and the authors concluded that this result was compatible with the null hypothesis of no carcinogenic effects of formaldehyde. Cancer diagnoses were pathologically confirmed and extensive information was collected about possible nonoccupational confounders. Because, by definition, this case-control study sampled on disease rather then exposure status, the study population included persons from many different jobs and industries where formaldehyde exposure occurred, and the assessment of such exposures was necessarily limited. Controls were samples from electoral lists; registered voters might differ from the overall population (and the cases) in some respects (e.g., socioeconomic status), although the investigators presumably collected data that would allow control of such differences. The very low prevalence of substantial formaldehyde exposures among study participants leads to low statistical power for detecting exposure-disease associations. The authors also mention that the probable formaldehyde exposure levels in the "high" group was a TWA of >1 ppm. They further state that the small number in this group likely led to imprecise results. The study also analyzed the data after correcting for confounding factors; these factors (listed above) may play a role in the cancer risk.

Animal Cancer Studies. As discussed previously in Section 2.2.1.2 subsection entitled *Chronic Inhalation Animal Studies*, chronic exposure to airborne formaldehyde concentrations ranging from about 6 ppm to 15 ppm induced increased incidences of nasal tumors (squamous cell carcinomas, squamous cell papillomas, or polyploid adenomas) in three bioassays with Fisher 344 rats (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Swenberg et al. 1980). Increased incidences of lower respiratory tract tumors or distant site tumors were not found in these studies, and exposure to concentrations of 2 ppm and lower induced no malignant nasal tumors.

In the earliest chronic inhalation rat bioassay (Kerns et al. 1983b; Swenberg et al. 1980), polyploid adenomas in the nasal cavity were found in 1/232, 8/236, 6/235, and 5/232 Fisher 344 rats (males and females were included) exposed 6 hours/day, 5 days/week for 24 months to 0, 2, 5.6, and 14.3 ppm, respectively. Malignant nasal tumors (predominately squamous cell carcinomas) were found in 0/232 control, 0/236 2-ppm, 2/235 5.6-ppm, and 106/232 14.3-ppm rats (Kerns et al. 1983b).

Monticello et al. (1996) exposed male Fisher 344 rats to 0, 0.7, 2, 6, 10, or 14 ppm, 6 hours/day, 5 days/week for 24 months. Nasal polypoid adenomas, located in or adjacent to the lateral meatus, were found in 10-ppm (5/90) and 15-ppm (14/147) rats. No polypoid adenomas were found in the control group or in the 0.7-, 2-, or 6-ppm groups. Squamous cell carcinomas were found in the nasal cavities of 1/90 6-ppm rats, 20/90 10-ppm rats, and 69/147 15-ppm rats. These tumors also were located predominately in the anterior lateral meatus. Squamous cell carcinomas were not found in the control, 0.7-, or 2-ppm groups. Buccal squamous cell carcinomas were observed in three 15-ppm rats and one 2-ppm rat.

Kamata et al. (1997) exposed groups of 32 male Fisher 344 rats to 0, 0.3, 2, or 15 ppm, 6 hours/day, 5 days/week for up to 28 months, and found nasal squamous cell carcinomas only in the 15-ppm group (13/32 rats). In contrast to the studies by Kerns et al. (1983b) and Monticello et al. (1996), no polyploid adenomas were found, but squamous cell papillomas were found in 3/32 rats in the 15-ppm group.

In experiments with male Sprague-Dawley rats, nasal tumors (predominately squamous cell carcinomas) were observed in 10/100 rats exposed to 14.2 ppm, 6 hours/day, 5 days/week for 588 days, compared with 0/100 in controls (Albert et al. 1982) and in 60/100 rats exposed to 14.8 ppm for up to 128 weeks, compared with 0/99 in controls (Sellakumar et al. 1985). No tumors were found in the trachea or lungs in these studies, and tumors found at extra-respiratory sites were not considered by the investigators to be exposure-related.

Wistar rats appear to be less carcinogenically responsive than Fisher 344 or Sprague-Dawley rats. Woutersen et al. (1989) observed nasal squamous cell carcinomas in only 1/26, 1/28, and 1/26 Wistar rats exposed to 0.1, 1, or 10 ppm, respectively 6 hours/day, 5 days/week for 28 months compared with 0/26 in controls; early physical damage to the nasal mucosa (electrocoagulation) increased the carcinogenic response only with subsequent exposure to 10 ppm (15/58 with 28-month exposure to 10 ppm versus 1/54 in nonexposed Wistar rats with electrocoagulation treatment). In 28 Wistar rats exposed to 10 ppm

for 3 months followed by a 25-month observation period, only one had a nasal squamous cell carcinoma and one had a nasal polypoid adenoma (Woutersen et al. 1989).

In an earlier experiment by the same laboratory, groups of 44–45 male Wistar rats were exposed to 0, 10, or 20 ppm, 6 hours/day, 5 days/week for 4, 8, or 13 weeks followed by observation periods as long as 126 weeks (Feron et al. 1988). Nasal tumors were found in 1/45 (polyploid adenoma), 1/43 (polyploid adenoma), and 4/44 (3 squamous cell carcinomas and 1 polyploid adenoma) 20-ppm rats exposed for 4, 8, or 13 weeks, respectively, compared with 0/45 in a control group. Two other nasal tumors found in the 10-ppm groups were not considered by Feron et al. (1988) to be induced by formaldehyde exposure. These results suggest that if nasal epithelial damage from intermediate exposure is sufficiently severe, then the risk for nasal tumors in later life may be increased.

Nasal tumors, similar to those observed in rats, were observed in two male B6C3F1 mice exposed to 14.3 ppm, 6 hours/day, 5 days/week for 24 months; no nasal tumors were found in control mice or mice exposed similarly to 2 or 5.6 ppm (Kerns et al. 1983b). No other neoplastic responses were found at other sites. In each group in this bioassay, less than 25 of the approximately 120 male mice in each group lived beyond 18 months. Reduced survival among males was attributed to fighting and infections of the genitourinary tract associated with group housing. The exact incidence of occurrence of nasal tumors in the Kerns et al. (1983b) mouse study could not be determined from the published report, but the available data suggest that mice are less carcinogenically responsive to inhaled formaldehyde than rats.

No nasal tumors or tumors at other respiratory tract sites were found in groups of 50 Golden Syrian hamsters exposed to either 10 ppm, 6 hours/day, 5 days/week for life or 30 ppm, 6 hours/day, once a week for life (Dalbey 1982). Hyperplastic and metaplastic areas were seen in the nasal epithelium of 5% of the hamsters exposed to 10 ppm, but were not seen in controls.

NTP (1998) noted that formaldehyde is reasonably anticipated to be a human carcinogen, and IARC (1995) determined that formaldehyde is probably carcinogenic to humans (Group 2A) based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals.

EPA (1991a; IRIS 1999) classified formaldehyde in Group B1 - probable human carcinogen, based on an evaluation of limited human evidence and sufficient laboratory animal evidence.
EPA (1991a) used dose-response data for nasal tumors in rats exposed to high concentrations of formaldehyde (from Kerns et al. 1983b) to extrapolate to human cancer risk at low exposure concentrations, using rates of DNA-protein cross links in target tissue as a measure of delivered dose. Relationships between formaldehyde air concentrations and rates of formation of DNA-protein cross links in nasal epithelial tissue of rats (Casanova et al. 1989) or of Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) and adjustments to continuous exposure were used to calculate lifetime human cancer unit risk estimates of $3.3x10^{-4}$ per ppm formaldehyde based on the monkey data, and $2.8x10^{-3}$ per ppm formaldehyde based on the rat data (see Section 2.4.3).

Using the monkey-based human cancer unit risk estimate, air concentrations associated with cancer risk levels of 10^{-4} to 10^{-7} from lifetime exposure are 0.3 to $3x10^{-4}$ ppm, respectively, and are plotted in Figure 2-1. The CEL values from each reliable study for cancer in each animal species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

Most of the available reports of controlled studies of health effects from oral exposure to formaldehyde have not provided information regarding how frequently dosing solutions were analyzed for formaldehyde content. Some studies reported how frequently formaldehyde solutions were prepared (e.g., in drinking water studies, Til et al. [1988b, 1989] and Tobe et al. [1989] prepared solutions weekly and twice weekly, respectively), or how frequently formaldehyde was added to the diet (e.g., Hurni and Ohder [1973] daily sprayed formaldehyde solutions [that were prepared weekly] on food just prior to feeding dogs). Other study reports, however, provide no information regarding solution-preparation frequency, conditions of storage, or analysis of test material for formaldehyde content (e.g., Johannsen et al. 1986; Soffritti et al. 1989; Takahashi et al. 1986a). Because of this reporting deficiency, and because formaldehyde solutions are very unstable (due to formaldehyde's high reactivity and volatility), the reader should be aware that there is uncertainty associated with oral dose levels reported in this profile.
Another issue of uncertainty regards the impurity of commercially available aqueous solutions of formaldehyde (often called formalin) which normally contain approximately 10–15% methanol to prevent polymerization. Reports of human poisonings from formalin and animal studies that used formalin (e.g., Marks et al. 1980; Takahashi et al. 1986a) are included in this profile. Attempts have

been made, however, to note when formalin was the source of the ingested formaldehyde, so that the reader will be aware of possible confounding effects from methanol.

Exposure to formaldehyde by the oral route can occur, but exposure is not as common as by the inhalation route because of the instability of formaldehyde in aqueous solution. Much of the information available about the effects of formaldehyde after oral exposure in humans comes from case reports of acute poisoning. Small amounts of formaldehyde can occur in foodstuffs, usually added as a preservative.

2.2.2.1 Death

In humans, death has been associated with acute oral exposure to formaldehyde. Four cases are described in detail here. Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg formaldehyde/kg) in a suicide attempt. The man was found unconscious by a co-worker about 1 hour after his shift began. In the emergency room, the subject regained consciousness but was lethargic. Laboratory results indicated significant acidosis. Approximately 3 hours after ingesting the formalin, the patient complained of abdominal pain and began retching without emesis; he was admitted for observation and treated with ethanol. The patient's abdominal pains became more severe and he had difficulty breathing. At 5.5 hours after ingestion, the patient became obtund, and both his respiratory rate and blood pressure fell significantly; he was intubated and placed on 100% oxygen. Shortly thereafter, the patient began to experience seizures; treatment with diazepam and phenytoin was unproductive, but pancuronium was effective in treating the seizures. Intravenous bicarbonate and ethanol therapies were begun after the seizures started. The patient was transported for dialysis, but on arrival, had clinical signs of intravascular coagulopathy. He subsequently sustained a cardiac arrest from which he could not be revived. At autopsy, the patient’s stomach was hard, white, and leathery; the esophagus and intestines appeared to be normal.

A 55-year-old woman and a 34-year-old man ingested, with suicidal intent, an unknown amount of what was reported to have been formalin (Koppel et al. 1990). The female patient was found in a coma and admitted to the hospital with shock (systolic blood pressure 50 mm Hg), respiratory insufficiency, and metabolic acidosis. The male patient, who had a history of alcohol abuse, was also hospitalized with shock (systolic blood pressure 60 mm Hg), respiratory insufficiency, and metabolic acidosis. Both patients underwent hemodialysis and hemofiltration treatment. Analysis of the formaldehyde samples

ingested by both patients showed no evidence that these products contained methanol, although it was expected to have been detected. A chemical-toxicological screening indicated that no drugs other than formaldehyde had been ingested; neither methanol or ethanol were detected in blood samples. Three weeks after ingestion of formaldehyde, the female patient died of cardiac failure refractory to catecholamine therapy. The male patient developed adult respiratory distress syndrome and died 8 weeks after formaldehyde ingestion with signs of cardiac failure.

Eells et al. (1981) describe the case of a 41-year-old woman who swallowed 120 mL formalin (37% formaldehyde solution; 624 mg formaldehyde/kg). The woman was brought to the emergency room within 30 minutes. The patient complained of abdominal pain and subsequently lost consciousness. Upon admission, the patient was cyanotic, apneic, and hypotensive. Laboratory results indicated significant acidosis. The patient was intubated, ventilation was initiated, and gastric lavage was performed. Intravenous fluid therapy consisting of Ringers solution followed by 5% dextrose, epinephrine, and sodium bicarbonate was initiated and the patient was transferred to intensive care. The patient was maintained via endotracheal respiration and dopamine therapy. The patient became anuric approximately 7.5 hours after admission, and her health continued to deteriorate over the next day; she died 28 hours after admission.

Mortality data for acute duration experimental animal studies do not present a consistent picture. Reports of death in animal studies after acute oral exposure were found (Tobe et al. 1989), although other studies showed no mortality. For instance, groups of male and female Wistar rats were given formaldehyde at 0, 10, 50, and 300 mg/kg/day in their drinking water (Tobe et al. 1989). Animals given 300 mg/kg/day were observed to have died as early as 9 days after the start of the treatment. The number and sex of rats that died were not reported. In a group of 34 pregant mice given gavage doses of 185 mg/kg/day on gestation days 6–15, 22 died by gestation day 18 (Marks et al. 1980). Marks et al. (1980) noted that the drinking water contained 0.6–0.75% methanol (60–75 mg/kg/day) which possibly could have contributed to the lethality. However, Johannsen et al. (1986) reported no mortality after acute-duration exposure of Sprague-Dawley rats of both sexes to doses #150 mg/kg/day. Similarly, Takahashi et al. (1986a) observed no mortality after exposure of male Wistar rats to 258 mg/kg/day of formaldehyde (as formalin) for acute duration.

Intermediate-duration exposure of animals to orally administered formaldehyde resulted in a more consistent picture of mortality. Vargova et al. (1993) observed no treatment-related mortality in male

Wistar rats exposed to doses of formaldehyde by gavage of #80 mg/kg/day for 4 weeks. No deaths were reported in weanling SPF-bred rats (Cpb WU, Wistar random) that received up to 125 mg/kg/day formaldehyde in their drinking water for 4 weeks (Til et al. 1988b), in male and female Sprague-Dawley rats given up to 150 mg/kg/day formaldehyde in drinking water for 90 consecutive days (Johannsen et al. 1986), or in male Wistar rats after administration of 258 mg/kg/day formaldehyde (as formalin) in drinking water for periods up to 32 weeks (Takahashi et al. 1986a). Mortality rates were calculated for male and female Wistar rats given 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for #12 months (Tobe et al. 1989). For the high-dose group, mortality at 3, 6, and 9 months was 10, 15, and 20% for male rats, respectively, and 25, 30, and 30% for female rats, respectively. No mortality was reported in the low- and mid-dose groups after exposure for periods #9 months (Tobe et al. 1989).

Four male and 4 female pure-bred Beagle dogs were administered 0, 50, 75, or 100 mg/kg/day formaldehyde in the diet for 90 consecutive days (Johannsen et al. 1986). No deaths or abnormal reactions were observed in the treated dogs.

In chronic-duration animal studies, no dose-related excess mortality was seen in male and female Sprague-Dawley rats after 104 weeks of exposure to doses #300 mg/kg/day (males) or in SPF-bred rats exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) in their drinking water for 2 years (Til et al. 1989). Deaths were significantly higher than control in males at 15 mg/kg/day in the Til study, but not at 82 mg/kg/day.

Mortality rates were calculated for male and female Wistar rats given 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months (Tobe et al. 1989). For the high-dose group, mortality at 12, 15, and 18 months was 45, 67, and 67% for male rats, respectively, and 55, 55, and 70% for female rats respectively (Tobe et al. 1989). All animals in the high-dose group died by 21 (females) or 24 (males) months.

The LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	ACUTE EXPOSURE						
	Death						
1	Human	once (IN)				517 M (death)	Burkhart et al. 1990 (formalin)
2	Human	once (IN)				624 F (death)	Eells et al. 1981 (formalin)
3	Rat (Wistar)	9 d (W)				300 (death observed in 9 days)	Tobe et al. 1989
	Systemic						
4	Human	once (IN)	Resp			517 M (decreased respiratory rate)	Burkhart et al. 1990 (formalin)
			Cardio			517 M (decreased blood pressure; cardiac arrest)	
			Gastro			517 M (abdominal pain and retching; hard, white & leathery stomach)	
			Hemato			517 M (intravascular coagulopathy)	
			Metab			517 M (acidosis)	
5	Human	once (IN)	Resp			624 F (apneic)	Eells et al. 1981 (formalin)
			Cardio			624 F (hypotensive)	
			Gastro		624 F (abdominal pain)		
			Renal			624 F (anuric)	
			Metab			624 F (acidosis)	

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
6	Human	once (IN)	Resp		234 F (increased cough; tachypnea)		Kochhar et al. 1986
			Cardio		234 F (tachycardia)		
			Gastro			234 F (dysphagia, ulceration and sloughing of soft palate and posterior pharyngeal wall; ulceration of epiglotis; pyriform fossae and arytenoids; edematous and ulcerated esophageal mucosa with black sloughing; areas of stomach hyperemic; and superficial ulceration in the distal body and antrum)	
			Hemato	234 F			
7	Rat (Sprague-Dawley)	2 wk (W)	Bd Wt	225			Johannsen et al. 1986
			Other		75 (decreased water consumption)		
8	Rat (Wistar)	1-2 wk (W)	Bd Wt	15 M	82 M (significantly decreased body weight)		Til et al. 1989
9	Rat (Wistar)	2 wk (W)	Bd Wt	50		300 (lost weight during normal weight-gain period)	Tobe et al. 1989
			Other		300 (reduced food and water intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Neurological						
10	Human	once (IN)				517 M (lethargy; loss of consciousness; seizure)	Burkhart et al. 1990 (formalin)
11	Human	once (IN)				624 F (loss of consciousness)	Eells et al. 1981 (formalin)
	Reproductive						
12	Rat (Wistar)	once		100 M		200 M (19% increase in total sperm heads and 5% increase in abnormal sperm heads)	Cassidy et al. 1983 (formalin)
	Developmental						
13	Mouse (CD-1)	gd 6-15 (GW)		185			Marks et al. 1980 (formalin)
	INTERMEDIATE EXPOSURE						
	Death						
14	Rat (Wistar)	up to 24 mo (W)				300 M (10% [3 mo], 15% [6 mo], 20% [9 mo] & 45% [12 mo] mortality)	Tobe et al. 1989
						300 F (25% [3 mo], 30% [6 mo], 30% [9 mo] & 55% [12 mo] mortality)	

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Systemic						
15	Rat (Sprague-Dawley)	90 d ad lib (W)	Resp	150			Johannsen et al. 1986
			Cardio	150			
			Gastro	150			
			Hemato	150			
			Hepatic	150			
			Renal	150			
			Endocr	150			
			Bd Wt	50 M	100 M (10-15% decrease in terminal body weight)		
				100 F	150 F (10-15% decrease in terminal body weight)		
			Other	50 M	100 M (>10 % decreased water intake)		
					50 F (>10 % decreased water intake)		
16	Rat (Wistar)	32 wk (W)	Gastro			258 (erosions and ulcers in limiting ridge of fundic mucosa)	Takahashi et al. 1986a (formalin)
			Bd Wt	258 M			

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
17	Rat (Wistar)	4 wk (W)	Resp	125			Til et al. 1988b
			Gastro	25[b]	125 (thickening of the limiting ridges & hyperkeratosis in the forestomach & focal atrophic inflammation in the glandular stomach; 1/10 females had moderate papillomatous hyperplasia)		
			Hemato	125			
			Hepatic	25 M 125 F	125M (decrease plasma protein and albumin concentrations)		
			Renal	125			
			Bd Wt	125			
			Other	25	125 (25-42 % decreased water intake; decreased food intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form[d]
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
18	Rat (Wistar)	less than or equal to 52 wks	Hemato	82 M 109 F			Til et al. 1989
		(W)	Renal	15 M	82 M (occult blood [wk 27]; increased urine density & decreased urine volume [wks 27 & 52])		
				21 F	109 F (increased urine density & decreased urine volume [wk 27])		
			Bd Wt	15 M	82 M (significantly decreased body weight after 1 week)		
				21 F	109 F (significantly decreased body weight after 24 weeks)		
			Other	15 M	82 M (decreased food and water intake)		
				21 F	109 F (decreased food and water intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
19	Rat (Wistar)	2 wk-12 mo (W)	Resp	300			Tobe et al. 1989
			Gastro	50		300 (forestomach squamous cell hyperplasia, erosions and/or ulcers and glandular stomach glandular hyperplasia at 12 months)	
			Hemato	300			
			Hepatic	50	300 (decreased serum protein, albumin, total cholesterol at 12 months)		
			Renal	50	300 (increased blood urea nitrogen at 12 months)		
			Bd Wt	50		300 (>20% decrease in body weight after 2 weeks)	
			Other		300 (decreased food and water intake)		
20	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)	Resp	80 M			Vargova et al. 1993 (formalin)
			Gastro	80 M			
			Hemato	80 M			
			Hepatic	40 M	80 M (increase in the incidence of hepatocellular vacuolation)		
			Renal	80 M			
			Bd Wt	80 M			

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
21	Dog (Beagle)	90 d (F)	Cardio	100			Johannsen et al. 1986
			Gastro	100			
			Hemato	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Bd Wt	75	100 (unspecified significant decrease in body weight)		
			Other	75 M 50 F	100 M (decreased food intake) 75 F (decreased food intake)		
	Immunological/Lymphoreticular						
22	Rat (Wistar)	4 wk (W)		125			Til et al. 1988b
23	Rat (Wistar)	2 wk-12 mo (W)		300			Tobe et al. 1989
24	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)			20 M (decrease in combined IgM & IgG titers, increased relative lymph node weight)		Vargova et al. 1993 (formalin)
25	Dog (Beagle)	90 d (F)		100			Johannsen et al. 1986
	Neurological						
26	Rat (Sprague-Dawley)	90 d (W)		150			Johannsen et al. 1986

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form[d]
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
27	Rat (Wistar)	4 wk (W)		125			Til et al. 1988b
28	Rat (Wistar)	12 mo (W)		300			Tobe et al. 1989
29	Dog (Beagle)	90 d ad lib (F)		100			Johannsen et al. 1986
	Reproductive						
30	Rat (Sprague-Dawley)	90 d ad lib (W)		150			Johannsen et al. 1986
31	Rat (Wistar)	4 wk (W)		125			Til et al. 1988b
32	Rat (Wistar)	12 mo (W)		300			Tobe et al. 1989
33	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)		80 M			Vargova et al. 1993 (formalin)
34	Dog (Beagle)	52 d gd 4-56 (F)		9.4 F			Hurni and Ohder 1973 (formalin)
35	Dog (Beagle)	90 d (F)		100			Johannsen et al. 1986

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form[d]
	Developmental							
36	Dog (Beagle)	52 d gd 4-56 (F)		9.4 F				Hurni and Ohder 1973 (formalin)
	CHRONIC EXPOSURE							
	Death							
37	Rat (Wistar)	up to 24 mo (W)				300	(mortality as early as 9 days; 45-55% mortality by 12 months; 100% mortality by 24 months)	Tobe et al. 1989

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Systemic						
38	Rat (Wistar)	up to 2 yr (W)	Resp	82 M, 109 F			*Til et al. 1989*
			Cardio	82 M, 109 F			
			Gastro	15[c] M, 21 F		82 M, 109 F (papillomatous hyperplasia with hyperkeratosis, chronic atrophic gastritis, focal ulceration in forestomach, glandular hyperplasia)	
			Hemato	82 M, 109 F			
			Musc/skel	82 M, 109 F			
			Hepatic	82 M, 109 F			
			Renal	15 M, 21 F		82 M, 109 F (increased incidence of renal papillary necrosis and increased relative kidney weight in females)	
			Endocr	82 M, 109 F			
			Dermal	82 M, 109 F			
			Ocular	82 M, 109 F			
			Bd Wt	15 M, 21 F	82 M, 109 F (body weights about 10-15% lower than controls)		
			Other	15 M, 21 F	82 M, 109 F (decreased food/water intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form[d]
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
39	Rat (Wistar)	up to 24 mo (W)	Resp	300					Tobe et al. 1989
			Cardio	300					
			Gastro	10	50	(forestomach hyperkeratosis)	300	(severe degenerative lesions in epithelium of forestomach and glandular stomach)	
			Hemato	300					
			Hepatic	50	300	(decreased serum protein, albumin, total cholesterol)			
			Renal	300					
			Endocr	300					
			Bd Wt	50			300	(40-45% decrease in terminal body weight)	
			Other	50	300	(25-50% decreased food/water intake)			
	Immunological/Lymphoreticular								
40	Rat (Wistar)	up to 2 yr (W)		82 M 109 F					Til et al. 1989
41	Rat (Wistar)	up to 24 mo (W)		300					Tobe et al. 1989
	Neurological								
42	Rat (Wistar)	up to 2 yr (W)		15 M 21 F	82M 109 F	(17% increase in relative brain weight) (8% increase in relative brain weight)			Til et al. 1989

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form[d]
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
43	Rat (Wistar)	up to 24 mo (W)		300			*Tobe et al. 1989*
	Reproductive						
44	Rat (Wistar)	up to 2 yr (W)		82 M 109 F			Til et al. 1989
45	Rat (Wistar)	up to 24 mo (W)		300			Tobe et al. 1989

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.3 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.2 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (F) = food; Endocr = endocrine; F = female; gastro = gastrointestinal; (GW) = gavage in water; gd = gestation day; (IN) = ingestion; Hemato = hematological; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

[d]Formalin designation herein means that the study either involved direct exposure to formalin (~40% aqueous solution of formaldehyde containing 10-15% methanol as a stabilizing agent) or used such a solution as a stock for the preparation of orally administered material.

Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral

Acute (≤14 days)

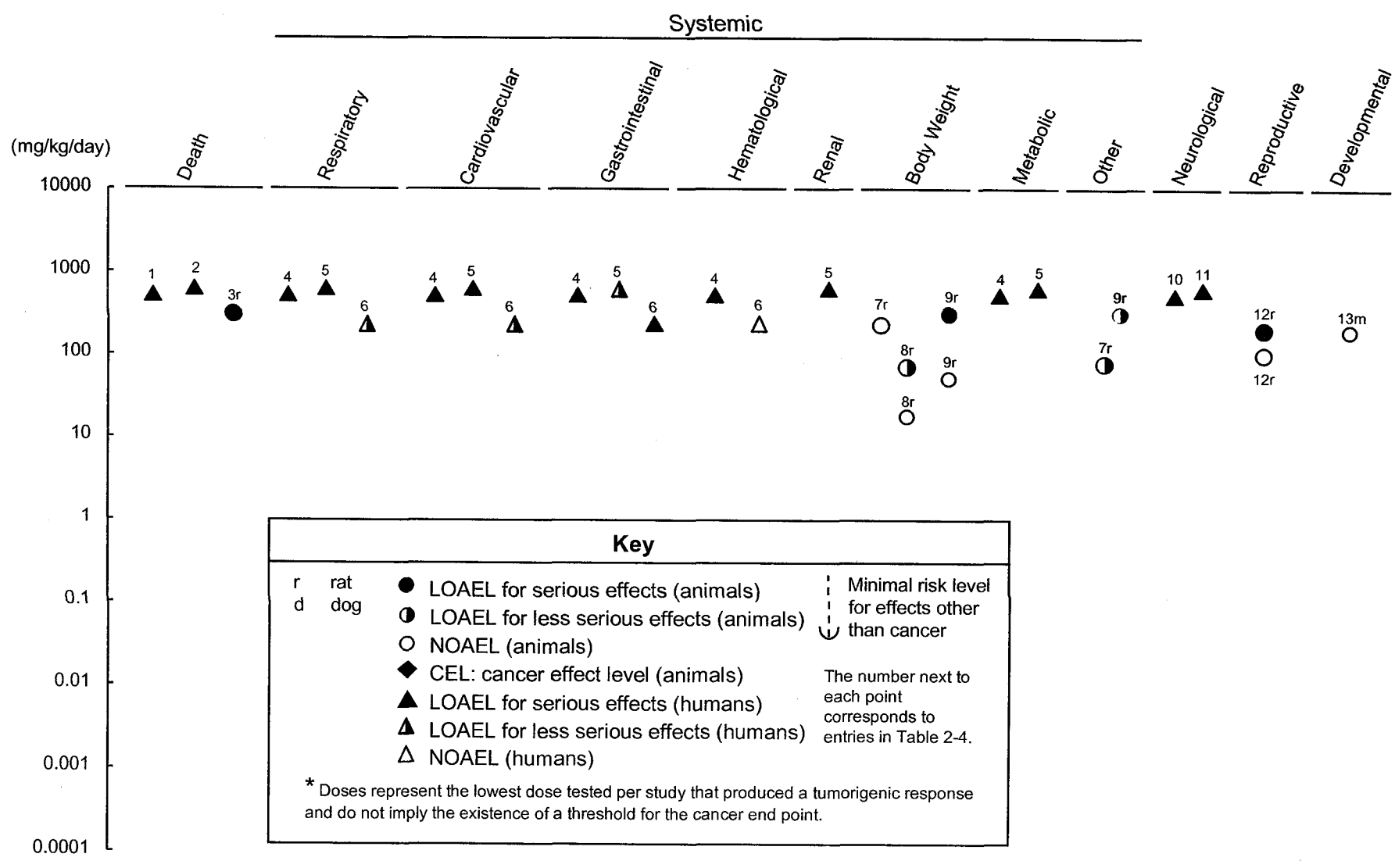


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Intermediate (15-364 days)

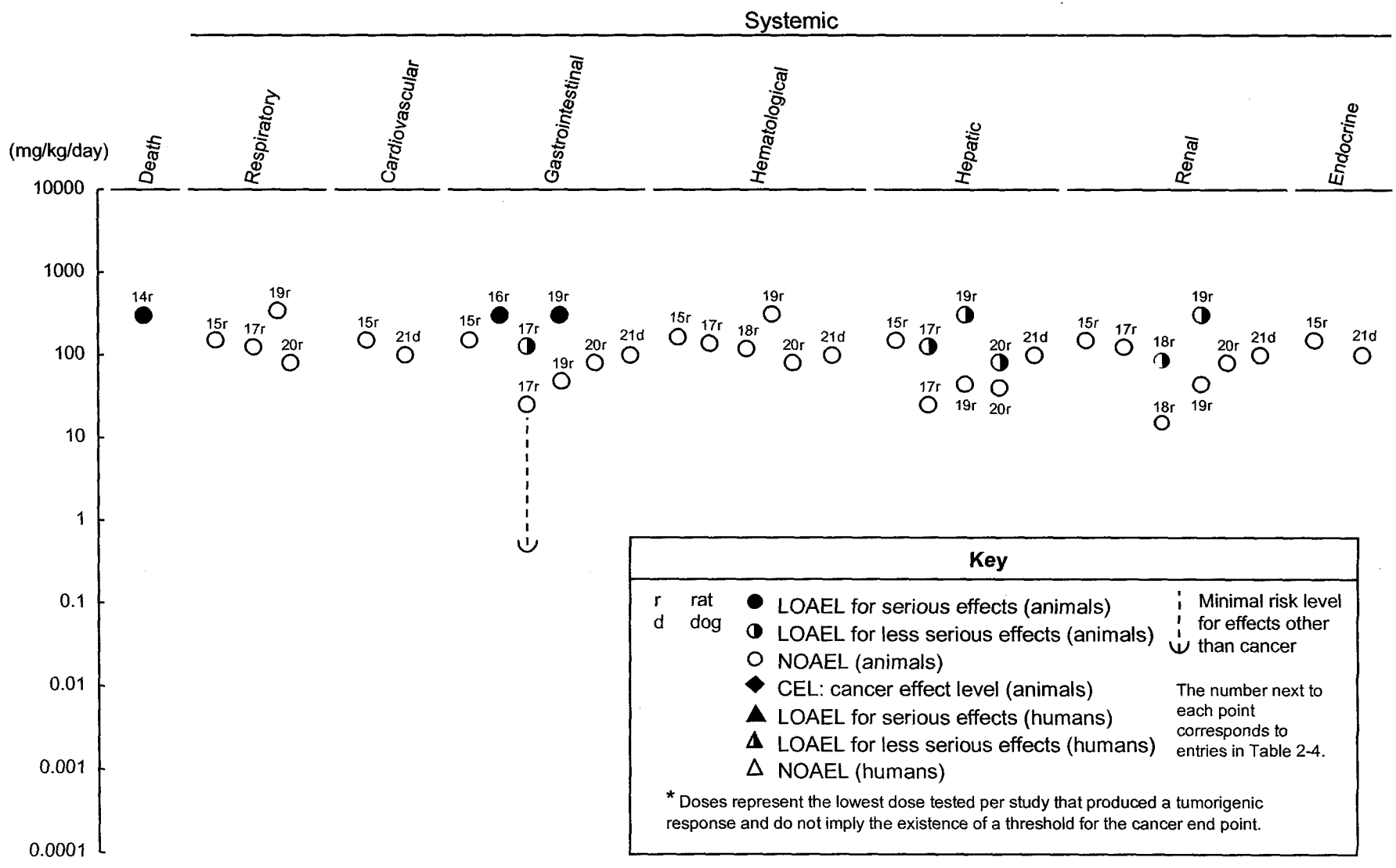


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Intermediate (15-364 days)

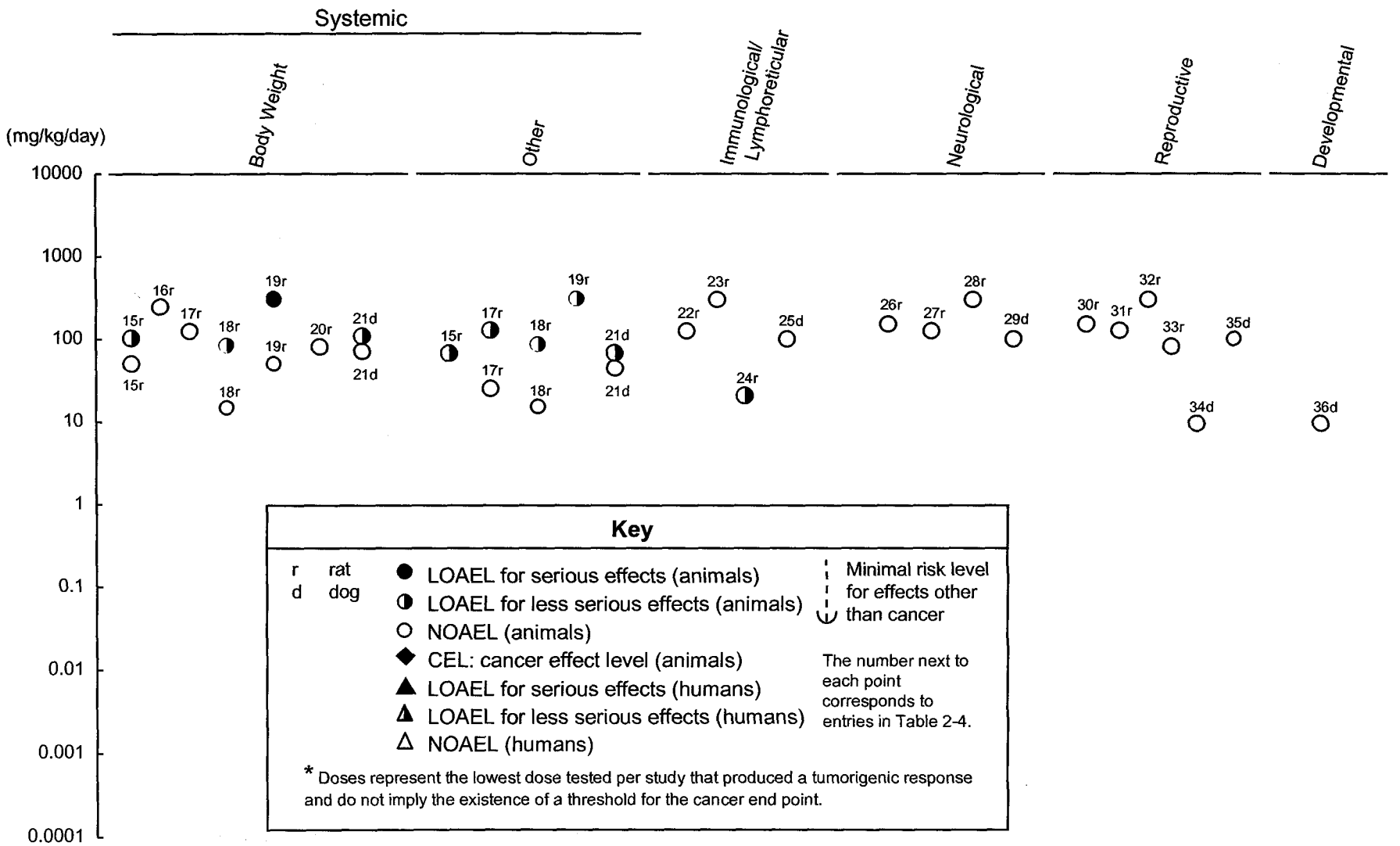


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Chronic (≥365 days)

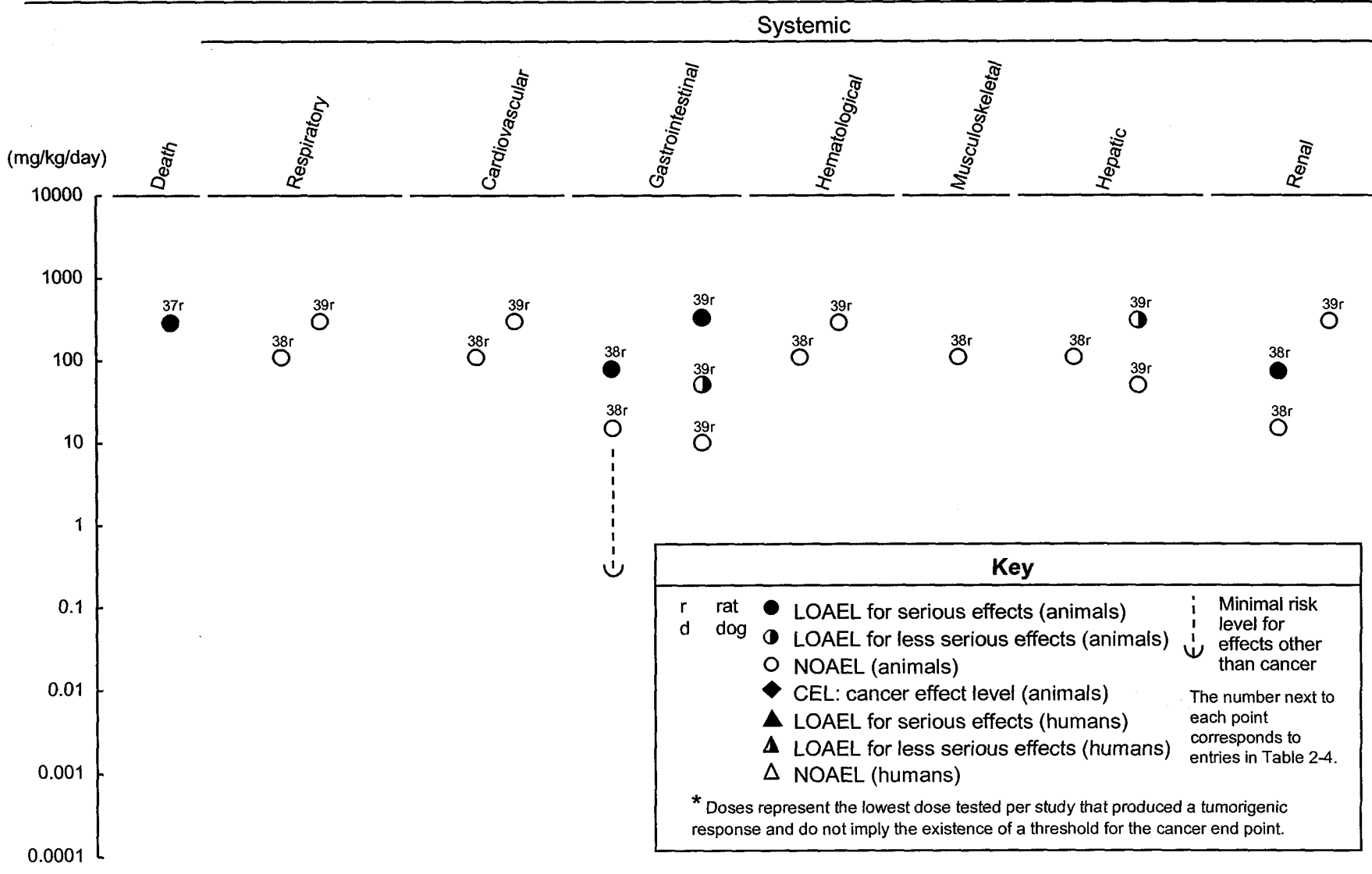
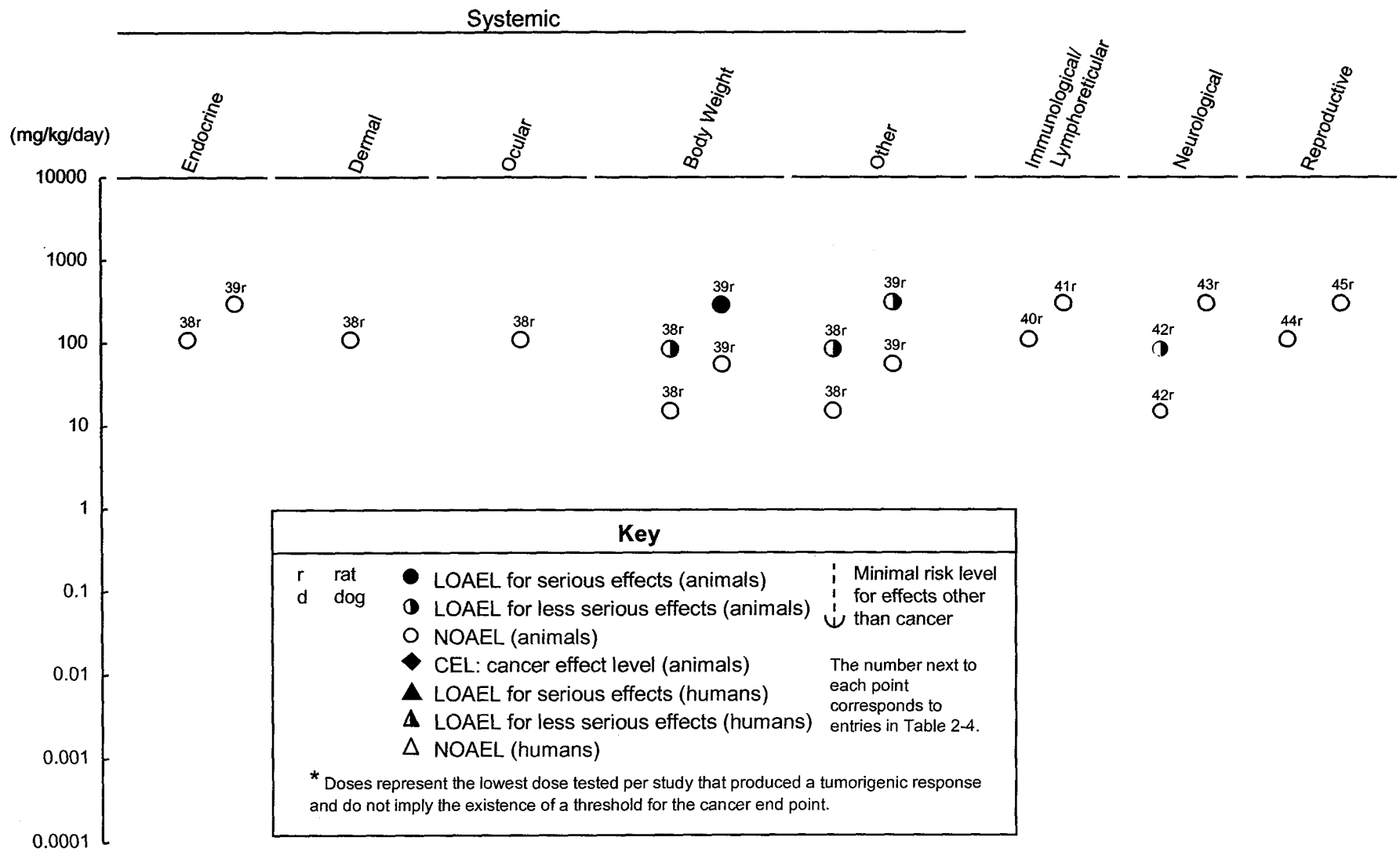


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Chronic (≥365 days)



2.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

Respiratory Effects. Respiratory effects have been observed in humans after ingestion of formaldehyde. A 55-year-old woman and a 34-year-old man ingested an unknown amount of formalin with suicidal intent and were admitted to the hospital (Koppel et al. 1990). Respiratory insufficiency was noted upon admission to the hospital. Both patients died; however, the man developed adult respiratory distress syndrome prior to death.

Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces (517 mg/kg) of a formaldehyde solution in a suicide attempt. The man was found unconscious by a co-worker about 1hour after his shift began. In the emergency room, the subject regained consciousness, but was lethargic. At 5.5 hours after ingestion, the patient became obtund, and his respiratory rate fell significantly; he was intubated and placed on 100% oxygen. He subsequently sustained a cardiac arrest from which he could not be revived.

Eells et al. (1981) described the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting 120 mL of formalin (37% formaldehyde solution; 624 mg/kg). Upon admission, the patient was cyanotic, apneic, and hypotensive. The patient was intubated and ventilation was initiated. The patient was maintained via endotracheal respiration and dopamine therapy; she died 28 hours after admission. Other adverse respiratory effects have been noted in other reports of human ingestion including difficulty breathing and speaking (Freestone and Bentley 1989), increased cough, and tachypnea after 234 mg/kg formaldehyde (Kochhar et al. 1986).

Intermediate-duration oral exposure data on respiratory effects in experimental animals are limited to organ weight and/or histopathological results, and are negative. After 90-day exposure to doses of #150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on lung weight or histopathology (Johannsen et al. 1986). Til et al. (1988b) saw no effect on the histopathology of the nose and pharynx of male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Vargova et al. (1993) saw no adverse effect on the histopathology of lung tissue of male Wistar rats after 4 weeks of gavage exposure to doses of

formaldehyde of #80 mg/kg/day. No adverse effects on lung weight or histopathology were seen in Beagle dogs exposed to 100 mg/kg/day of formaldehyde in the diet for 90 days (Johannsen et al. 1986).

Chronic-duration exposure data are similarly limited in scope. Til et al. (1989) saw no adverse effect on nose and lung tissue or lung weight in male and female Wistar rats exposed to doses #82 mg/kg/day (male) or 109 mg/kg/day (females) in drinking water for up to 2 years. Tobe et al. (1989) also saw no effect on lung weight or histopathology from doses of formaldehyde of #300 mg/kg/day in drinking water administered to male and female Wistar rats for up to 24 months.

Cardiovascular Effects. Shock and cardiac failure have been noted in patients after intentional ingestion of formaldehyde solution (Koppel et al. 1990). Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg/kg formaldehyde) in a suicide attempt. The man was found unconscious by a co-worker about 1hour after his shift began. In the emergency room, the subject regained consciousness, but was lethargic. At 5.5 hours after ingestion, his blood pressure fell significantly. He subsequently sustained a cardiac arrest from which he could not be revived. Other reports of cardiovascular effects in humans after ingestion of formaldehyde include hypotension after 624 mg/kg formaldehyde (as formalin) (Eells et al. 1981), circulatory collapse (Freestone and Bentley 1989), and sinus tachycardia after 234 mg/kg formaldehyde (Kochhar et al. 1986).

Intermediate-duration exposure data on cardiovascular effects in experimental animals are limited to organ weight and/or histopathological results, and are negative. After 90-day exposure to doses of #150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on heart weight or histopathology (Johannsen et al. 1986). No significant effects on the histopathology of the heart were observed in Wistar rats after 12 months of exposure to up to 300 mg/kg/day in drinking water (Tobe et al. 1989). In addition, 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet found no effect on heart weight or histopathology (Johannsen et al. 1986).

Til et al. (1989) saw no adverse effect on heart tissue or organ weight in male and female Wistar rats exposed to doses #82 mg/kg/day (male) or #109 mg/kg/day (females) in drinking water for up to 2 years. Tobe et al. (1989) also saw no effect on heart weight or histopathology of doses of formaldehyde of #300 mg/kg/day in drinking water administered to male and female Wistar rats for up to 24 months.

Gastrointestinal Effects. Formaldehyde is corrosive to mucosal tissues. Intentional ingestion of formaldehyde has been associated with extensive congestion, hemorrhaging, and necrosis of the gastrointestinal mucosa (Koppel et al. 1990). Burkhart et al. (1990) described the case of a 58-year-old man who swallowed 4 ounces (517 mg/kg formaldehyde) of formalin in a suicide attempt. Approximately 3 hours after ingesting the formalin, the patient complained of abdominal pain and began retching without emesis; he was admitted for observation and treated with ethanol. The patient's abdominal pains became more severe, and he subsequently died from cardiac arrest. At autopsy, the patient's stomach was hard, white, and leathery; the esophagus and intestines appeared to be normal.

Eells et al. (1981) described the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting 120 mL formalin (624 mg/kg formaldehyde). The patient complained of abdominal pain and subsequently lost consciousness; she died 28 hours after admission. Freestone and Bentley (1989) describe gastrointestinal effects after presumed gargling with formaldehyde, including dysphagia due to esophageal mucosal damage. The patient was placed on parenteral feeding to allow resting of the gut and to improve nutritional status. After several weeks in intensive care, the patient was taken off of ventilation; after two additional months, the patient was released.

A 26-year-old woman who ingested 234 mg/kg formaldehyde exhibited extensive gastrointestinal damage (Kochhar et al. 1986). Immediately after ingesting formaldehyde, the patient experienced repeated vomiting with occasional streaks of blood. Anti-emetics and antacids were prescribed but did not relieve symptoms. Examination of the oropharynx revealed ulceration and sloughing of the soft palate and posterior pharyngeal wall. Indirect laryngoscopy revealed ulceration of the epiglottis, pyriform fossae, and arytenoids. At 96 hours, an upper gastrointestinal endoscopy revealed that the esophageal mucosa was edematous and ulcerated with patches of black slough along the entire length. Areas of the stomach were hyperemic, and there was superficial ulceration in the distal body and antrum; the duodenal mucosa appeared normal. The patient underwent a feeding jejunostomy and made an uneventful recovery. At 4 weeks, a repeat endoscopy revealed a normal esophagus. The stomach appeared normal with the exception of slight hyperemia and limited distensibility of the antrum. Barium examination revealed scarring of the antrum and distal portion of the gastric body. At 6 weeks, the patient was asymptomatic.

Intermediate-duration exposure data on gastrointestinal effects in experimental animals are limited to organ weight and/or histopathological results, but are sufficient to describe a no-effect level for gastrointestinal effects in rats. After 90-day exposure to doses up to 150 mg/kg/day formaldehyde in

drinking water, male and female Sprague-Dawley rats showed no adverse effects on the histopathology of the gastrointestinal mucosa (Johannsen et al. 1986). In contrast, erosions and/or ulcers, associated with regenerating mucosa, were noted in the limiting ridge of the fundic mucosa in glandular stomach of male Wistar rats exposed to 0.5% formalin (258 mg/kg/day formaldehyde) in drinking water for 32 weeks (Takahashi et al. 1986a). Erosions were described as "diffuse deep gastric pits with clearly increased numbers of mucous neck cells in the fundic mucosa". Benign papillomas in the forestomach also were noted in 8 of the 10 exposed rats in this study, compared with none in 40 controls. Increased incidences of forestomach squamous cell hyperplasia and glandular stomach glandular hyperplasia were observed in Wistar rats exposed for 12 months to 300 mg/kg/day in drinking water, but not in rats exposed to 50 mg/kg/day (Tobe et al. 1989). Til et al. (1988b) saw thickening of the limiting ridges of the stomach and hyperkeratosis in the forestomach of male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. One of the 10 females receiving this dose also exhibited moderate papillomatous hyperplasia, presumably of the glandular stomach. Focal atrophic inflammation was also observed in the glandular stomach. No adverse effects of treatment were observed at 25 mg/kg/day formaldehyde in either sex. An intermediate-duration MRL of 0.3 mg/kg/day was derived from the data of Til et al. (1988b). The MRL of 0.3 mg/kg/day was based on a NOAEL of 25 mg/kg/day for lack of gastrointestinal effects in rats and calculated as described in the footnote to Table 2-4 and in Appendix A of this profile.

Vargova et al. (1993) saw no adverse effect on the histopathology of stomach tissue of male Wistar rats after 4 weeks of gavage exposure to doses of #80 mg/kg/day formaldehyde. In addition, no effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on stomach weight or histopathology (Johannsen et al. 1986).

Til et al. (1989) observed adverse gastrointestinal effects at 82 mg/kg/day formaldehyde in male and 109 mg/kg/day formaldehyde in female Wistar rats exposed in drinking water for up to 2 years. Lesions were first seen after 53 weeks. These adverse effects included papillomatous hyperplasia with hyperkeratosis, chronic atrophic gastritis, focal ulceration in the forestomach, and hyperplasia in the glandular stomach. No adverse gastrointestinal effects were noted in the male rats receiving a dose of 15 mg/kg/day. A chronic-duration oral MRL of 0.2 mg/kg/day was derived from the data of Til et al. (1989). The MRL of 0.2 mg/kg/day was based on a NOAEL of 15 mg/kg/day for lack of gastrointestinal effects in male rats and was calculated as described in the footnote to Table 2-4 and in Appendix A of this profile.

Tobe et al. (1989) also saw forestomach hyperkeratosis at a drinking-water dose of 50 mg/kg/day and severe degenerative lesions in the epithelium of the forestomach and glandular stomach at 300 mg/kg/day in male and female Wistar exposed for up to 24 months.

Hematological Effects. Some hematological effects have been noted in humans after acute ingestion, but do not appear to be primary effects in formaldehyde poisoning. Burkhart et al. (1990) described intravascular coagulopathy in the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg/kg formaldehyde) in a suicide attempt. However, Kochhar et al. (1986) indicated that normal hematology was observed in a 26-year-old female who ingested a formaldehyde dose of 234 mg/kg (Kochhar et al. 1986). Other reports of human ingestion do not indicate adverse effects on the hematological system (Eells et al. 1981; Freestone and Bentley 1989; Koppel et al. 1990).

Intermediate-duration exposure data on hematological effects in experimental animals are limited to routine hematological parameters and are negative. After 90-day exposure to doses of #150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on hematocrit or hemoglobin (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on hemoglobin concentration, packed cell volume, or erythrocyte counts in male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. In a companion study, no effect was seen on hematological variables in male and female rats exposed to doses #82 mg/kg/day (males) or 109 mg/kg/day (females) for #52 weeks (Til et al. 1989). Vargova et al. (1993) saw a statistically significant increase in the hematocrit of male Wistar rats after 4 weeks of gavage exposure to doses of 40–80 mg/kg/day formaldehyde. At 80 mg/kg/day, erythrocyte count and hemoglobin were statistically significantly increased, whereas mean corpuscular hemoglobin was significantly depressed compared to control animals (Vargova et al. 1993). Vargova et al. (1993) reported that the hemotological effects noted, although statistically significant, were within the background range for Wistar rats, and were therefore of questionable clinical significance. No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on hematological parameters including hematocrit and hemoglobin (Johannsen et al. 1986).

Til et al. (1989) observed no adverse hematological effects in male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years. Similarly, Tobe et al. (1989) observed no exposure-related effects on red blood cell count, hematocrit, or hemoglobin in rats exposed to drinking water doses up to 300 mg/kg/day for up to 24 months.

Musculoskeletal Effects. No reports of musculoskeletal effects in humans after acute-, intermediate-, or chronic-duration oral exposure to formaldehyde were found in the literature.

Til et al. (1989) observed no adverse histopathological effects on the skeletal muscle of male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years.

Hepatic Effects. Intentional ingestion of formaldehyde in a suicide attempt has been associated with hepatomegaly, icterus, and congestion of the hepatic parenchyma (Koppel et al. 1990). Some reports of human ingestion of formaldehyde include hepatotoxicity and increased liver enzymes (Freestone and Bentley 1989), although other reports do not indicate hepatic effects (Eells et al. 1981).

Intermediate-duration exposure data on hepatic effects in experimental animals are limited to measurement of liver weight and histopathology and are mostly negative. After 90-day exposure to doses of #150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on liver weight or histopathology (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on liver weight or histopathology in male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water; however, a decrease in plasma protein and albumin concentration was observed. Vargova et al. (1993) saw an increase in the incidence of hepatocellular vacuolization in male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on liver weight, histopathology, or activities of serum enzymes indicative of liver damage (Johannsen et al. 1986).

Til et al. (1989) observed no adverse effects on organ weight or histopathology of the liver of male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years. Likewise, hepatic weight determinations and histopathology were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months. However, serum protein, albumin, and total cholesterol were all statistically significantly decreased in both sexes at 300 mg/kg/day at 12 months in this study. In exposed rats, serum hepatic enzyme levels (alkaline phosphatase, glutamate-oxaloacetic transaminase, and glutamic-pyruvic transaminase) were either not different from or were significantly lower than control values (Tobe et al. 1989).

Renal Effects. Renal failure has been associated with acute intentional ingestion of formaldehyde (Eells et al. 1981; Freestone and Bentley 1989; Koppel et al. 1990). In the case reported by Eells et al. (1981), the patient, who ingested 624 mg/kg formaldehyde (as formalin), became anuric approximately 7.5 hours after ingestion, and her health continued to deteriorate over the next day; she died 28 hours after admission. Koppel et al. (1990) also describe renal failure prior to death, occurring soon after ingestion of an unknown quantity of formaldehyde. However, in the report by Freestone and Bentley (1989), hypoalbuminemia and renal failure were noted upon admission to the hospital after the patient gargled with formaldehyde. Dopamine was given until renal function improved. After several weeks in intensive care, the patient was taken off of ventilation; after two additional months, the patient was released.

Intermediate-duration exposure data on renal effects in experimental animals are limited to kidney weight measurement and histopathology and are mostly negative. After 90-day exposure to doses of #150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on kidney weight or histopathology (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on kidney histopathology in male Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Vargova et al. (1993) saw no effect on the weight or histopathology of the kidneys in male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on kidney weight or histopathology (Johannsen et al. 1986). Til et al. (1989) reported, however, that male and female Wistar rats had increased urine density, decreased urine volume, and occult blood (males only) after exposure for 27 to 82 weeks to 109 mg/kg/day formaldehyde in drinking water, respectively.

In a 2-year drinking water study, Til et al. (1989) observed an increase in the incidence of renal papillary necrosis in male rats exposed to 82 mg/kg/day and an increase in renal papillary necrosis accompanied by increased relative kidney weight in female rats exposed to 109 mg/kg/day. Kidney weight determinations and histopathology were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months, but blood urea nitrogen was increased in the 300-mg/kg/day group at 12 months.

Endocrine Effects. No reports describing endocrine effects of acute-, intermediate-, or chronic-duration oral exposure to formaldehyde in humans or acute-duration oral exposure in animals were found.

After 90-day exposure to doses of #150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on adrenal or thyroid weight or histopathology (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on adrenal and thyroid weight in male Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Vargova et al. (1993) saw no effect on the weight of the adrenals or pituitary in male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on adrenal and thyroid weight or histopathology (Johannsen et al. 1986).

Til et al. (1989) observed no effect on the weight of the adrenal, pituitary, and thyroid, or histopathology of the adrenal, pituitary, thyroid, or pancreas in male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years. Adrenal, pituitary, and thyroid weight determinations and histopathology, in addition to histopathology of the pancreas, were not influenced by exposure in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

Dermal Effects. No reports of dermal effects of acute-, intermediate-, or chronic-duration oral exposure of humans to formaldehyde were found in the literature.

No adverse histopathology was noted in skin samples from male and female Wistar rats receiving #109 mg/kg/day formaldehyde in drinking water after 2 years of exposure (Til et al. 1989)

Ocular Effects. No reports of ocular effects after acute-, intermediate-, or chronic-duration oral exposure of humans, or acute- or intermediate-duration oral exposure of animals to formaldehyde were found in the literature.

Til et al. (1989) observed no effect on the histopathology of the Harderian and exorbital lachrymal glands and eye of male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years.

Body Weight Effects. No reports of body weight effects in humans after oral exposure to formaldehyde were located.

Groups of Sprague-Dawley rats (sex not specified) were administered formaldehyde at 0, 37.5, 75, 150, or 225 mg/kg/day by gavage for 2 weeks (Johannsen et al. 1986). Mean body weight decreased at concentrations above 75 mg/kg/day. However, another pilot study conducted by Johannsen et al. (1986), Sprague-Dawley rats given formaldehyde at 0, 75, 150, or 225 mg/kg/day in drinking water for 2 weeks showed no significant changes in final body weights. Til et al. (1989) noted a decrease in body weight gain (unspecified) after 1 week of exposure of male Wistar rats to 82 mg/kg/day formaldehyde in drinking water, with statistically significant decreases in food consumption reported at 82 mg/kg/day for males and 109 mg/kg/day for females. No effect on body weight was noted until week 24 in female rats in the same study exposed to a high dose of 109 mg/kg/day. Body weight was not affected in male and female Wistar rats exposed to formaldehyde in drinking water at doses #125 mg/kg/day for 4 weeks (Til et al. 1988b). Likewise, Vargova et al. (1993) saw no effect on body weight in male Wistar rats exposed by gavage 5 days/week for 4 weeks, to doses of #80 mg/kg/day formaldehyde.

Johannsen et al. (1986) noted that significant decreases in body weights occurred in both sexes of Sprague-Dawley rats exposed to 150 mg/kg/day in drinking water for 90 days and in males exposed to 100 mg/kg/day, and that these decreases were associated with decreased water, but not food, consumption. Terminal mean body weights at these dose levels were about 10–15% lower than control values, whereas at 50 mg/kg/day for both sexes, and at 100 mg/kg/day for female rats, they were within 10% of control body weight values. In contrast, no significant effects on body weights were noted in male Wistar rats exposed to 0.5% formalin (258 mg/kg/day formaldehyde) in drinking water for 32 weeks (Takahashi et al. 1986a). Male and female Beagle dogs exposed to 100 mg/kg/day formaldehyde in the diet for 90 days had significantly reduced body weights, compared with controls, but not at lower exposure levels of 50 or 75 mg/kg/day (Johannsen et al. 1986). The magnitude of the decreased body weight was not specified. Significantly reduced food consumption was noted in males, but not in females, in the 100-mg/kg/day group and in females, but not males, in the 75-mg/kg/day group.

Wistar rats exposed for up to 2 years to estimated daily drinking water doses of 300 mg/kg/day lost weight during the first 2 weeks of exposure, whereas control rats and rats exposed to up to 50 mg/kg/day increased their body weights by about 20–30% during the same period (Tobe et al. 1989). Mean body weights and food and water intakes were markedly decreased in the 300-mg/kg/day rats, compared with

controls, throughout the study. After 5–10 weeks of exposure, body weights were about 20–30% lower than controls. Mean terminal body weights were about 40–45% lower than controls. At doses up to 50 mg/kg/day, terminal body weights were within 10% of control body weights throughout the study.

In another chronic drinking water study, mean body weights were significantly decreased, compared with controls, in male Wistar rats after 1 week and in female rats after 24 weeks of exposure to doses of 82 and 109 mg/kg/day, respectively (Til et al. 1989). These decreases were associated with decreases in food and water intake. Terminal body weights were approximately 10–15% lower than controls. Body weights were within 10% of control values in male and female rats exposed to up to 15 and 21 mg/kg/day, respectively.

Metabolic Effects. Metabolic effects have been noted in patients after ingestion of formaldehyde. Metabolic acidosis, high plasma formic acid, and hyperlactatemia were noted in two patients who intentionally ingested formaldehyde in suicide attempts (Koppel et al. 1990). Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg/kg formaldehyde) in a suicide attempt. The man was found unconscious by a co-worker about 1 hour after his shift began. Laboratory results at the emergency room indicated significant acidosis. Intravenous bicarbonate and ethanol therapies were begun after the seizures started. Eells et al. (1981) described the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting 120 mL of formalin (624 mg/kg formaldehyde). Laboratory results indicated significant acidosis. Intravenous fluid therapy consisting of Ringers solution followed by 5% dextrose, epinephrine, and sodium bicarbonate was initiated and the patient was transferred to intensive care; she died 28 hours after admission.

No reports were found of metabolic effects in animals orally exposed to formaldehyde.

Other Systemic Effects. Some effects of acute-duration oral exposure to formaldehyde have been seen on food and water consumption in animal studies, and may be related to taste aversion at higher doses in some cases. For example, Johannsen et al. (1986) reported that Sprague-Dawley rats given formaldehyde at 0, 75, 150, or 225 mg/kg/day in drinking water for 2 weeks showed no significant changes in food consumption, but mean water consumption decreased proportionately to dose in all three treated groups. In contrast, food and water consumption were reduced at levels above 75 mg/kg/day in other groups of Sprague-Dawley rats given formaldehyde at 0, 37.5, 75, 150, or 225 mg/kg/day by intubation for 2 weeks (Johannsen et al. 1986).

Intermediate-duration exposure data on food and water consumption are also available from animal studies. In Sprague-Dawley rats exposed to formaldehyde in drinking water for 90 days, decreases in water intakes (>10% of control values) were found in females exposed to 100 or 150 mg/kg/day and in males exposed to 50, 100 or 150 mg/kg/day, but in both sexes, food consumption was not significantly affected (Johannsen et al. 1986). Four-week exposures to 125 mg/kg/day in drinking water were associated with 25–42% decreased water intake and decreased food intake in male and female Wistar rats (Til et al. 1988b). Food consumption was significantly decreased in male Beagle dogs during 90 day dietary exposure to 100 mg/kg/day; food consumption was significantly decreased in females at 75 mg/kg/day(Johannsen et al. 1986).

With chronic drinking water exposure to formaldehyde, statistically significant decreases in food intake (ranging from about 7–14% of control values) and water intake (ranging from about 20–50% of control values) occurred at various intervals throughout a 2-year period of exposure to 82 mg/kg/day in male Wistar rats and to 109 mg/kg/day in female Wistar rats, but not at respective exposure levels #15 and 21 mg/kg/day (Til et al. 1989). In the other 2-year drinking water study by Tobe et al. (1989), significantly decreased food intake (about 10–25% of control values) and water intake (about 40–50% of control values) occurred throughout the exposure period in male and female Wistar rats exposed to 300 mg/kg/day, but not at dose levels of 50 mg/kg/day and lower. In general, the repeated oral exposure animal studies indicate that dosage levels associated with decreased food and/or water consumption were associated with decreased body weights and with the development of gastrointestinal tract lesions.

2.2.2.3 Immunological and Lymphoreticular Effects

Little information is available about immunological and lymphoreticular effects of formaldehyde ingestion in humans. Splenomegaly was observed in one woman who ingested formaldehyde in a suicide attempt (Koppel et al. 1990). However, this effect was most likely secondary to extensive hemorrhaging and necrosis of the gastrointestinal system.

Til et al. (1988b) saw no effect on spleen or thymus weight in male or female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water.

No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on spleen weight or histopathology (Johannsen et al. 1986).

Vargova et al. (1993) administered 20, 40, or 90 mg/kg/day formaldehyde 5 days/week for 4 weeks to male Wistar rats by gavage. Increased absolute and relative lymph node weights were observed beginning at 40 mg/kg/day. Antibody production was assayed by measurement of total blood IgG and IgM, a hemagglutination assay, a plaque-forming cell assay, and by measurement of IgM production in spleen cells. Only the hemagglutination assay showed a significant effect; the combined IgG and IgM titers were significantly lower than controls at 20 mg/kg/day and above, although individual IgM and IgG titers were only significantly different from controls at 40 and 80 mg/kg/day.

Weanling, SPF-bred rats were exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) formaldehyde in their drinking water for up to 2 years (Til et al. 1989). There was no effect of treatment on spleen weight or histopathology, or the histopathology of the mesenteric and axillary lymph nodes. Spleen weight determinations and histopathology, in addition to histopathology of the lymph nodes, were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

The LOAEL value decreased IgG and IgM titers and increased lymph node weights in rats (Vargova et al. 1993) and the highest NOAEL values from each reliable study for immunological/lymphoreticular effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Little information is available about the neurological effects of formaldehyde ingestion in humans. However, neurological effects appear to be prevalent in reported cases of formaldehyde ingestion. A woman who ingested formaldehyde in a suicide attempt was found in a coma (Koppel et al. 1990). Other neurological effects observed include lethargy, seizure, and loss of consciousness at 517 mg/kg formaldehyde (Burkhart et al. 1990). Loss of consciousness was also observed in another woman (Eells et al. 1981) after ingesting 624 mg/kg formaldehyde.

No effect of 90-day treatment of male and female Sprague-Dawley rats with doses of #150 mg/kg/day formaldehyde in drinking water was found on brain weight or histopathology (Johannsen et al. 1986). Til et al. (1988b) saw no effect on brain weight in male or female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Tobe et al. (1989) saw no effect on the weight or

histopathology of the brain of male and female Wistar rats exposed to doses of #300 mg/kg/day formaldehyde in drinking water for 12 months. No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on brain weight or histopathology (Johannsen et al. 1986).

Weanling Wistar rats were exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) in their drinking water for up to 2 years (Til et al. 1989). Relative brain weights were statistically significantly increased (by 7–17%) in the high-dose groups of both sexes. However, no effect of treatment on brain histopathology or the histopathology of the spinal cord or sciatic nerve was observed. Brain weight determinations and histopathology were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No reports were found describing reproductive effects in humans after acute-, intermediate-, or chronic-duration oral exposure to formaldehyde.

Male Wistar rats (5 per group) were weighed and fasted for 18 hours overnight (Cassidy et al. 1983). Rats were then administered single dosages of 100 and 200 mg/kg formaldehyde orally. Eleven days after dosing, rats were weighed, sacrificed, and necropsied. There were no significant changes in testes weights observed in animals treated with 100 or 200 mg/kg formaldehyde. At 200 mg/kg formaldehyde, testicular sperm head counts were significantly increased (19%) compared to control values. The percentage of abnormal sperm heads also significantly increased (5%) in the 200 mg/kg dose groups compared to control groups. The toxicological significance of these changes in sperm head number and percentage of abnormal sperm heads is not known since no functional tests of reproductive competence were conducted.

Pregnant CD-1 mice were given formaldehyde at 0, 74, 148, and 185 mg/kg by gavage on gestation days 6–15 (Marks et al. 1980). The formaldehyde solution given to the animals in this study contained

12–15% methanol as a preservative. These animals received formaldehyde solution at 185 mg/kg, which contained 0.6–0.75% methanol, resulting in a concurrent dose of 60–75 mg/kg/day of methanol. On gestation day 18, the mice were sacrificed, implantation sites were counted, and general condition of each conceptus were recorded. Formaldehyde at 74 or 148 mg/kg/day had no consistent and statistically significant effects on indices of reproduction (e.g., the number of resorptions and the number of implantation sites per dam), but only 12 of the 34 dams who were exposed to 185 mg/kg/day survived to gestation days 18. Marks et al. (1980) noted that the methanol could have contributed to the lethality. Among the 12 surviving 185-mg/kg/day dams, only 8 (67%) remained pregnant at gestation day 18; the average percent of resorptions per litter was increased in these dams, compared with controls, but not to a statistically significant extent.

Formaldehyde was evaluated in the Chernoff/Kavlock developmental toxicity screen (Seidenberg and Becker 1987). Based on range-finding studies, timed-pregnant ICR/SIM mice were administered a single minimally toxic dose (not reported) by gavage on gestation days 8–12. Three or four compounds and a vehicle (corn oil or distilled water) were tested concurrently. Dams were allowed to deliver. The litters were counted and weighed on days 1 and 3. Dead pups were examined for external abnormalities. Dams that had not given birth by gestation days 21 or 22 were necropsied, and their uteri were examined for possible implantation sites. Formaldehyde was designated as a nonteratogen or non-embryotoxin based on results of the developmental toxicity screen.

No adverse effects of 90-day treatment of male and female Sprague-Dawley rats with doses of #150 mg/kg/day formaldehyde in drinking water were found on gonad weight or histopathology (Johannsen et al. 1986). Til et al. (1988b) saw no effect on testis weight in male or ovary weight in female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Tobe et al. (1989) saw no effect on the weight or histopathology of the testis of male and ovary of female Wistar rats exposed to doses of #300 mg/kg/day formaldehyde in drinking water for 12 months. Vargova et al. (1993) saw no effect on testis or prostate weight of exposure to 80 mg/kg/day formaldehyde by gavage 5 days/week for 4 weeks in male Wistar rats. No effect of 90-day treatment of male and female Beagle dogs with doses of #100 mg/kg/day formaldehyde in the diet was found on gonad weight or histopathology (Johannsen et al. 1986).

Weanling Wistar rats were exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) in their drinking water for up to 2 years (Til et al. 1989). There was no effect of

treatment on ovary or testis weight or histopathology, or the histopathology of the mammary gland, epididymides, prostate, or uterus. Testis and ovary weight determinations and histopathology were negative, as was histopathological evaluation of the uterus in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

Hurni and Ohder (1973) investigated the effects of oral administration of formaldehyde on reproductive function in female beagle dogs during gestation. Formaldehyde was sprayed on the pelleted food at dietary levels of 125 and 375 ppm (calculated by authors to be equivalent to 3.1 and 9.4 mg/kg, respectively). Although the feed was not assayed for formaldehyde content, the authors reported that formaldehyde solutions, prepared weekly from a commercial 40% aqueous solution, were sprayed daily on the food just prior to feeding. Ten to 11 mated females were fed the treated feed on gestation days 4–56. Exposure to formaldehyde did not affect pregnancy rates, maternal body weights, or litter size.

The serious LOAEL value for rats (Cassidy et al. 1983) and the highest NOAEL value from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to formaldehyde.

Pregnant CD-1 mice were given formaldehyde at 0, 74, 148, and 185 mg/kg by gavage on gestation days 6–15 (Marks et al. 1980). On gestation day 18, mice were sacrificed, implantation sites were counted, and general condition of each conceptus was recorded. Live fetuses were weighed individually, sexed internally, and examined for external malformations. The viscera of at least one-third of the fetuses of each litter, as well as stunted fetuses and those having external malformations, were examined for abnormalities. The heads of the fetuses which were subjected to visceral examination were cut off at the base and prepared for free-hand sectioning. The formaldehyde solution given to the animals in this study contained 12–15% methanol as a preservative. Formaldehyde solution at 185 mg/kg contained 0.6–0.75% methanol or 60–75 mg/kg/day. No attempt was made to remove the methanol. There were no statistically significant effects on fetal weight, ratio of males to females, or incidences of visceral or

skeletal fetal malformations in any exposed group, compared with the control group, even though at the highest dose group, only 12 of 34 dams survived to gestation day 18.

Formaldehyde was evaluated in the Chernoff/Kavlock developmental toxicity screen (Seidenberg and Becker 1987). Based on range-finding studies, timed-pregnant ICR/SIM mice were administered a single minimally toxic dose (not reported) by gavage on gestation days 8–12. Dams were allowed to deliver. The litters were counted and weighed on days 1 and 3. Dead pups were examined for external abnormalities. Dams that had not given birth by gestation days 21 or 22 were necropsied, and their uteri were examined for possible implantation sites. Formaldehyde was designated as a nonteratogen or nonembryotoxin based on results of the developmental toxicity screen. Neonatal development was not affected by formaldehyde treatment. Formaldehyde had no effect in the number of live neonates per litter or on the average neonatal body weight at birth in this investigation.

No exposure-related effects on pregnancy success, maternal weight gain, gestation length, litter size, pup body weight, number of stillborn pups, or numbers of live pups that survived to weaning were found in a study in which groups of 9–10 pregnant Beagle dogs were fed diets delivering reported doses of 0, 3.1, or 9.4 mg/kg/day on gestation days 4–56 (Hurni and Ohder 1973). In the few stillborn pups that were found, no internal or skeletal malformations were observed. Formaldehyde solutions were prepared weekly from a commercial 40% aqueous solution and sprayed daily on the food just prior to feeding. The study identifies 9.4 mg/kg/day as a NOAEL for maternal and fetal developmental effects.

The highest NOAELs for developmental effects in the Hurni and Ohder (1973) and Marks et al. (1980) studies are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No reports of genotoxic effects in humans or animals were found after oral exposure to formaldehyde.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans orally exposed to formaldehyde.

Takahashi et al. (1986a) administered 0 or 0.5% formalin (about 0.185% formaldehyde=1,850 ppm formaldehyde) in drinking water to groups of 10 male Wistar rats for 32 weeks, and evaluated surviving animals for neoplasms at 40 weeks. An estimated dose of 258 mg/kg/day was calculated using an average reported body weight of 0.280 kg and a water consumption rate of 0.039 L/day calculated with an allometric equation based on body weight (EPA 1988e). No carcinoma-bearing animals were reported; however, 8 of 10 (80%) rats showed benign papillomas of the forestomach in the exposed group compared with none in 40 control rats. No tumors (benign or malignant) were found in the fundus, pylorus, or duodenum of the glandular stomach in exposed rats, but erosions and/or ulcers associated with regenerating mucosa were found along the limiting ridge of the fundic mucosa in exposed rats.

Soffritti et al. (1989) administered formaldehyde in drinking water to Sprague-Dawley rats for life beginning at various ages. Groups of 50 male and 50 female rats were exposed to 0 (methanol:water control), 10, 50, 100, 500, 1000, or 1,500 ppm from 7 weeks of age for life. Another control group consisted of 100 male and 100 female rats exposed to plain drinking water. Two groups of 18–20 male and 18–20 female breeders were exposed to 0 or 2,500 ppm formaldehyde starting at 25 weeks of age for life. Offspring of the breeders, 36–59 males and 37–49 females, received, for life, the same levels of formaldehyde as their parents. Estimated average doses were calculated, using reference values for Sprague-Dawley rats of 0.431 kg body weight and 0.054 L water consumed/day (EPA 1988e), as follows: 0, 1, 6, 13, 63, 125, 188, and 313 mg/kg/day. In rats treated from 7 weeks of age, leukemia was reported in controls and exposed groups at the following incidences: 8/100 (methanol control), 7/200 (plain control), and 3/100, 9/100, 9/100, 12/100, 13/100, and 18/100 for the 10- through 1,500-ppm groups, respectively. Leukemia was described as lymphoblastic leukemias and lymphosarcomas, immunoblastic lymphosarcomas, or hemolymphoreticular neoplasias. Lymphoblastic leukemia-lymphosarcomas were predominant among the leukemias noted. Pair-wise comparisons using the Fisher exact test (performed by Syracuse Research Corporation) indicate that only the high-dose incidence was significantly ($p<0.05$) increased compared with the methanol controls, but comparisons to the combined control incidence indicated significantly increased incidence at the 500-, 1,000- and 1,500-ppm levels. In the breeders exposed from 25 weeks of age, incidences for leukemia were 1/40 for controls and 4/36 for the

2,500-ppm group, and 6/108 for control offspring and 4/73 for 2,500-ppm offspring. Pair-wise comparisons of these incidences indicate no statistical difference between control and exposed groups.

Stomach and intestinal tumors were also reported in the Soffritti et al. (1989) study. In rats treated from 7 weeks of age, a few stomach tumors were found (2/100 at 10 ppm, 1/100 at 1,000 ppm, and 2/100 at 1,500 ppm, but none in the other groups), but no statistically significant association with exposure was found. A few intestinal tumors were also reported (1/100 at 10 ppm, 2/100 at 50 ppm, 1/100 at 1,000 ppm, and 6/100 at 1,500 ppm), but only the incidence at 1,500 ppm was significantly ($p<0.05$) increased compared with the methanol control using the Fisher Exact test (performed by Syracuse Research Corporation). No significant difference was found in incidence of either type of gastrointestinal tract tumor in the control and 2,500-ppm exposed breeders, but offspring displayed significantly ($p<0.05$) increased incidence of stomach tumors (5/73 versus 0/108) and intestinal tumors (8/73 versus 0/108). The neoplasms included benign tumors (papillomas and acanthomas of the forestomach and adenomas) and malignant tumors (including adenocarcinomas and leiomyosarcomas). Leiomyosarcoma was the most frequent malignant tumor. The majority of the malignant tumors of the intestine was found in the duodenum, jejunum, and ileum.

Two other chronic-duration rat drinking water studies showed no evidence for formaldehyde-induced carcinogenicity. Groups of 70 male and 70 female Wistar rats were exposed for 2 years to formaldehyde in drinking water at concentrations that delivered average measured doses of 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) (Til et al. 1989). Average drinking water concentrations were reported to be 0, 20, 260, and 1,900 ppm (mg/L). In high-dose animals, histopathological examination revealed gastric changes (including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis), but no increased incidences of nonneoplastic lesions were found in groups exposed to lower concentrations compared with controls. No statistically significant increased incidences of tumors, benign or malignant, were found in exposed groups compared with controls. Til et al. (1989) concluded that exposure to 82–109 mg/kg/day formaldehyde in drinking water produced severe damage to the gastric mucosa, but no tumors. In the other experiment, groups of Wistar rats (20 males, 20 females) were exposed to formaldehyde in their drinking water at concentrations of 0, 200, 1,000 or 5,000 ppm for 24 months (Tobe et al. 1989). Estimated average doses of 0, 10, 50, and 300 mg/kg/day were reported by the authors. All animals in the 5,000-ppm group died before 24 months and showed degenerative lesions in the forestomach (erosions and/or ulcers and hyperplasia of the squamous epithelium with or without

hyperkeratosis) and glandular stomach (erosions and/or ulcers accompanied by submucosal inflammatory cell infiltrates). In animals exposed to 50 mg/kg/day formaldehyde, forestomach hyperkeratosis was observed in 1 of 6 males and in 1 of 8 females. There were no lesions of the forestomach or glandular stomach in the 10-mg/kg/day groups. There were no significant differences in the incidences of any tumors in any exposed group compared with controls.

The evidence for the carcinogenicity of formaldehyde in rats exposed to formaldehyde-containing drinking water is not strong due to inconsistency of findings across studies and inconsistent evidence of a dose-response relationship for either leukemia or gastrointestinal tumors in the Soffritti et al. (1989) study.

Among the four studies that assessed the potential carcinogenicity of formaldehyde in drinking water (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989), only Soffritti et al. (1989) reported increased incidence of leukemia in exposed rats. Feron et al. (1990) have questioned whether the increased leukemias may have been “chance effects unrelated to formaldehyde ingestion”, due to reported wide variation in leukemia incidences in groups of untreated Sprague-Dawley rats of the same colony, citing reports of leukemia incidences in controls as high as 19% (the highest incidence in Soffriti et al. exposed groups was 18/100). Another limitation to the strength of the evidence for formaldehyde-induced leukemia is the lack of a consistent dose-response relationship in the Soffritti et al. study. Although IARC (1995) has noted that a statistically significant trend for increasing leukemia incidence with increasing exposure concentration can be demonstrated in the Soffritti et al. data for rats exposed from 7 weeks of age to dose levels ranging from 1 to 188 mg/kg/day; the second part of the Soffriti et al. (1989) study found no statistically increased incidence of leukemia in groups of breeding pairs of rats or their offspring exposed for life to the higher dose level of 313 mg/kg/day. A further limitation is the absence of corroborating evidence for effects at sites distant from portals-of-entry in the other drinking-water rat studies, and in inhalation-exposure animal studies.

Findings for formaldehyde-induced gastrointestinal tract tumors are not consistent across the available drinking-water rat studies. Significantly increased incidences of intestinal tumors were found only in rats exposed to 188 mg/kg/day from 7 weeks of age and in offspring of breeding pairs of rats exposed to 313 mg/kg/day, but were not found in groups exposed to lower concentrations or to the breeding pairs exposed to 313 mg/kg/day (Soffritti et al. 1989). Stomach tumors were found at increased incidence only in the 313-mg/kg/day offspring of the breeding pairs in the Soffriti et al. (1989) study and in 8/10 rats

exposed to 258 mg/kg/day in the Takahashi et al. (1986a) study. Takahashi et al. (1986a) reported only benign forestomach papillomas, whereas Soffritti et al. (1989) reported papillomas, adenocarcinomas, and leiomyosarcomas. In contrast, Til et al. (1989) found no increased incidence of gastrointestinal tract tumors in rats exposed to average dose levels up to 82 or 109 mg/kg/day for life, and Tobe et al. (1989) likewise found no increase in gastrointestinal tumors in rats exposed to up to 300 mg/kg/day for life. Til et al. (1989) noted that the difference between their finding of forestomach papillary epithelial hyperplasia and the finding Takehashi et al. (1986a) of forestomach papillomas might be ascribed to the use of different lesion-classification criteria. Although there are inconsistencies among the available studies with respect to formaldehyde-induced gastrointestinal tract tumors from oral exposure, the studies consistently show that exposure to drinking water dose levels >50 mg/kg/day can damage epithelial tissue of the gastrointestinal tract, especially at dose levels >100-200 mg/kg/day. The possibility of tumor occurrence as a portal-of-entry effect from high-level exposure appears biologically plausible given the reactive nature of formaldehyde, its cytotoxicity at high levels that exceed protective mechanisms, and the findings for upper respiratory tract tumors in rats exposed to high, but not low, levels of airborne formaldehyde.

Given the equivocal nature of the evidence for carcinogenicity from existing studies of rats exposed to formaldehyde in drinking water, no CEL values are recorded in Table 2-4 or plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

Studies regarding death in humans after dermal exposure to formaldehyde were not located. Repeated dermal exposure of mice to solutions containing up to 10% formaldehyde produced no increased mortality. Iversen (1988) applied 4% formaldehyde to the shaved skin of Sencar mice twice weekly for 58 weeks. No increase in mortality was observed. Similarly, applications of 1 or 10% formaldehyde to the backs of hr/hr Oslo mice for 2 days/week for 60 weeks did not affect mortality (Iversen 1986).

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal health effects in humans or animals after dermal exposure to formaldehyde.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-5.

Respiratory Effects. No reports were located regarding respiratory effects in humans after predominantly dermal exposure to formaldehyde or in animals after acute or intermediate-duration dermal exposure to formaldehyde.

Iversen (1988) tested the carcinogenic potential of formaldehyde via classical skin-painting experiments. Formalin (37% formaldehyde volume for volume) was dissolved in distilled water and used at final concentrations of 1 and 10% formaldehyde. Hairless mice (hr/hr Oslo strain, in which spontaneous tumors have not been noted) were used. One group consisting of 16 males and 16 females was dosed with 200 µL of 1% formaldehyde in water on the skin of the back twice per week (Tuesdays and Fridays) for a total of 60 weeks. A second group of identical composition received a 10% formaldehyde solution in an identical manner for 60 weeks. Small, nonspecific granulomas were found in the lungs of two animals from the 10% group. No exposure-related lesions were found in the nasal mucosa.

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form[a]
ACUTE EXPOSURE						
Systemic						
Human (patients with skin problems)	patch test, 48 hr	Dermal		1% soln	(3.7% of 1619 patients showed positive reactions for formaldehyde)	Kiec-Swierczynska 1996
Human (patients with skin problems)	patch test, 48 hr	Dermal		1% soln	(7.8% of patients showed positive reactions to formaldehyde)	Marks et al. 1995
Human (patients with eczematous dermatitis)	patch test, 48 hr	Dermal		2% soln	(1.6% of 1081 patients showed positive reactions to formaldehyde)	Meding and Swanbeck 1990
Human (patients with eczematous dermatitis)	patch test, 48 hr	Dermal		1% soln	(2.6% of 4713 patients showed positive reactions to formaldehyde)	Menne et al. 1991
Rat (Sprague-Dawley)	single dose to eye	Ocular		1% soln	(eye irritation; increased protein in aqueous humor)	Krootila et al. 1986
Gn Pig (Hartley)	rubbed daily into skin up to 9 d	Dermal		0.1 mL 0.4% soln	(erythema at day 6; increased skin-fold thickness at day 9)	Wahlberg 1993 (formalin)
		Bd Wt	0.1 mL 4% soln			

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form[a]
Hamster (Golden Syrian)	gd 8, 9, 10 or 11 2 hr	Bd Wt	0.5 mL F 37 % soln			Overman 1985 (formalin)
Immunological/Lymphoreticular						
Human (sensitized patients)	patch test, 48 hr			0.1% soln (positive reaction in 8/35 allergic subjects)		DeGroot et al. 1988
Human (sensitized patients)	patch test, 48 hr			0.015% soln (positive reaction in 1/25 allergic subjects)		Fischer et al. 1995
Human (formaldehyde sensitized patients)	patch test, 48 hr			0.025% soln (positive reaction in 1/20 allergic subjects)		Flyvholm et al. 1997
Human formaldehyde sensitized patient	patch test, 48 hr				1% soln (patient had an anaphylactic response)	Maurice et al. 1986
Mouse (BALB/c)	1 d on shaved flanks; 7 days later on dorsum of each ear		18.5% soln (serum IgE levels)			Hilton et al. 1996 (formalin)

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form[a]
Mouse (BALB/c)	2x in 10 d on shaved flanks; 5 days later on dorsum of each ear			3.7% soln	(increased cell proliferation of draining lymph node cells; increased production of the cytokine, IFN-gamma)			Hilton et al. 1996 (formalin)
Mouse (BALB/c)	1 d on shaved flanks; 7 days later on dorsum of each ear		6.8 mg in 0.05 mL (serum IgE levels)					Potter and Wederbrand 1995 (formalin)
Gn Pig (Hartley)	6 intra-dermal injections followed by 48 hr occluded dermal exposure			0.25% soln	(sensitized skin of 100% of animals to 2% soln)			Hilton et al. 1996 (formalin)
Reproductive								
Hamster (Golden Syrian)	gd 8, 9, 10 or 11 2 hr					0.5 mL 37 % soln	(increased resorptions)	Overman 1985 (formalin)
Developmental								
Hamster (Golden Syrian)	Gd 8, 9, 10 or 11 2 hr		0.5 mL 37 % soln					Overman 1985 (formalin)

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form[a]
INTERMEDIATE EXPOSURE						
Immunological/Lymphoreticular						
Gn Pig (Hartley)	3 weekly 6-hr occluded exposures			5% soln	(sensitized skin of 70% of animals to 1% soln)	Hilton et al. 1996 (formalin)
CHRONIC EXPOSURE						
Systemic						
Mouse (hr/hr Oslo)	60 wk 2 d/wk 1 x/d	Resp	0.2 mL 10% soln	0.2 mL 10% soln	(nonspecific granulomas in the lungs)	Iversen 1986 (formalin)
		Dermal	0.2 mL 10% soln	0.2 mL 10% soln	(slight hyperplasia of epidermis, small skin ulcers)	

[a]Formalin designation herein means that the study either involved direct exposure to formalin (~40% aqueous solution of formaldehyde containing 10-15% methanol as a stabilizing agent) or used such a solution as a stock for the preparation of dermally administered material. Percent in table refers to percent formaldehyde.

Bd Wt = body weight; d = day(s); F= female; Gd - gestational day; Gn Pig = guinea pig; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; wk = week(s); x = times; soln = solution

Dermal Effects. As discussed earlier in Section 2.2.1, occupational exposures to formaldehyde have been associated with dermal irritation and the diagnosis of allergic contact dermatitis by patch tests. Reported historical percentages of subjects with skin problems showing positive allergic responses to formaldehyde in patch tests performed by dermatologists using aqueous solutions with 1 or 2% formaldehyde include 7.8% in North America between 1992 and 1994 (Marks et al. 1995), 1.6% in a 1983–1984 Swedish study (Meding and Swanbeck 1990), 2.6% in a 1988–1989 European study (Menné et al. 1991), and 3.7% in a 1990–1994 Polish study (Kiec-Swierczynska 1996). Fischer et al. (1995) generally concluded that, in more than 30 years of experience with patch test reporting, about 1–4% of tested subjects are sensitive to formaldehyde. With standard patch testing protocols, formaldehyde concentrations of 2% and higher may produce skin irritation in nonsensitized individuals demonstrating that concentrations that evoke a skin irritation response can be similar to those evoking allergic skin responses (Fischer et al. 1995; Maibach 1983). Because of the reactive and irritating properties of formaldehyde, early use of formaldehyde concentrations as high as 5% in patch tests, and inexperience on the part of test administrators, Maibach (1983) speculated that many cases of irritant responses have been incorrectly interpreted as allergic responses. Lack of specific exposure information for many cases precludes determining the degree to which reported cases of dermal sensitization may have been caused by direct dermal contact to formaldehyde in liquids or by contact with formaldehyde gas in air, but the widespread use of formaldehyde or formaldehyde-releasing chemicals in cosmetics and cleaning agents (Flyvholm 1991; Rastogi 1992) suggest that the dermal route of exposure may be the more important sensitizing route. Studies showing that allergic skin responses in sensitized subjects exposed to formaldehyde in aqueous solutions are rare at concentrations below 0.025–0.05% are discussed in Section 2.2.3.3.

A study by Nethercott and Holness (1988) examined the prevalence of cutaneous disease in selected funeral service workers in Toronto, Canada. Eighty-four workers from funeral homes in the Toronto area were evaluated via a questionnaire which focused on past and family medical histories, present symptoms, and work practices. Physical examination of the participants' skin was performed, and all participants underwent skin-patch testing for formaldehyde and glutaraldehyde sensitivity. Embalmers were divided into high- and low-exposure groups for comparative analysis. Cutaneous examinations revealed a greater incidence of contact dermatitis among exposed workers (11%) compared to controls (0%), and the prevalence of positive skin-patch tests for formaldehyde was greater among exposed workers (3%) than among controls (0%). Among exposed workers, there were no differences between

the high- and low-exposure groups with regard to prevalence of contact dermatitis or positive skin-patch results.

Cases of contact dermatitis caused by formaldehyde released from "no-iron" textiles were described frequently in the literature from the late 1950s until the mid-1970s; after this period, the finishing processes for these types of textiles were changed so that only small amounts of formaldehyde are released after finishing (see Peters and Heese 1997 for review). In most cases of clothing-induced contact dermatitis, the dermatitis developed specifically in areas of very close contact between the skin and the clothing (e.g., the underarms, the elbows, the insides of the thighs).

Formaldehyde has also been shown to cause dermal allergic reactions in nurses and doctors (Rudzki et al. 1989). One hundred-sixty-seven doctors, 92 dentists, and 333 nurses were patch-tested with a standard panel of allergens plus allergens common to their work environment. Among nurses, formaldehyde was the disinfectant that most frequently caused allergic reactions (9.6%). Three doctors also had positive skin tests for formaldehyde.

Albino guinea pigs (Hartley strain) were treated with 0.1 mL of various dilutions of formalin (1, 3, and 10% formalin; –0.4, 1.2, and 4% formaldehyde) to demarcated test sites, and the formalin solution was gently rubbed into the skin with a cotton-tipped applicator (Wahlberg 1993). An unexposed control site and a vehicle control were used in each series. The sites were left unoccluded and the treatments were repeated once daily immediately after skin-fold measurements. Each site was examined prior to skin-fold measurements for the presence of erythema, edema, fissuring, and scaling. From a mean of 10 sites, erythema appeared on day 2 (4%), day 5 (1.2%), and day 6 (0.4%). Increased skin-fold thickness was statistically significant on day 3 (4%), day 7 (1.2%), and day 9 (.04%) after daily treatment with various concentrations of formaldehyde.

Iversen (1988) tested the carcinogenic potential of formaldehyde via classical skin-painting experiments. Formalin (37% formaldehyde volume for volume) was dissolved in distilled water and used at final concentrations of 1 and 10% formaldehyde. Hairless mice (hr/hr Oslo strain, in which spontaneous tumors have not been noted) were used. Two groups consisting of 16 males and 16 females were dosed with 0.2 mL of 1 or 10% formaldehyde in water on the skin of the back twice per week (Tuesdays and Fridays) for a total of 60 weeks. Animals dosed with 10% formaldehyde, but not with 1% solutions,

generally had slight epidermal hyperplasia, and a few mice had cutaneous ulcers. These studies indicate that formaldehyde applied dermally is irritating to the skin (hyperplasia and ulcers) and can also induce an inflammatory response.

Ocular Effects. As discussed in Section 2.2.1.2 (in the Respiratory Effects and Ocular Effects sections), health surveys of occupationally-exposed workers and acute controlled exposure studies with volunteers have demonstrated that exposure to formaldehyde air concentrations in the range of 0.4–3.0 ppm and above can cause eye irritation.

To examine the dependence of ocular response to formaldehyde irritation on the trigeminal sensory nerve, Krootila et al. (1986) topically applied a 1% solution of formaldehyde in an aqueous phosphate buffer (pH 7.4) to the right eye of a group of unoperated male Sprague-Dawley rats and two groups of denervated rats. Rats were anesthetized with pentobarbital for the experiments and operations. Sensory denervation of the right eye was accomplished in one group by coagulation of the intracranial, opthalmic branch of the right trigeminal nerve, and, in the other group, unilateral sympathetic denervation was accomplished by removing the right superior cervical ganglion. Application of 1% formaldehyde to the eye of unoperated rats caused a breakdown of the blood-aqueous barrier of the eye indicated by increased protein concentration in the aqueous humor or increased leakage of Evans blue dye from the iris vessels. This response was also observed in rats without the right superior cervical ganglion, but was absent in rats with a coagulated right trigeminal nerve. The authors concluded that the irritative response of the eye to formaldehyde is dependent on the trigeminal sensory nerve, but not the superior cervical ganglion.

Body Weight Effects. No studies were located regarding body weight effects in humans following dermal exposure to formaldehyde.

Exposure-related effects on body weight were not found in pregnant hamsters dermally exposed during gestation to 0.5 mL solutions of 37% formaldehyde (Overman 1985) or in guinea pigs dermally exposed for 9 days to 4% formaldehyde solutions (Wahlberg 1993). In the Overman (1985) experiment, the control and exposed pregnant hamsters were anesthetized during treatment to prevent grooming; exposure was for 2 hours on gestation day 8, 9, 10, or 11.

2.2.3.3 Immunological and Lymphoreticular Effects

As discussed earlier in Section 2.2.1.2, 2.2.1.3, and 2.2.3.2, formaldehyde is a commonly diagnosed contact allergen, accounting for about 1–4% of cases presented at dermatology clinics (Fischer et al. 1995; Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991). Studies of concentration-response relationships for skin allergic reactions induced by occluded dermal exposures to formaldehyde in formaldehyde-sensitive subjects suggest that a dermal allergic response to formaldehyde concentrations below about 0.025–0.05% is rare. In a serial dilution test, the lowest concentration tested, 0.1%, produced allergic reactions in 8/35 formaldehyde-sensitive subjects (DeGroot et al. 1988). Another serial dilution test, examining concentrations of 1, 0.5, 0.25, 0.13, 0.063, 0.032, and 0.015% in 25 formaldehyde-sensitive subjects, found decreasing frequency of response with decreasing exposure concentration; positive reactions were found in 3/25 at 0.063%, 1/25 at 0.032%, and 1/25 at 0.015% (Fischer et al. 1995). Flyvholm et al. (1997) reported that, in an occluded patch test study of 20 sensitized subjects and 20 healthy volunteers, no skin irritation occurred in the controls exposed to 1% formaldehyde. In sensitized subjects, the frequency of response decreased with decreasing formaldehyde concentrations as follows: 9/20 at 0.5%, 3/20 at 0.1%, 2/20 at 0.05%, and 1/20 at 0.025%.

A report by Maurice et al. (1986) describes the case study of 20-year-old woman who experienced anaphylactic shock after exposure to a dialyzer sterilized with formaldehyde. The woman, who required long-term hemodialysis due to renal failure, had previously experienced mild episodes of localized, delayed-type hypersensitivity contact dermatitis from adhesives sterilized with formaldehyde. After experiencing the episode of anaphylaxis, the patient was tested for formaldehyde sensitivity by a skin-prick test using 0.1 and 1% formaldehyde solutions, and a skin-patch test using a 1% solution. The patient developed a strong positive response to skin pricks using both 0.1 and 1% formaldehyde solutions. Twenty-six hours after skin application of formaldehyde, the patient developed anaphylactic symptoms characterized by laryngeal edema and bronchospasm. The patient was treated with subcutaneous epinephrine and all symptoms other than angioedema resolved rapidly.

Potter and Wederbrand (1995) examined the IgE response to dermal exposure to formaldehyde in female BALB/c mice. Ten mice per dose received 0.42–6.8 mg formaldehyde in 50 µL water:acetone (50:50), administered topically to the shaved flank. Seven days later, the animals received 25 µL of a half-strength solution, applied to the dorsal surface of each ear. Serum samples were collected 14 days after

the initial treatment. Dermal exposure to 0.42–6.8 mg formaldehyde in acetone:water did not induce IgE production.

Hilton et al. (1996) assessed the sensitizing properties of topical applications of formaldehyde in guinea pigs using standard tests (guinea pig maximization test and Buehler test) and in mice using a test for IgE production after dermal exposure, a local lymph node assay, and an assay for cytokine secretion by draining lymph node cells. In the guinea pig maximization test, pretreatment with a series of intradermal injections of 0.25% formaldehyde solutions and occluded patch exposure to 10% formaldehyde produced sensitization to 48-hour occluded patch dermal exposures to 2% formaldehyde solutions in 100% of treated animals. In the Buehler test, a series of 6-hour occluded patch dermal exposures to 5% formaldehyde solutions produced sensitization to subsequent exposures to 1% formaldehyde in 70% of treated animals. In mice treated with topical applications of solutions containing up to 50% formalin (approximately 18.5% formaldehyde), no increase in serum IgE concentrations occurred, whereas in mice similarly treated with solutions containing 25% trimellitic anhydride, a well-documented respiratory sensitizing agent, serum concentrations of IgE were markedly increased. Application of 10, 25, or 50% formalin solutions (3.7, 9.25, and 18.5% formaldehyde) to the dorsum of ears of mice stimulated cellular proliferation in lymph node cells cultured from draining auricular lymph nodes excised from the mice. Profiles of cytokines produced by draining lymph node cells from mice topically treated with 10, 25, or 50% formalin solutions were different from those produced by a solution of 10% trimellitic anhydride; formalin solutions stimulated production of IFN-γ, whereas trimellitic anhydride stimulated production of IL-10. The investigators concluded that these data are consistent with studies of occupationally-exposed workers suggesting that formaldehyde is a contact dermal allergen, but an equivocal agent for respiratory sensitization.

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 2-5.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following dermal exposure to formaldehyde.

2.2.3.5 Reproductive Effects

No reports of reproductive effects in humans after dermal exposure were found.

Overman (1985) conducted a study designed to evaluate the embryotoxic effects of topical exposure to formaldehyde in pregnant hamsters. Virgin female hamsters (Lak LVG[SYR] Golden Syrian) were bred and then treated directly on the skin with 0.5 mL formaldehyde solution (37%) on gestation days 8, 9, 10, or 11 for 2 hours. The animals (including controls) were anesthetized during treatment to prevent grooming. After the 2-hour treatment period, the skin of the animals was washed thoroughly with water to remove any remaining formaldehyde. Fetuses were recovered by laparotomy at gestation day 15, fixed in Bouin's fixative or in 95% ethyl alcohol. Fixed fetuses were blotted dry, weighed, measured (crown-rump length), and examined for malformations by free-hand sectioning technique. Fetuses fixed in ethyl alcohol were cleared and stained for skeletal tissue observation. Exposure did not significantly affect maternal weight gain, but a statistically significant increased incidence of resorptions in treated litters was observed (3–8% of sites resorbed versus none in controls). Overman (1985) suggested that this effect may have been caused by the stress of treatment during pregnancy rather than to a direct effect of formaldehyde, noting that exposed animals scratched at treated areas and were “irritable and hard to handle” for 1 to 2 days after treatment.

The LOAEL value of 0.5 mL of a 37% solution for increased resorptions is recorded in Table 2-5.

2.2.3.6 Developmental Effects

No reports of developmental effects in humans after dermal exposure to formaldehyde were found.

In the hamster study by Overman (1985) described in the previous section, formaldehyde treatment did not significantly change fetal crown rump length or fetal body weights. After treatment on day 8, two fetuses from the same litter were significantly smaller than their littermates (>3 sd below mean). After treatment on day 10, one fetus of normal size had a subcutaneous hemorrhage in the dorsal cervical region. There were no skeletal malformations found, and no other malformations were observed during the course of the study.

The NOAEL value of 0.5 mL of 37% solution for no developmental effects is recorded in Table 2-5.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to formaldehyde. Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Studies on cancer incidence in humans exposed occupationally to formaldehyde are discussed in Section 2.2.1.8.

In one laboratory animal study reported by Iversen (1986), the carcinogenic potential of formaldehyde using classical skin painting experiments was determined. Formalin (37% formaldehyde volume/volume) was dissolved in distilled water at final concentrations of 1 and 10% formaldehyde. Groups of hairless mice (hr/hr Oslo strain) consisting of 16 males and 16 females were dosed with 0.2 mL of 1% formaldehyde in water on the skin of the back twice per week for a total of 60 weeks. A second group of identical composition was dosed with a 10% formaldehyde solution in like manner for 60 weeks. A third group of mice was initially painted with 51.2 µg dimethylbenz(a)anthracene (DMBA) in 0.1 mL acetone and 9 days later, received a twice weekly treatment regimen of paintings with 10% formaldehyde in water. Animals dosed with 10% formaldehyde generally had slight epidermal hyperplasia, and a few animals had cutaneous ulcers and scratches. In animals dosed with DMBA followed by formaldehyde, 3 animals developed lung adenomas, while 11 animals developed a total of 25 skin tumors (3 squamous cell carcinomas and 22 papillomas). There was no evidence of any other tumor type. Skin painting with either 1 or 10% formaldehyde alone had no significant carcinogenic potential; however, dermal exposure to 10% formaldehyde after DMBA dosing significantly reduced the latency period of DMBA-induced tumors.

No statistically significant increased incidence of formaldehyde-induced skin tumors was found in a second study with SENCAR mice, a strain of mouse bred for maximal sensitivity to chemically induced tumors (Iverson 1988). Groups of 16 male and 16 female mice were dosed with 0.1 mL acetone or 0.2 mL 4% formaldehyde (in water) twice weekly for 58 weeks. Two animals with small benign skin papillomas were found in the exposed group and also in the acetone-control group. In this study, twice weekly dermal application of 0.2 mL 4% formaldehyde following application of a single 51.2 µg dose of DMBA did not significantly affect the skin tumor yield compared with DMBA alone, but, like in the

study with hr/hr Oslo mice, decreased the latency period for the appearance of DMBA-induced skin tumors. The report of this study did not mention if non-neoplastic skin lesions were produced by exposure with 4% formaldehyde solutions.

2.3 TOXICOKINETICS

The toxicokinetics of formaldehyde after inhalation, oral, or dermal exposure has been reported in several species by many investigators. The toxicokinetics in all of the animals studied is similar across species lines. 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. After oxidation of formaldehyde to formate, the carbon atom is further oxidized to carbon dioxide (CO_2) or incorporated into purines, thymidine, and amino acids via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Exogenous formaldehyde appears to be readily absorbed from the respiratory and gastrointestinal tracts, but poorly absorbed following dermal application. Formaldehyde is metabolized to formate by the enzyme formaldehyde dehydrogenase; this appears to take place at the initial site of contact. Being normal components of intermediary metabolism, neither formaldehyde nor formate are stored to any significant extent in any tissue of the body. Formate is either excreted in the urine (primarily as formic acid), incorporated into other cellular molecules, or oxidized to carbon dioxide and exhaled.

In the metabolic labeling studies using ^{14}C-formaldehyde discussed below, it should be noted that the detection of the ^{14}C radiolabel does not imply that it is still in the form of unmetabolized formaldehyde.

2.3.1 Absorption

Formaldehyde vapors are readily absorbed from the respiratory tract. Due to rapid metabolism to formate, little, if any, intact formaldehyde can be found in the blood of humans or animals exposed to formaldehyde. Formaldehyde is also readily absorbed from the gastrointestinal tract and meets with the same metabolic fate as formaldehyde after inhalation exposure. The studies available in the open literature suggest that very little formaldehyde is absorbed via the dermal route. In all cases, absorption appears to be limited to cell layers immediately adjacent to the point of contact. Entry of formaldehyde into the blood (i.e., systemic absorption) occurs to a very limited extent, if at all.

2.3.1.1 Inhalation Exposure

Formaldehyde is absorbed by the tissues of the respiratory tract during inhalation exposure in several species. Heck et al. (1985) determined the fate of inhaled formaldehyde in humans. Four men and two women were exposed to a 1.9 ppm air concentration of formaldehyde in a large walkin chamber for 40 minutes. Shortly before and shortly after the exposure, venous blood samples were taken from each person (each person served as his/her own control) and the blood was analyzed for formaldehyde content. Mean venous blood formaldehyde concentrations in humans prior to exposure showed a blood concentration of 2.61±0.41 μg/g of blood. Individual variability was markedly present. Immediately after a 40-minute exposure, mean blood concentration of formaldehyde was 2.77±0.28 μg/g of blood. There was no significant difference between pre- and postexposure blood concentrations of formaldehyde at the formaldehyde air concentrations tested in this study. This result suggests that formaldehyde was absorbed only into the tissues of the respiratory tract. The absence of increased formaldehyde concentrations in the blood is likely due to its rapid metabolism in these tissues and/or fast reaction with cellular macromolecules.

Heck et al. (1985) also determined the fate of inhaled formaldehyde in the rat. Male Fischer 344 rats were placed in a nose-only inhalation chamber and exposed to a 14.4±2.4 ppm air concentration of formaldehyde for 2 hours, were sacrificed, and a venous blood sample was collected and analyzed for formaldehyde content. Unexposed control rats had a mean formaldehyde blood level of 2.24±0.07 μg/g of blood. Rats exposed to the 14.4 ppm air concentration of formaldehyde had blood concentrations of 2.25±0.07 μg/g. These results indicate that during a nose-only inhalation exposure of rats to this concentration of formaldehyde, no significant quantities of formaldehyde could be detected in the blood. Lack of increase in blood formaldehyde levels indicates that only local absorption took place and absorbed formaldehyde was metabolized before reaching the bloodstream. In a similar study by Heck et al. (1983), Fischer 344 rats were exposed by inhalation to ^{14}C-formaldehyde at 8 ppm for 6 hours. Concentrations of total ^{14}C radioactivity (most likely as ^{14}C-formate) in the whole blood and plasma were monitored for an additional 8 days. Plasma concentrations of ^{14}C increased over the exposure period, reaching a maximum at the termination of exposure. Plasma ^{14}C concentrations then declined slowly over the next few days.

Using dogs as a model, Egle(1972) determined the respiratory fate of formaldehyde and other aldehydes. This study measured the retention of formaldehyde along the entire respiratory tract, both upper and

lower portions, and measured the effects of ventilation rate, tidal volume, and concentration of inhaled formaldehyde. Mongrel dogs of both sexes (at least 4 dogs per experiment) were anesthetized and exposed to 0.15–0.35 µg (122–235 ppm) of formaldehyde vapor produced from formalin. The retention of formaldehyde was measured over the entire respiratory tract, including the upper region only (nose and trachea, down to the bifurcation of the trachea), lower region only (from the bifurcation of the trachea, bronchioles, and below), and over the entire respiratory tract. Retention of formaldehyde (amount of formaldehyde not returning after an exhalation) when the entire upper and lower respiratory tract was exposed to formaldehyde vapors was near 100% and seemed to be independent of the airborne concentration of formaldehyde or variations in the tidal volume. When the upper respiratory tract was isolated from the lungs, the 2-way exposures showed a 100% uptake of formaldehyde. The 1-way exposures of formaldehyde showed that the retention of formaldehyde was slightly lower than in the 2-way exposure, but the uptake of formaldehyde still exceeded 95% at all respiratory rates. When the lower respiratory tract was isolated and examined, the uptake of formaldehyde still exceeded 95%; however, it appeared to decrease slightly as the ventilation rates increased. This study concluded that when formaldehyde is inhaled at the concentrations studied, very little formaldehyde vapor would actually reach the lower respiratory tract.

In another study by Casanova et al. (1988), blood levels of formaldehyde were determined in Rhesus monkeys after exposure to 6 ppm formaldehyde for 6 hours/day, 5 days/week for 4 weeks. Immediately after the last exposure, the monkeys were sedated and blood samples were collected within 7 minutes and at 45 hours after exposure. Blood samples were analyzed for formaldehyde content by gas chromatography/mass spectrometry (GC/MS). Mean blood concentrations at 7 minutes and 45 hours postexposure were 1.84 and 2.04 µg/g, respectively. Blood concentrations of formaldehyde in the three nonexposed monkeys (2.42 µg/g) were not significantly different from those of the exposed group. The authors concluded that exposure to moderately high levels of formaldehyde had no effect on blood concentrations due to rapid local metabolism.

2.3.1.2 Oral Exposure

Formaldehyde is absorbed from the gastrointestinal system after ingestion. Eells et al. (1981) described the case of a 41-year-old woman who swallowed 120 mL (624 mg/kg) of a formaldehyde solution (as formalin). Formic acid accumulated in the blood rapidly after formaldehyde ingestion. Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of a formaldehyde solution

containing methanol in a suicide attempt. Blood methanol levels continued to climb throughout 12 hours of observation. The apparent half-life for formaldehyde was 3.3 hours.

In a study by Galli et al. (1983), the absorption, fate, and excretion of the complexes between ^{14}C-formaldehyde and milk proteins in mice and rats, and their toxicological significance were examined. Male Sprague-Dawley rats were given a single oral dose of 2.2 g (18 µCi) ^{14}C-labeled grana cheese. Groups of rats were sacrificed 4, 8, 16, 32, and 64 hours after the end of food consumption. Blood, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, and adipose tissues were removed, and urine and feces were collected from metabolic chambers. In all cases, the biological samples were immediately frozen after removal until used for radioactivity measurement. Within 32 hours of administration, 67% of the radioactivity had been excreted in the feces and urine and 28% of the radioactivity had been exhaled as $^{14}CO_2$ in rats, indicating absorption from the ingested cheese. In the companion study, male Swiss albino mice (CD-1) were given a single oral dose of 0.5 g (4 µCi) ^{14}C-labeled grana cheese. The cheese was made by following the usual process but using milk with added ^{14}C-formaldehyde. Rats fed with unlabeled cheese were used as controls. Groups of mice were sacrificed after 2, 4, 8, 16, 32, 64, and 96 hours and 8 and 12 days. Within 32 hours of administration, 64% of the radioactivity had been excreted in the feces and urine and 24% of the radioactivity had been exhaled as $^{14}CO_2$, indicating absorption from the ingested cheese.

A study by Barry and Tome (1991) sought to quantitate the concentration of formaldehyde in the milk of goats given feed containing varying amounts of formaldehyde-treated soybean oil-meal. The goat ration consisted of 750 g medium quality grass hay, 600 g maize-based concentrate, and 600 g soybean oil-meal; the soybean oil-meal was either treated with formaldehyde, untreated, or a 50:50 mixture. Five lactating adult Alpine goats each received 1 of 3 diets (no formaldehyde; 28 mg/kg formaldehyde; a 50:50 mixture of the 2 rations, equal to 14 mg/kg formaldehyde) for 1 week. Milk samples from the last 5 days of each dosing period were collected and analyzed for formaldehyde content by high performance liquid chromatography. Mean milk formaldehyde concentrations were 0.033, 0.083, and 0.153 mg/kg in the 0, 14, and 28 mg/kg/day groups, respectively. These values were significantly different from each other ($p<0.05$), and were highly correlated with formaldehyde intake ($r=0.938$, $p<0.01$), and indicate absorption from the gastrointestinal tract.

Buckley et al. (1988) measured formaldehyde levels in the milk and blood of dairy cows given formalin-treated whey. Twelve Holstein cows in their first trimester of lactation were used in a series of three

feeding trials lasting 35 days and separated from each other by 14 days. Six of the cows received a diet consisting of low-energy pelleted concentrate, liquid acid whey, and grass hay. The whey was fed once a day beginning at 10:00 am, and all whey was consumed by 4:30 pm. In the three trials, the calculated amounts of ingested formalin were 19.9, 39.7, and 59.4 mg/kg/day, respectively. The remaining six cows received untreated whey throughout the three trials. Morning milk was sampled on days 3, 2, 3, 4, 5, 6, 13, 20, 27, and 34 of each 35-day trial. Blood samples were collected on the day before initiation of the third trial, and on days 9 and 33. Formaldehyde levels were below detectable limits prior to and at 46 hours after the completion of each trial. The levels of formaldehyde in milk were positively correlated to dose ($p<0.01$, no other details given). In a companion study (Buckley et al. 1988), formaldehyde levels were measured in the muscle tissues of dairy calves fed formalin-treated whey. Eighteen Holstein bull calves were fed diets containing whey treated with formalin at doses of 0, 0.05, or 0.1% (n=6 per treatment group). Calves were individually fed the formalin-treated whey in two equal feedings daily. Two calves from each treatment group were sacrificed at days 81, 88, and 95. Blood samples were collected on the day before sacrifice. At sacrifice, sections of muscle, kidney, liver, and heart were obtained for formaldehyde determinations. Concentrations of formaldehyde in fresh muscle samples of the high-dose group (0.256 µg/g) were significantly greater than those of controls (0.178 µg/g) ($p<0.05$). Concentrations of formaldehyde in fresh blood and frozen heart, kidney, liver, and muscle samples of treated animals were similar across treatment groups.

2.3.1.3 Dermal Exposure

Jeffcoat et al. (1983) studied the absorption and disposition of ^{14}C-formaldehyde administered topically to Fischer 344 rats, Dunkin-Hartley guinea pigs, and Cynomolgus monkeys. One day prior to formaldehyde exposure, each monkey had a portion of its posterior shaved and had a carotid artery catheter implanted. Monkeys were placed in restraining chairs for drug delivery, and plexiglass hoods were placed around the animals' heads for the collection of expired air. Animals were dosed with 2 mg ^{14}C-formaldehyde in 200 µL of aqueous carrier solution, applied to an 18 cm^2 area. The ^{14}C content in each dose was approximately 590–730 µCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Urine and feces were collected at daily intervals for 3 days. Expired air was passed through two sodium hydroxide (NaOH) traps which were changed each time a blood sample was collected. Rats and guinea pigs were housed individually in glass metabolism cages, which allowed the collection of urine, feces, and the combination of expired air and evaporation products from excreta. One day prior to formaldehyde exposure, each animal had a portion of its back shaved and had a carotid artery catheter

implanted. Animals were dosed with an aqueous solution which was applied to a 2 cm^2 area. The dose applied was either 0.1 mg in 10 µL of solution or 11.2 mg in 40 µL of solution; the ^{14}C content in each dose was approximately 30 µCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Animals were sacrificed 72 hours after exposure began. Data from the monkeys were more variable than the rats and guinea pigs. The sum of ^{14}C recovered in the excreta of monkeys (urine, feces, and expired air) was <1%. The concentration of ^{14}C in the blood was extremely low, averaging approximately 0.015% of the dose over the estimated blood volume. After 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The application site contained approximately 9.5% of the ^{14}C dose. In rats dosed with 0.05 or 5.6 mg/cm^2 ^{14}C-formaldehyde, the total recoveries of ^{14}C for the low and high doses were 73.4 and 60.4%, respectively. Approximately 28% of the low dose and 22% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.12% of the low dose and 0.13% of the high dose over the total estimated blood volume. At 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The application site contained approximately 16% of the low-^{14}C dose and 3% of the high dose. In guinea pigs receiving 0.05 or 5.6 mg/cm^2 ^{14}C-formaldehyde, total recoveries of ^{14}C for the low and high doses were 70 and 63.6%, respectively. Approximately 21% of the low dose and 24% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 6% of the low dose and 8% of the high dose was excreted in the urine and feces combined. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.1% of the low dose and 0.09% of the high dose of the estimated blood volume. After 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The application site contained approximately 16% of the low-^{14}C dose and 4% of the high dose. It appears that the skin of the monkey is much less permeable to formaldehyde than the skin of the rodent. Significant evaporation of formaldehyde from the skin application site also probably occurred in this study.

Bartnik et al. (1985) sought to characterize the absorption and excretion of percutaneously applied formaldehyde in male and female WISW rats. Twenty-four hours prior to dosing, the dorsal skin hair of all rats was carefully clipped to avoid abrasions. Ten male and 4 female rats were dosed with 200 mg of cream containing 0.1% ^{14}C-formaldehyde. The dosing area of each rat was covered with a glass capsule; in all cases except two males, the glass capsules were perforated, resulting in a nonocclusive application. The dose areas of the remaining two males were covered with solid glass capsules, resulting in an

occluded application. The cream remained on the skin for 48 hours, during which time urine, feces, and air samples were collected. Air samples were passed through a series of filters to separate ^{14}C-formaldehyde and $^{14}CO_2$. At the end of the study, rats were sacrificed, the treated area of skin was removed and dissolved, fecal samples and the remaining carcass were homogenized, and air-trap samples were processed for ^{14}C determinations. The amount of ^{14}C remaining in the treated skin was similar in occluded and nonoccluded animals (69.9 versus 70.2%). Total percutaneous absorption in 48 hours was 6.1% of the applied radioactivity. Of this amount, 38% was recovered in urine, 11% in the feces, 21% as respired CO_2, and 30% in the carcass. Absorption was lower in occluded (3.4%) than in nonoccluded animals (6.1%). The authors speculate that the greater formaldehyde absorption seen in the animals with nonoccluded dose sites was due to some of the volatilized formaldehyde being inhaled by the animals prior to being trapped. The authors did not specify the fate of dose in the treated skin (i.e., loose or bound on surface, or actually integrated into skin).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located that described the distribution of formaldehyde or its metabolites in humans after inhalation exposure. Several studies are available that describe the distribution of formaldehyde in laboratory animals. Heck et al. (1983) examined the fate of ^{14}C-formaldehyde in Fischer 344 rats. Rats were exposed by inhalation to ^{14}C-formaldehyde at 8 ppm for 6 hours. Concentrations of total radioactivity in the whole blood and plasma were monitored for 8 days. The terminal half-life of the ^{14}C was approximately 55 hours, which was considerably longer than the known half-life of formaldehyde (about 1.5 minutes in monkeys), indicating both the metabolism of ^{14}C-CH_2O to other molecules (i.e., formate) and incorporation into other molecules. Radioactivity in the packed blood cell fraction was multiphasic; it initially increased during exposure, declined during the first hour postexposure, then began to increase again, reaching a maximum at approximately 35 hours postexposure. The terminal phase of the packed red blood cell fraction had a very slow decline in radioactivity, which would likely continue for several weeks after exposure ended (half-life >55 hours).

Heck et al. (1983) also examined distribution of ^{14}C-formaldehyde in formaldehyde-naive and formaldehyde-pretreated male Fischer 344 rats. Pretreated rats were exposed whole-body to 15 ppm formaldehyde 6 hours/day for 9 days. On the tenth day, these rats and the formaldehyde-naive rats (never

exposed to formaldehyde vapors) were then exposed head-only to ^{14}C-formaldehyde at concentrations of 14.9 ppm for 6 hours. All rats were sacrificed immediately after completion of the ^{14}C-formaldehyde exposure. Immediately after completion of the inhalation exposure, ^{14}C concentrations were greatest in the mucosal tissues. At 15 ppm, ^{14}C concentrations were as follows: nasal mucosa, 2 µmole equivalents/g tissue; trachea, 0.3 µmole equivalents/g tissue; and plasma, 0.1 µmole equivalents/g tissue. Radioactive concentrations were relatively equivalent in all of the mucosal linings monitored. Tissue concentrations of ^{14}C in naive and pretreated rats did not differ from each other. Tissue concentrations of ^{14}C were low, resembling plasma concentrations; the ratio of ^{14}C in internal organs to that in plasma were: esophagus, 4.94±1.23; kidney, 3.12±0.47; liver, 2.77±0.25; intestine, 2.64±0.48; lung, 2.05±0.36; spleen, 1.59±0.50; heart, 1.09±0.09; brain, 0.37±0.06; testes, 0.31±0.05; and erythrocytes, 0.30±0.08.

Distribution studies by Chang et al. (1983) investigated the effects of previous formaldehyde exposure on its distribution after inhalation exposure in male Fischer 344 rats and male B6C3F1 mice. Some rats and mice were exposed to only one dose of ^{14}C-formaldehyde (15 ppm for 6 hours) (naive mice), while another group was exposed to formaldehyde (nose-only) at a concentration of 15 ppm for 6 hours/day for 4 days and then additionally exposed to ^{14}C-formaldehyde (nose-only) at a concentration of 15 ppm for 6 hours (pretreated group). After exposure, the mice were immediately sacrificed and prepared for whole-body radiography. The amounts of radioactivity deposited in the nasal cavities of naive and pretreated rats were similar. Pretreated rats had less visceral radioactivity compared to naive animals. However, more radioactivity was found in the nasal cavity of naive mice than in pretreated mice. The decreased visceral radioactivity seen in the pretreated mice was thought to be due to decreased grooming and mucociliary clearance.

Early studies by Casanova-Schmitz et al. (1984a) examined the mechanisms of labeling of macromolecules (DNA, RNA, and proteins) in the respiratory and olfactory mucosa and bone marrow of male Fischer 344 rats. Rats were exposed nose-only for 6 hours to 0.3, 2, 6, 10, or 15 ppm mixtures of ^{14}C and ^{3}H-formaldehyde 1 day after a 6-hour exposure to the same concentration of unlabeled formaldehyde. The predominant route of macromolecule labeling was metabolic incorporation. There was some evidence of DNA-protein cross linking present in the nasal tissues. It was found that concentrations of ^{14}C DNA in respiratory and olfactory mucosa tissues increased linearly with dose; at any given dose, the concentrations of ^{14}C DNA in respiratory mucosa tissues were approximately two to three times that in olfactory mucosa tissues. Incorporation of ^{14}C into DNA increased with exposure concentrations #6 ppm, but decreased at 10 and 15 ppm, suggesting an inhibition of DNA synthesis.

Studies by Casanova et al. (1991a, 1991b) described the formation of DNA-protein cross links in the respiratory tract measured in male Fischer 344 rats and Rhesus monkeys. Rats were exposed nose-only to a mixture of ^{14}C-labeled and nonradiolabeled formaldehyde at concentrations of 0.3, 0.7, 2, 6, or 10 ppm for 6 hours. Formaldehyde-DNA-protein cross links were detected at all concentrations tested. Male Rhesus monkeys were exposed to 0.7, 2, or 6 ppm formaldehyde ^{14}C-labeled and nonradiolabeled mixture for 6 hours, and it was determined that approximately 90% of all ^{14}C was associated with the thymine, while 10% was associated with the guanine and adenine. Concentrations of formaldehyde-protein cross links were greatest in the middle turbinate tissues and lowest in the nasopharyngeal tissues. Some evidence of cross link formation was seen in the larynx/trachea/carina and major intrapulmonary airway tissues of two monkeys in the high-dose group. No evidence of cross link formation was seen in the sinus or lung tissues at any exposure concentration.

2.3.2.2 Oral Exposure

In a study by Galli et al. (1983), the fate of the complexes between ^{14}C-formaldehyde and milk proteins in mice and rats, and their toxicological significance were examined. Male Sprague-Dawley rats were given a single oral dose of 2.2 g (18 μCi) ^{14}C-labeled grana cheese. The cheese was made by following the usual process but using milk with added ^{14}C-formaldehyde. Animals fed with unlabeled cheese were used as controls. Groups of rats were sacrificed 4, 8, 16, 32, and 64 hours after the end of food consumption. Blood, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, and adipose tissues were removed, and urine and feces were collected from metabolic chambers. In all cases, the biological samples were immediately frozen after removal until used for radioactivity measurement. Peak radioactivity concentrations in the tissues occurred 16 hours after food consumption. The maximum concentrations of ^{14}C-activity equivalent to a value of 0.08% of the dose were present after 8 hours in the rat blood. In the companion study, male Swiss albino mice (CD-1) were given a single oral dose of 0.5 g (4 μCi) ^{14}C-labeled grana cheese. The highest concentrations of radioactivity in the liver, kidney, adipose tissue, spleen, testes, brain, and muscle occurred 4 hours after administration. The maximum concentrations of ^{14}C-activity equivalent to a value of 0.03% of the dose were present after 2 hours in the blood of mice.

Buckley et al. (1988) measured formaldehyde levels in the milk and blood of dairy cows given formalin-treated whey. There was a high degree of variability in milk and blood concentrations, presumably due to the variable amount of time (several minutes to 7 hours) taken to consume the treated feed. In a

companion study, Buckley et al. (1988) measured formaldehyde levels in the muscle tissues of dairy calves fed formalin-treated whey. Eighteen Holstein bull calves were fed diets containing whey treated with formalin at doses of 0, 0.05, or 0.1%. Calves were individually fed the formalin-treated whey in two equal feedings daily. Two calves from each treatment group were sacrificed at days 81, 88, and 95. Blood samples were collected on the day before sacrifice. At sacrifice, sections of muscle, kidney, liver, and heart were obtained for formaldehyde determinations. Concentrations of formaldehyde in fresh muscle samples of the high-dose group (0.256 µg/g) were significantly greater than those of controls (0.178 µg/g). Concentrations of formaldehyde in fresh blood and frozen heart, kidney, liver, and muscle samples were similar across treatment groups.

2.3.2.3 Dermal Exposure

Jeffcoat et al. (1983) studied the disposition of ^{14}C-formaldehyde administered topically to Fischer 344 rats, Dunkin-Hartley guinea pigs, and Cynomolgus monkeys. One day prior to formaldehyde exposure, each monkey had a portion of its posterior shaved and had a carotid artery catheter implanted. Monkeys were placed in restraining chairs for drug delivery, and a plexiglass hood was placed around their heads for the collection of expired air. Animals were dosed with an aqueous solution which was applied to an 18 cm^2 area. A dose of 2 mg in 200 µL of solution was applied to the skin surface; the ^{14}C content in each dose was approximately 590–730 µCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Urine and feces were collected at daily intervals for 3 days. Expired air was passed through two NaOH traps which were changed each time a blood sample was collected. At 72 hours after dosing, the animals were sacrificed and the following tissues were collected and analyzed for ^{14}C content: heart, liver, lung, spleen, kidney, leg, brain, gonads, application site skin, and distant skin; the remaining carcass was also analyzed for ^{14}C content. Rats and guinea pigs were housed individually in glass metabolism cages, which allowed the collection of urine, feces, and the combination of expired air and evaporation products from excreta. One day prior to formaldehyde exposure, each animal had a portion of its back shaved and had a carotid artery catheter implanted. Animals were dosed with an aqueous solution which was applied to a 2 cm^2 area. The dose applied was either 0.1 mg in 10 µL of solution or 11.2 mg in 40 µL of solution; the ^{14}C content in each dose was approximately 30 µCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Urine and feces were collected at daily intervals for 3 days. Air exiting the metabolism cages was passed through two NaOH traps which were changed each time a blood sample was collected and at 48 and 72 hours after dosing. At 72 hours after dosing, the animals were sacrificed and the following tissues were collected and analyzed for ^{14}C content: heart, liver, lung, spleen, kidney, leg, brain, gonads, application site skin, and distant skin; the remaining

carcass was also analyzed for ^{14}C content. Data from the monkeys were more variable than the rats and guinea pigs. The sum of ^{14}C recovered in the excreta (urine, feces, and expired air) was <1%. The concentration of ^{14}C in the blood was also low, averaging approximately 0.015% of the dose over the estimated blood volume. At 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The total amount of radioactivity recovered in all internal organs combined was <0.05% of the applied dose; the ^{14}C was distributed fairly evenly across all tissues.

In rats, the application site contained approximately 9.5% of the ^{14}C activity, with a total recoveries of ^{14}C for the low and high doses of 73.4 and 60.4%, respectively. Less than 3% of ^{14}C in the air was in the form of CO_2. About 7% of the low dose and 9% of the high dose was excreted in the urine and feces combined. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.12% of the low dose and 0.13% of the high dose over the total estimated blood volume. After 72 hours, no large accumulation of ^{14}C radioactivity occurred in any tissue measured in rats. The application site contained approximately 16% of the low-^{14}C dose and 3% of the high dose.

In guinea pigs, total recoveries of ^{14}C for the low and high doses were 70 and 63.6%, respectively. Approximately 21% of the low dose and 24% of the high dose were collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 6% of the low dose and 8% of the high dose was excreted in the urine and feces combined. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.1% of the low dose and 0.09% of the high dose over the total estimated blood volume. After 72 hours, no large accumulation of ^{14}C occurred in any tissue measured. The application site contained approximately 16% of the low-^{14}C dose and 4% of the high dose. The authors concluded that topically applied formaldehyde, once absorbed, was primarily excreted by the urinary and fecal routes.

2.3.3 Metabolism

Formaldehyde is rapidly metabolized and storage is not a factor in its toxicity. The metabolism of formaldehyde to formate (via formaldehyde dehydrogenase/class III alcohol dehydrogenase) takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde, and the formate is quickly removed by the supporting blood supply (Heck et al. 1982). Formaldehyde

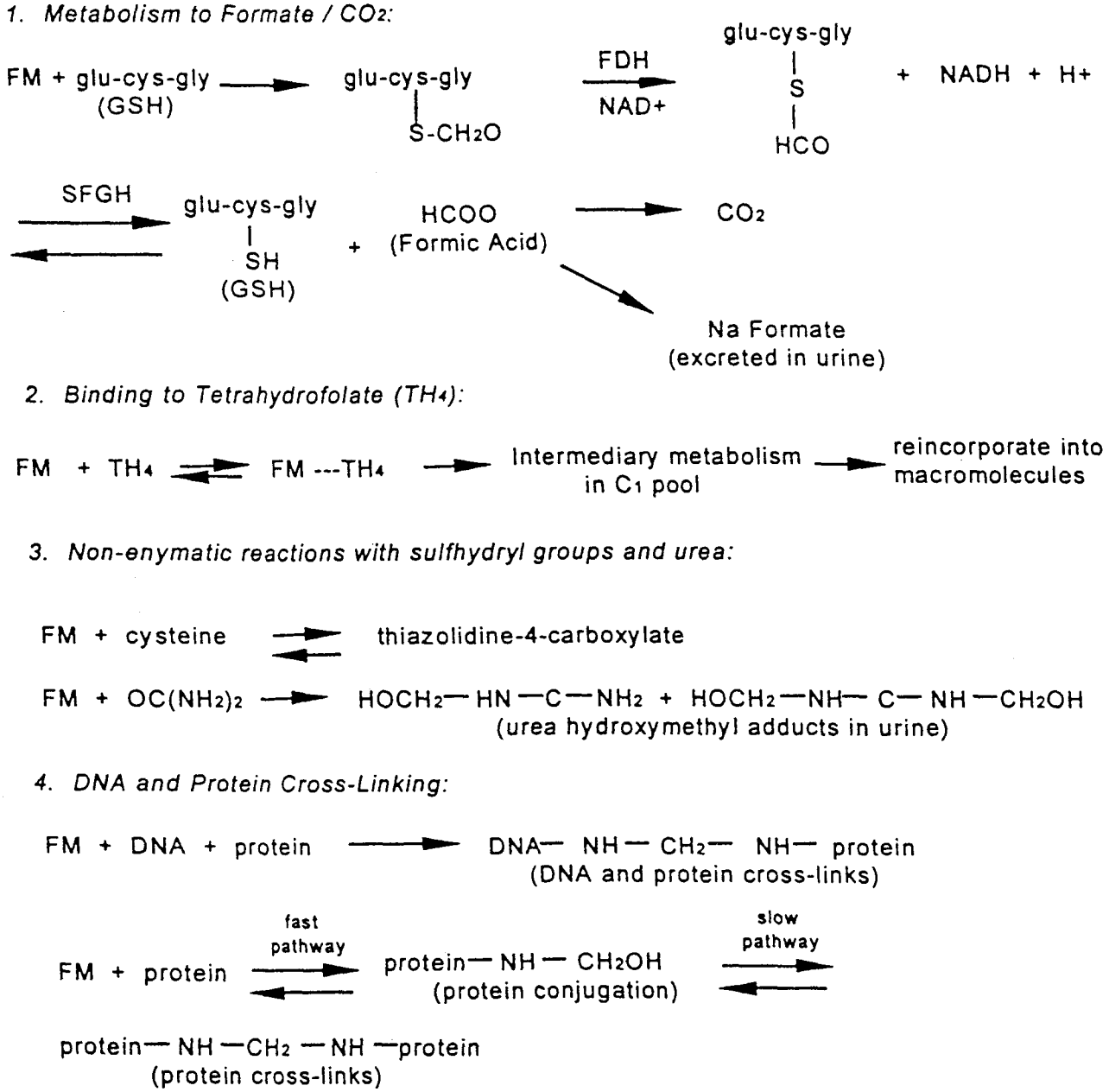
dehydrogenase (FDH) is the major metabolic enzyme involved in the metabolism of formaldehyde in all of the tissues studied; it is widely distributed in animal tissues, particularly in the rat nasal mucosa, and is specific for the glutathione adduct of formaldehyde. If formaldehyde is not metabolized by FDH, then it can form cross linkages between proteins, between protein and single-stranded DNA (see Figure 2-3) or enter the 1 carbon intermediary metabolic pool by initially binding to tetrahydrofolate (Bolt 1987). Several enzymes can catalyze the reaction that oxidizes formaldehyde to formic acid (i.e., nonspecific aldehyde dehydrogenase and catalase); however, FDH is the primary enzyme that performs this function and is specific for formaldehyde; other aldehydes are left intact in the presence of FDH. Endogenous or exogenous formaldehyde enters the FDH metabolic pathway and is eliminated from the body as metabolites, primarily as formate or CO_2. Formaldehyde dehydrogenase activity does not increase (i.e., not inducible) in response to formaldehyde exposure (Casanova-Schmitz et al. 1984b); thus no increase in metabolism occurs.

A summary of the metabolic pathways for formaldehyde metabolism is represented in Figure 2-3.

2.3.3.1 Inhalation Exposure.

Heck et al. (1985) determined the fate of inhaled formaldehyde in the human. Four men and two women were exposed to a 1.9±0.06 ppm air concentration of formaldehyde in a large walk-in chamber for 40 minutes. Shortly before and shortly after the exposure, venous blood samples were taken from each person (each person served as his/her own control) and the blood was analyzed for formaldehyde content. Mean venous blood formaldehyde concentrations in humans prior to exposure showed a blood concentration of 2.61±0.41 µg/g of blood. Individual variability was markedly present. Immediately after a 40-minute exposure, mean blood concentration of formaldehyde was 2.77±0.28 µg/g of blood. There was no significant difference between pre- and postexposure blood concentrations of formaldehyde at the formaldehyde air concentrations tested in this study, most likely indicating rapid metabolism and/or local absorption in the respiratory tract mucosa rather than systemic absorption into the blood. In the same report by Heck et al. (1985), the fate of inhaled formaldehyde was determined in the rat. Male Fischer 344 rats were placed in a nose-only inhalation chamber and exposed to a 14.4±2.4 ppm air concentration of formaldehyde for 2 hours, were sacrificed, and a venous blood sample was collected and analyzed for formaldehyde content. Unexposed control rats had a mean formaldehyde blood level of 2.24±0.07 µg/g of blood while rats exposed to the 14.4 ppm air concentration of formaldehyde had blood concentrations of 2.25±0.07 µg/g. These results indicate that during a nose-only

Figure 2-3. Metabolic Pathways of Formaldehyde Biotransformation



Key to Figure:

FM = Formaldehyde TH4 = Tetra hydrofolate DNA = Deoxyribonucleic Acid GSH = Glutathione
NAD+ = Nicotinomide adenosine dinucleotide SFGH = S-Formyl Glutathione hydrolase
FDH = Formaldehyde Dehydrogenase

Sources: Bolt 1987; Restani & Balli 1991; d'A. Heck et al. 1990; IARC 1995; WHO 1989; Casanova-Schmitz et al. 1984

inhalation exposure of rats to this concentration of formaldehyde, no significant quantities of formaldehyde can be detected in the blood, most likely indicating fast metabolism and/or local absorption in the respiratory tract mucosa.

Heck et al. (1982) studied the effects of formaldehyde exposure on nasal mucosal tissue in male Fischer 344 rats. Rats were exposed to clean air or air containing 6 ppm formaldehyde for 10 days, 6 hours/day. Immediately after the last exposure, animals were sacrificed and nasal mucosal tissues were isolated. The tissues were homogenized and formaldehyde was extracted and analyzed by GC/MS. The mean concentration of formaldehyde in the nasal mucosal tissues of rats exposed to 6 ppm formaldehyde (0.39 µmol/g tissue) was not significantly different from the mean concentrations found in the tissues of control animals (0.42 µmol/g tissue). The authors attributed this to the rapid metabolism of formaldehyde to formate or the rapid irreversible binding of formaldehyde to macromolecules.

The ability of respiratory and olfactory tissues to oxidize formaldehyde was examined in male Fischer 344 rats. To determine the effects of repeated formaldehyde exposure on enzyme activities, rats were exposed to 15 ppm formaldehyde 6 hours/day for 10 days. At the completion of formaldehyde exposure, rats were sacrificed and respiratory and olfactory mucosal tissues were harvested. The enzymatic capacity of the tissues was determined in the presence and absence of glutathione. Tissue homogenates from both the respiratory and olfactory mucosae demonstrated the ability to oxidize formaldehyde; the oxidation of formaldehyde occurred at similar rates in the respiratory and olfactory mucosal homogenates (Casanova-Schmitz et al. 1984b).

The effects of glutathione depletion on the cross linking of formaldehyde with macromolecules (DNA, RNA, and proteins) in the respiratory and olfactory mucosa and bone marrow of male Fischer 344 rats were examined by Casanova and Heck (1987). Rats were exposed nose-only for 3 hours to 0.9, 2, 4, 6, or 10 ppm mixtures of ^{14}C- and ^{3}H-formaldehyde 1 day after a 3-hour exposure to the same concentration of unlabeled formaldehyde. Two hours prior to the second exposure, five of the rats were injected with phorone in corn oil, and the other three were injected with corn oil alone. Phorone successfully depleted nonprotein sulfhydryls levels to minimal values. The metabolic incorporation of label into macromolecules was significantly decreased by this treatment, whereas the amount of DNA-protein cross linking significantly increased. Since formaldehyde oxidation depends on glutathione, this experiment suggests that when this process is inhibited, formaldehyde levels rise high enough to form DNA-protein cross links.

2.3.3.2 Oral Exposure.

Eells et al. (1981) describe the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting approximately 120 mL of formalin (624 mg/kg formaldehyde). Formic acid accumulated in the blood rapidly after formaldehyde ingestion.

2.3.3.3 Dermal Exposure

No information on metabolism of formaldehyde after dermal exposure was found in the literature.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Heck et al. (1983) examined the fate of ^{14}C-formaldehyde in male Fischer 344 rats. Rats were exposed to 0.63 or 13.1 ppm formaldehyde for 6 hours. Upon completion of the exposure, the rats were placed in metabolic cages which allowed the continuous collection of urine, feces, and expired air; they remained in the cages for 70 hours and were then sacrificed. The average $^{14}CO_2$ excretion was biphasic, with a rapid decline over the first 12 hours followed by a more gradual decline in excretion over the remainder of time. Changing the concentration of formaldehyde did not affect the proportion of dose recovered in each type of excreta. Radioactivity in urine accounted for 17.6 and 17.3% of the total radioactivity detected for low- and high-dose rats, respectively; radioactivity in feces accounted for 4.2 and 5.3% of the total respective amounts of recovered radioactivity. Exhalation was the major route of excretion, accounting for 39.4% of the low dose and 41.9% of the high dose. The amount of ^{14}C remaining in the carcass after 70 hours was roughly equivalent (38.9% of low dose; 35.2% of high dose) to that expired over the same period. At 15 ppm, ^{14}C concentrations exposure were as follows: nasal mucosa, 2 µmole equivalents/g tissue; trachea, 0.3 µmole equivalents/g tissue; and plasma, 0.1 µmole equivalents/g tissue.

2.3.4.2 Oral Exposure

In a study by Galli et al. (1983), the excretion of the complexes between ^{14}C-formaldehyde and milk proteins in mice and rats, and their toxicological significance were examined. Male Sprague-Dawley rats were given a single oral dose of ^{14}C-labeled grana cheese. Rats fed with unlabeled cheese were used as

controls. Groups of rats were sacrificed at 4, 8, 16, 32, and 64 hours after the end of food consumption. Blood, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, and adipose tissues were removed, and urine and feces were collected from metabolic chambers. In all cases, the biological samples were immediately frozen after removal until used for radioactivity measurement. Within 32 hours of administration in rats, 67% of the radioactivity had been excreted in the feces and urine and 28% of the radioactivity had been exhaled as $^{14}CO_2$. The half-life calculated from the regression line of the β phase (where $C_{(t)}=C_0\ [e^{-\alpha t} + e^{-\beta t}]$) in blood was found to be 26.4 hours for the rats. The liver was the only tissue where the radioactivity concentration/g tissue was equivalent to more than 0.1% of the administered dose 64 hours after the ingestion of ^{14}C-labeled cheese. Excretion of radioactivity by all routes from rats was completed within 32 hours. In the companion study, male Swiss albino mice (CD-1) were given a single oral dose of 0.5 g (4 μCi) ^{14}C-labeled grana cheese. Mice were sacrificed 2, 4, 8, 16, 32, 64, and 96 hours and 8 and 12 days. Within 32 hours of administration, 64% of the radioactivity had been excreted in the feces and urine and 24% of the radioactivity had been exhaled as $^{14}CO_2$. The half-life calculated from the regression line of the β phase in blood was found to be 27.8 hours for the mice. After 96 hours in all of the mouse tissues, the radioactivity concentration/g tissue was lower than 0.5% of the administered dose, and no radioactivity was detectable after 8 days. Excretion of radioactivity by all routes from mice was completed within 32 hours.

A study by Barry and Tome (1991) sought to quantitate the concentration of formaldehyde in the milk of goats given feed containing varying amounts of formaldehyde-treated soybean oil-meal. Mean milk formaldehyde concentrations were 0.033, 0.083, and 0.153 mg/kg in the 0, 14, and 28 mg/kg/day groups, respectively. These values were significantly different from each other ($p<0.05$) and were highly correlated with formaldehyde intake ($r=0.938$, $p<0.01$). The authors concluded that dietary formaldehyde is excreted in the milk of goats.

Buckley et al. (1988) measured formaldehyde levels in the milk and blood of dairy cows given formalin-treated whey. Twelve Holstein cows in their first trimester of lactation were used in a series of three feeding trials lasting 35 days and separated from each other by 14 days. Six of the cows received a diet consisting of low-energy pelleted concentrate, liquid acid whey, and grass hay. The whey was fed once a day beginning at 10:00 am, and all whey was consumed by 4:30 pm. In the three trials, the calculated amounts of ingested formalin were 19.9, 39.7, and 59.4 mg/kg/day, respectively. The remaining six cows received untreated whey throughout the three trials. The average total excretion of formaldehyde in milk in each of the three dose groups during each trial was 0.53, 1.41, and 2.80 mg, respectively.

2.3.4.3 Dermal Exposure

Jeffcoat et al. (1983) studied the elimination of ^{14}C-formaldehyde administered topically to Fischer 344 rats, Dunkin-Hartley guinea pigs, and Cynomolgus monkeys. Data from the monkeys were more variable than the rats and guinea pigs. The sum of ^{14}C recovered in the excreta (urine, feces, and expired air) was >1%. In rats, total recoveries of ^{14}C for the low and high doses were 73.4 and 60.4%, respectively. Approximately 28% of the low dose and 22% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 7% of the low dose and 9% of the high dose was excreted in the urine and feces combined. In guinea pigs, total recoveries of ^{14}C for the low and high doses were 70 and 63.6%, respectively. Approximately 21% of the low dose and 24% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 6% of the low dose and 8% of the high dose was excreted in the urine and feces combined. The authors concluded that the fate of topically applied formaldehyde differed significantly from that of formaldehyde administered internally.

Bartnik et al. (1985) sought to characterize the absorption and excretion of percutaneously applied formaldehyde in male and female WISW rats using occluded and nonoccluded application. Ten male and four female rats were dosed with 200 mg of cream containing 0.1% ^{14}C-formaldehyde. Excretion of ^{14}C (presumably formate) via feces, urine, and expired air was consistently lower in animals with occluded dose sites (0.2 versus 0.7%; 1.2 versus 2.3%; and 0.9 versus 1.3%, respectively). The authors speculate that the greater formaldehyde absorption seen in the animals with nonoccluded dose sites was due to some of the volatilized formaldehyde being inhaled by the animals prior to being trapped. The authors did not specify the fate of dose in the treated skin (i.e., loose or bound on surface, or actually integrated into skin).

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in

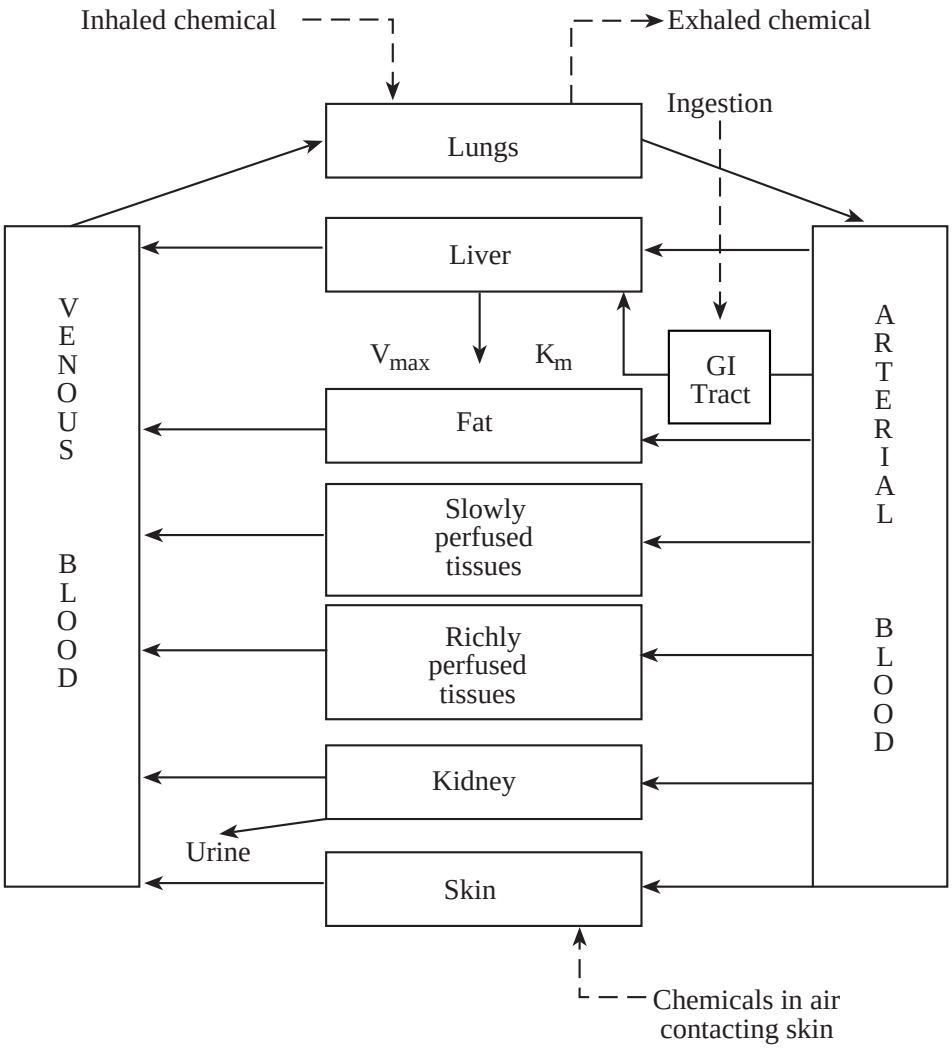
humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

PBPK models for formaldehyde are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Pharmacokinetic models to describe, as a function of formaldehyde air concentration, the rate of formation of formaldehyde-induced DNA-protein cross links in different regions of the nasal cavity have been developed for rats and monkeys (Casanova et al. 1991; Heck and Casanova 1994). Rates of formation of DNA-protein cross links have been used as a dose surrogate for formaldehyde tissue concentrations in extrapolating exposure-response relationships for nasal tumors in rats to estimate cancer risks for humans (EPA 1991a; see Section 2.4.3). The models assume that rates of cross link formation are proportional to tissue concentration of formaldehyde and include saturable and nonsaturable elimination pathways, and that regional and species differences in cross link formation are primarily dependent on anatomical parameters (e.g., minute volume and quantity of nasal mucosa) rather than biochemical parameters. The models were developed with data from studies in which concentrations of DNA-protein cross links were measured in different regions of the nasal cavities of rats (Casanova et al. 1989) and Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) exposed by inhalation to radiolabeled formaldehyde. In agreement with the observed data, the models predict that overall rates of DNA-protein cross link formation in rat respiratory mucosa are higher than rates in Rhesus monkeys, and that there is a nonlinear, convex relationship between this dose surrogate in nasal tissues and increasing air concentrations of formaldehyde (Casanova et al. 1991). Similar nonlinear, convex exposure-response relationships have also been observed in formaldehyde-exposed rats for nasal tumor incidence (Kerns et al. 1983b; Monticello et al. 1996) and cell proliferation indices in regions of the rat nasal epithelium where tumors develop (Monticello et al. 1996).

Computational fluid dynamics (CFD) models of airflow in the nasal passages of rats, monkeys, and humans have been developed to determine the degree to which interspecies and interregional differences in uptake patterns along airway passages may account for differing distributions of formaldehyde-induced upper respiratory tract lesions in rats and primates. These models enable extrapolation of exposures associated with upper respiratory tract tissue damage in rats or monkeys to human exposures

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

(Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell et al. 1993, 1997a,1997b; Morgan 1997; Morgan et al. 1991; Subramaniam et al. 1998). Airflow pattern is expected to be one of three important determinants of upper respiratory tract tissue uptake, along with interactions at the airway/tissue interface such as off-gassing and tissue properties influencing absorption rates (e.g., mucociliary clearance or rate of metabolism).

Driving forces behind the development of these airflow models include: (1) differences in nasal anatomy and breathing patterns between rats and primates; (2) observations that nonneoplastic respiratory tract lesions in rats exposed to 6 ppm formaldehyde are confined to epithelial tissue in specific anterior regions of the nose posterior to the vestibule (Chang et al. 1983; Morgan et al. 1986b), whereas monkeys exposed to 6 ppm formaldehyde show a wider distribution of similar epithelial lesions in the nose posterior to the vestibule and some extension of the lesions into the tracheal and bronchial regions (Monticello et al. 1989); (3) histochemical localization observations suggesting that regional differences in formaldehyde dehydrogenase, a key enzyme in formaldehyde detoxification, were insufficient to account for localized toxicity in the rat nose (Keller et al. 1990); and (4) observations of correlations between sites of formaldehyde-induced lesions in the nasal epithelium of rats and Rhesus monkeys and site-specific rates of DNA-protein cross link formation (a putative internal dosimeter for formaldehyde as discussed earlier; Casanova et al. 1989, 1991, 1994) or site-specific rates of cellular proliferation (Monticello et al. 1989, 1996).

Using three-dimensional reconstructions of the nasal passages of a F344 rat (Kimbell et al. 1993), a Rhesus monkey (Kepler et al. 1995), and a human (Subramaniam et al. 1998), CFD models were developed to predict patterns of airflow and regional uptake of formaldehyde in the nose of these species. The rat and monkey models were constructed from tracings of embedded tissue specimens, whereas the human model was constructed from tracings of magnetic resonance image scans. The CFD models assume that: (1) rat, monkey, and human nasal epithelial tissues are similar in all characteristics except thickness and location in nasal airways (values for these parameters were estimated from the literature or measured); (2) formaldehyde is absorbed only during inspiration, and that major patterns of inhaled airflow during resting breathing are similar to those at steady-state; (3) air is an incompressible Newtonian fluid; (4) the air-phase diffusivity of formaldehyde is constant throughout the nasal passages; (5) the nasal airway walls are inflexible and have no mucus movement or nasal hairs; and (6) formaldehyde absorption is maximal (i.e., fast and complete) in mucus-covered, nonsquamous epithelium regions of the nose so that concentrations at the surface of these airway walls are taken to be zero.

Simulations of airflow patterns were comparable with descriptions and measurements of flow in nasal molds of each species (Kepler et al. 1998; Kimbell et al. 1997a; Subramaniam et al. 1998).

Regions of high flux predicted by the rat and monkey CFD models correlated with the distribution of formaldehyde-induced squamous metaplasia in nasal passages of rats exposed to 10 or 15 ppm formaldehyde for 6 months (Kimbell et al. 1993, 1997a) and of Rhesus monkeys exposed to 6 ppm formaldehyde for 6 weeks (Kepler et al. 1998). Results from these studies support the hypothesis that airflow patterns are key determinants of the amount of formaldehyde reaching the site of formaldehyde-induced nasal lesions.

The rat CFD model and a modified version of the Casanova et al. (1991) pharmacokinetics model of formaldehyde disposition in the rat nasal lining have been linked to make predictions of DNA-protein cross link formation rates in nasal epithelial regions as a function of formaldehyde concentration in air (Cohen Hubal et al. 1997). The rat nasal lining model assumed a single compartment with three competing disposition processes for formaldehyde: saturable metabolism, nonsaturable metabolism, and DNA-protein cross link formation. The model parameters were kinetic rate constants for formation and loss of DNA-protein cross links, the nasal-lining thickness, rate constants for formaldehyde metabolism by saturable pathways (V_{max} and K_m), and a pseudo-first-order rate constant for nonsaturable formaldehyde metabolism. Saturable and nonsaturable metabolic rate constants were estimated by iterative fitting of the model to whole-nose data for DNA-protein cross links in rats exposed for 6 hours to radiolabeled formaldehyde, collected by Casanova et al. (1989). The combined airflow and pharmacokinetics models were then used to predict DNA-protein concentrations in the rat nasal epithelial region with high tumor incidence; predicted values compared well with measured DNA-protein cross link values in this region of the rat nasal epithelium (Cohen Hubal et al. 1997).

The Chemical Industry Institute of Toxicology and the U.S. EPA (CIIT 1998) are currently exploring options in using the CFD and pharmacokinetic models to extrapolate exposure-response relationships for formaldehyde-induced rat nasal tumors and related end points, such as rates of cellular proliferation in specific regions of the nasal epithelium, to derive estimates of cancer risk in humans exposed to inhaled formaldehyde. One approach being explored makes predictions for nasal and lung tumor risk in humans exposed to inhaled formaldehyde using two-stage clonal-growth cancer models incorporating data on cell division rates, numbers of cell at risk, tumor incidence, and site-specific flux of formaldehyde (see also CIIT 1998; Conolly et al. 1992; Conolly and Andersen 1993; Morgan 1997). A second approach (a

benchmark dose approach) makes predictions of nasal cancer risk in humans using curve fitting of relevant rat exposure-response data (e.g., nasal tumors or precursor lesions such as preneoplastic foci or squamous papillomas, rates of cellular proliferation, or rates of DNA-protein cross link formation) and CFD modeling and/or pharmacokinetic modeling for extrapolation purposes (CIIT 1998).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Formaldehyde is a small, reactive, water soluble molecule (molecular weight 30.03) which is readily absorbed in the tissues of the respiratory tract (inhalation exposure) and gastrointestinal tract (oral exposure). Absorption from the nasal portion of the respiratory tract is estimated to be at or near 100%. Studies in obligate nose-breathing animals (rats, mice) have demonstrated near 100% absorption in the nasal cavity/mucosa (Casanova-Schmitz et al. 1984a; Casanova et al. 1991; Heck et al. 1982, 1983) primarily in the anterior nasal mucosa in rats (Chang et al. 1983). Absorption from the nasal mucosa, trachea, and bronchi is expected for the oronasal-breathing animals (primates, humans, dogs etc.). Tracheal and bronchial absorption ultimately results from deeper penetration because of the formaldehyde vapors not passing over and coming into contact with the nasal mucosa; however, near 100% absorption of the formaldehyde vapor is still likely, at least in the dog (Egle 1972) and very likely in humans as well. Studies in humans exposed to 1.9 ppm for 40 minutes failed to detect increases in blood formaldehyde levels, which is probably related to formaldehyde's very fast metabolism by one or a combination of metabolic pathways (see Figure 2-3) and not due to lack of local absorption. Similar results were obtained in rats exposed to 14.4 ppm for 2 hours (Heck et al. 1985). Little information is available on the oral absorption characteristics of formaldehyde in humans; however, based on two studies, either the formaldehyde is quickly metabolized to formate in the gastrointestinal tract and the formate is absorbed fairly quickly, the formaldehyde is absorbed quickly and is metabolized to formate in the blood, or a combination of the two mechanisms is responsible for the sharp increases in blood formate levels (Burkhart et al. 1990; Eells et al. 1981). Formaldehyde appears to be rapidly absorbed after oral exposure in rats (Galli et al. 1983) and food-producing animals (Barry and Tome 1991; Buckley et al. 1988). Dermal absorption in monkeys has been shown to be quite low (0.5% of the applied dose); most was either lost to evaporation or bound within the skin (Jeffcoat 1983).

Distribution. Formaldehyde does not appear to be absorbed into the blood stream as an intact molecule, except possibly at very high doses that overwhelm the metabolic capabilities of the tissue with which it comes into contact. Given this rapid metabolic capability of animal tissues, the distribution of the intact formaldehyde molecule to other more distant organs (kidney, fat, spleen, etc.) in the body is not likely and is not considered a major factor in formaldehyde toxicity. Toxicity is generally demonstrated at the point of formaldehyde contact (see Mechanisms of Toxicity, below). Heck et al. (1983) found that in rats, inhaled ^{14}C-formaldehyde (8 ppm for 6 hours) had elevated concentrations of radioactivity in their blood for several days after exposure (terminal half-life 55 hours). Since it is known that blood formaldehyde levels do not increase after inhalation exposure (Heck et al. 1985), the data suggested that there was an incorporation of ^{14}C into the macromolecules of the body. The long plasma half-life may also have been due to formaldehyde's rapid metabolism to formate or CO_2 awaiting excretion into the urine and lung, respectively.

In one study (Casanova et al. 1991), much of the ^{14}C was localized in the nasal mucosa; however, detectable levels of ^{14}C activity were noted in the esophagus, kidney, liver, intestine, lung, spleen, heart, brain, testes, and erythrocytes in some reports (Heck et al. 1983; Swenberg et al. 1983). The geometry of the nasal passages of different species, which results in different airflow patterns through the nose, has a large effect on the local distribution of formaldehyde vapor as well (Schreider 1986). In a study by Casanova-Schmitz et al. (1984a) using male rats exposed to concentrations of 0.3–15 ppm of ^{14}C and ^{3}H labeled formaldehyde for 6 hours, concentrations of ^{14}C-formaldehyde in respiratory and olfactory mucosa tissues increased linearly with dose and at any given dose, the concentrations of ^{14}C-formaldehyde in respiratory mucosa tissues were approximately 2–3 times that in olfactory mucosa tissues. The ^{3}H and ^{14}C radioisotopes were chosen to distinguish between metabolic incorporation of oxidized formaldehyde metabolites (^{14}C) and covalent binding (^{3}H) into macromolecules. At all exposure concentrations, RNA was the most heavily ^{14}C-labeled macromolecule in the respiratory and olfactory mucosa. DNA from the respiratory and olfactory mucosa was ^{14}C-labeled at equivalent or greater levels than proteins. In the bone marrow, DNA was the most heavily ^{14}C-labeled macromolecule. DNA-protein cross links have also been identified in male rats and male Rhesus monkeys exposed to formaldehyde concentrations of #9.87 ppm for 6 hours. Concentrations of formaldehyde-protein cross links were greatest in the middle turbinate tissues and lowest in the nasopharyngeal tissues, with some evidence of cross link formation seen in the larynx, trachea, carina, and major intrapulmonary airway tissues of two of the monkeys tested (Casanova et al. 1989a).

Metabolism. Formaldehyde is a normal metabolic product of animal metabolism, with varying endogenous levels present at all times (Bolt 1987). The major sources of endogenously produced formaldehyde are glycine and serine.

Formaldehyde is rapidly metabolized and storage is not a factor in its toxicity. The metabolism of formaldehyde to formate (via FDH/class III alcohol dehydrogenase) takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde and is quickly removed by the supporting blood supply (Heck et al. 1982). FDH is the major metabolic enzyme involved in the metabolism of formaldehyde in all of the tissues studied; is widely distributed in animal tissues, particularly in the rat nasal mucosa; and is specific for the glutathione adduct of formaldehyde. If formaldehyde is not metabolized by FDH, then it can form cross linkages between protein and single-stranded DNA (see Figure 2-3) or enter the 1 carbon intermediary metabolic pool by initially binding to tetrahydrofolate (Bolt 1987). Several enzymes can catalyze the reaction that oxidizes formaldehyde to formic acid (i.e., nonspecific aldehyde dehydrogenase and catalase); however, FDH is the primary enzyme tasked to perform this function and is specific for formaldehyde; other aldehydes are left intact in the presence of FDH. Endogenous or exogenous formaldehyde enters FDH metabolic pathway and is eliminated from the body as metabolites, primarily as formate or CO_2. FDH activity does not increase (i.e., not inducible) in response to formaldehyde exposure (Casanova-Schmitz et al. 1984b). Heck et al. (1985) provided some indirect evidence in both the human and the rat that inhaled formaldehyde (1.9 ppm for 40 minutes for the human, 14.4 ppm for 2 hours in the rat) is quickly metabolized (probably by FDH) and did not raise blood formaldehyde concentrations beyond the measured endogenous levels, although this finding may have also been due to low systemic absorption. Little information about the metabolism of formaldehyde after oral or dermal exposures was available.

Increasing the amounts of formaldehyde in the diet of some lactating ruminants (cows, sheep, goats, etc.) will increase the amount of intact formaldehyde present in their milk (Barry and Tome 1991; Buckley et al. 1988). Neither of these reports offered an explanation for these findings. However, given the marked differences in blood and plasma characteristics and the differences in gastrointestinal anatomy, it is plausible to assume that there are some fundamental differences between formaldehyde metabolism in ruminant animals and in humans (or other monogastrics), which leads to increased milk levels of formaldehyde. There is a close relationship between the amount of formaldehyde ingested and the amount of formaldehyde present in the milk (Barry and Tome 1991). Milk formaldehyde concentrations

are not influenced by the level of milk production, which suggests that the passage of formaldehyde from the blood to the milk is a passive event (Barry and Tome 1991).

Excretion. Given the rapid conversion of formaldehyde to formate and subsequent incorporation into naturally occurring cellular constituents, excretion does not appear to be a factor in the toxicity of formaldehyde. The metabolism of formaldehyde to formate takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde. Exogenous formaldehyde enters this pathway and is eliminated from the body as metabolites, primarily CO_2. For example, in rats exposed to ^{14}C-formaldehyde via inhalation, 40% of the radioactivity was recovered as $^{14}CO_2$ (Heck et al. 1983). After oral exposure to formaldehyde in male rats administered 2.2 g (18 μCi) of ^{14}C-formaldehyde, 67% of the radioactivity dose was excreted in the feces and 32% exhaled as CO_2 within 32 hours after dosing. The ^{14}C plasma elimination half-life was calculated to be 26.4 hours (Galli et al. 1983); however, it is unclear what percentage of this activity involves intact formaldehyde and what involves metabolites (i.e., formate). In a similar study in male mice administered 0.5 g (4 μCi) of ^{14}C-formaldehyde, 64% of the total dose of radioactivity was eliminated via the feces and 24% eliminated as exhaled CO_2. The plasma half-life was calculated to be 27.8 hours in this study (Galli et al. 1983). Intact formaldehyde is excreted in the milk in goats (Barry and Tome 1991) and dairy cows (Buckley et al. 1988).

2.4.2 Mechanisms of Toxicity

The exact mechanism by which formaldehyde exerts its irritant, corrosive, and cytotoxic effects is not known. Aldehydes as a group are reactive chemicals with a highly electronegative oxygen atom and less electronegative atoms of carbon(s), and hence have a substantial dipole moment. The carbonyl atom is the electrophilic site of these type of molecules, making it react easily with nucleophilic sites on cell membranes and in body tissues and fluids such as the amino groups in protein and DNA (Feron et al. 1991).

It is also known that formaldehyde can form cross links between protein and DNA *in vivo*. Casanova-Schmitz et al. (1984a) reported that the predominant route of formaldehyde metabolism was metabolic incorporation into macromolecules (DNA, RNA, and proteins) in the respiratory and olfactory mucosa and bone marrow of male Fischer 344 rats. Rats were exposed nose-only for 6 hours to 0.3, 2, 6, 10, or 15 ppm mixtures of ^{14}C and ^{3}H-formaldehyde 1 day after a 6-hour exposure to the same concentration of unlabeled formaldehyde. There was some evidence of DNA-protein cross linking

present in the nasal tissues. Concentrations of ^{14}C DNA in respiratory and olfactory mucosa tissues increased linearly with dose; at all doses, the concentrations of ^{14}C DNA in respiratory mucosa tissues were approximately two to three times that in olfactory mucosa tissues. Later studies by Casanova et al. (1991a, 1991b) described the formation of DNA-protein cross links in the respiratory tract measured in male Fischer 344 rats as well as in Rhesus monkeys. Rats were again exposed nose-only to a mixture of ^{14}C-labeled and nonradiolabeled formaldehyde, using concentrations of 0.3, 0.7, 2, 6, or 10 ppm for 6 hours. Formaldehyde was again observed in the form of formaldehyde-DNA-protein cross links, and was detected at all concentrations tested. Male Rhesus monkeys were exposed to 0.7, 2, or 6 ppm formaldehyde ^{14}C-labeled and nonradiolabeled mixture for 6 hours and it was determined that approximately 90% of all ^{14}C was associated with the thymine, while 10% was associated with the guanine and adenine. Concentrations of DNA-protein cross links were greatest in the middle turbinate tissues and lowest in the nasopharyngeal tissues, with some evidence of cross link formation observed in the larynx/trachea/carina and major intrapulmonary airway tissues of two monkeys in the 6-ppm dose group. No evidence of cross link formation was seen in the sinus or lung tissues at any exposure concentration.

The mechanism by which formaldehyde exerts its toxicological effects is not known; however, it is known that formaldehyde readily combines with free, unprotonated amino groups of amino acids to yield hydroxymethyl amino acid derivatives and a proton (H^+), which is believed to be related to its germicidal properties. Higher concentrations will precipitate protein (Loomis 1979). Either one of these mechanistic properties or perhaps other unknown properties may be responsible for the irritation effects seen with formaldehyde exposure. It is probable that formaldehyde toxicity occurs when intracellular levels saturate formaldehyde dehydrogenase activity, overwhelming the natural protection against formaldehyde, and allowing the unmetabolized intact molecule to exert its effects locally. The primary metabolite of formaldehyde, formate, is not expected to be as reactive as formaldehyde itself and is subject to excretion as a salt in the urine, entrance into the one-carbon metabolic pool for incorporation into other cellular components, or further metabolism to carbon dioxide.

The toxicity of formaldehyde is route-dependent. Irritation at the point of contact is seen by inhalation, oral, and dermal routes. High doses are cytotoxic and result in degeneration and necrosis of mucosal and epithelial cell layers. These observations are consistent with the hypothesis that toxic effects are mediated by formaldehyde itself and not by metabolites. No specific target molecule has been identified, although DNA-protein cross links have been identified (Casanova and Heck 1987). As discussed in

Section 2.2, oral and inhalation toxicity studies with animals generally have found that toxic effects from formaldehyde are restricted to portal-of-entry tissue, but there are scattered reports of toxic effects at sites distant from portals-of-entry. The mechanism whereby distant site toxicity may be expressed is unclear, but given the highly reactive nature of formaldehyde and the ubiquitous metabolic capability of cells to metabolize formaldehyde, it is plausible that distant site effects may occur only when the capacity for local disposition of formaldehyde is exceeded.

An example of a local effect of formaldehyde vapor was demonstrated in the rat nasal epithelium. In rat studies where cell turnover was measured (a measure of formaldehyde cytotoxicity), the no-effect level is approximately 2 ppm (Monticello et al. 1991; Swenberg et al. 1983) for 6 hours/day exposures for #9 days. At higher concentrations (6, 10, or 15 ppm), higher rates of cell turnover were seen (Monticello et al. 1991), and a dose-response was observed. The increase in cell proliferation (as measured by thymidine incorporation) was more sensitive to formaldehyde exposure than histopathological changes. Similar results were seen in a 6-week experiment at these same doses in which the rats were exposed 5 days/week. The relationship between concentration and total dose has been studied in experiments where rats were exposed to a range of concentrations for various lengths of time so that the total inhaled dose was constant (Wilmer et al. 1987, 1989). Studies have shown that formaldehyde concentration in the inspired air may be more important than exposure duration in determining the extent of nasal damage (Wilmer et al. 1987, 1989) (see Section 2.5). Monticello et al. (1996) also determined that the nasal cell target population size, increased cell proliferation of specific target cells (due to differences in regional airflow with the rat nasal cavity), and the nonlinear kinetics of formaldehyde binding to DNA explain why specific regions of the rat nose are more prone to develop formaldehyde-induced nasal squamous cell carcinomas than other sites in the nasal cavity.

Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells has been studied. Monticello et al. (1996) assessed the role of regional increases in nasal epithelial cell proliferation in the formation of formaldehyde-induced nasal cancer in male Fisher 344 rats whole-body exposed to formaldehyde up to 15 ppm for 24 months. The majority of formaldehyde-induced neoplasms consisted of squamous cell carcinomas and polyploid adenomas; however, cell proliferation was not affected by formaldehyde exposures of 6.01 ppm or less. Increases in the cell labeling index were significant at the 10 and 15 ppm exposure levels, and there was a highly significant correlation between formation of tumor cells and proliferating cells within the rat nasal cavity.

Although there is evidence to suggest that exposure concentration is more important than exposure duration in determining the extent of formaldehyde-induced nasal epithelial damage, the development of formaldehyde-induced nasal squamous cell carcinomas is likely to require repeated and prolonged damage to the nasal epithelium. Several key points or events determine the mechanism by which formaldehyde induces cancer in rats. First, a single high dose (#40 ppm) for acute durations is not likely sufficient to induce squamous cell carcinoma cancer (Bhalla et al. 1990; Monteiro-Riviere and Popp 1986; Wilmer et al. 1987); repeated exposures for protracted durations are required to induce nasal cancer in rats. Second, the data indicate that a sequence of cellular events must occur in order to induce nasal carcinomas. The induction of nasal cancer in rats by formaldehyde requires repeated exposure for prolonged periods of time to high concentrations that are both irritating and that cause cell damage to a population of the nasal mucosa cells lining the nose. Exposure to high concentrations for prolonged periods during inhalation exposure overwhelms or otherwise exhausts the inherent defense mechanisms to formaldehyde (mucociliary clearance, FDH, DNA repair). This cellular and tissue damage inflicted by unmetabolized formaldehyde is then followed by a regenerative hyperplasia and metaplasia phase (Chang et al. 1983; Feron et al. 1988; Rusch et al. 1983; Wilmer et al. 1987; Woutersen et al. 1987, 1989), which results in increased cell-turnover rates within the mucosa. Formaldehyde has been demonstrated to be genotoxic in some (but not all) cell lines and test systems (Basler et al. 1985; Donovan et al. 1983; Grafstrom et al. 1985, 1993; Rithidech et al. 1987; Snyder and Van Houten 1986; Valencia et al. 1989; Woodruff et al. 1985; Yager et al. 1986). DNA-protein cross links have been demonstrated in experimental animals after inhalation exposure to formaldehyde and can cause mutation or chromosomal aberrations if not repaired prior to cell replication. The DNA damage that occurs in these altered cells is carried into subsequent cell populations and thereby greatly enhances the progression of preneoplastic cells to cancer. In this manner, formaldehyde likely can act as a complete carcinogen (providing initiation, promotion, and progression) with repeated and prolonged duration of exposure at cytotoxic concentrations. Point mutations in the p53 tumor suppressor gene were found in 5 of 11 nasal tumors examined from rats exposed to 15 ppm formaldehyde for 2 years (Recio et al. 1992). The tissues in the Recio et al. (1992) study were reanalyzed using antibodies against p53. One was a monoclonal antibody to mutant p53, and the other a polyclonal antibody directed against epitopes in mutant and wild type p53 (Wolf et al. 1995). Morphologically normal nasal mucosa and metaplastic and hyperplastic tissues were negative for p53 immunoreactivity. In squamous cell carcinomas (the five with previously identified p53 mutations and three of six tumors with no mutations identified), p53 immunoreactivity was focal to diffuse, and the authors stated that their results using these antibodies were solely from reactions with mutant p53.

2.4.3 Animal-to-Human Extrapolations

The target organs for formaldehyde appear to be similar in humans and laboratory animals exposed to airborne, ingested, or dermally-applied formaldehyde. As discussed in Section 2.2.1, airborne formaldehyde is an acute contact irritant in humans and laboratory animals, causing irritation of the eyes and upper respiratory tract during an inhalation exposure. Repeated exposure to airborne formaldehyde has been associated with region-specific damage to the upper respiratory tract epithelium in rats, monkeys, and mice (e.g., Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989, 1996), and evidence for similar lesions has been found in nasal tissue specimens sampled from occupationally-exposed workers (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Lifetime exposure to formaldehyde concentrations between 10 and 15 ppm produced nasal tumors in rats, but no evidence of malignant neoplastic lesions has been found in numerous rat studies at concentrations #2 ppm (e.g., Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Some studies of formaldehyde-exposed workers, typically exposed to average concentrations below 2 ppm, have found evidence for an increase in nasopharyngeal cancer death rate, whereas other studies of other groups of exposed workers have found no cases of nasopharyngeal cancer (see Section 2.2.1.8). Gastric lesions have been induced in rats (e.g., Til et al. 1988b) and in humans (Burkhart et al. 1990; Eells et al. 1981; Kochhar et al. 1986; Koppel et al. 1990) after oral exposure.

Formaldehyde is produced endogenously in all animal species studied. Absorption, distribution, metabolism, and excretion of formaldehyde are similar across species; however, species differences in upper respiratory tract anatomy and physiology likely play a role in determining the location of nonneoplastic (and neoplastic) lesions from inhaled formaldehyde. Formaldehyde-induced epithelial lesions, such as squamous metaplasia, showed a wider distribution of occurrence in the upper respiratory tract of Rhesus (Monticello et al. 1989) and Cynomolgus (Rusch et al. 1983) monkeys than similar lesions which were mostly confined to the anterior portion of the nasal cavity in formaldehyde-exposed rats (Bhalla et al. 1991; Monteiro-Riviere and Popp 1986; Morgan et al. 1986a; Wilmer et al. 1987; Woutersen et al. 1987). The differences in location of these lesions are likely due to differences in airflow pattern through the nasal cavity, resulting in different deposition patterns. The fact that rats are obligate nose-breathers and monkeys have an oronasal breathing pattern likely also has an impact on the location of these lesions. Other species differences have been noted between rats and mice. Mice tend to be more efficient at reducing their minute volumes during formaldehyde exposures than rats, which may

partially account for the differences in the decreased incidences of nonneoplastic lesions (Maronpot et al. 1986) and neoplastic lesions in mice compared rats (Chang et al. 1981, 1983).

Available studies of animals exposed by the oral or inhalation routes clearly show that formaldehyde-induced health effects are restricted to portals-of-entry and that inhaled formaldehyde, at concentrations $6 ppm, produces nasal tumors in rats (as discussed earlier in Section 2.2.1.8). In contrast, epidemiology studies of occupationally-exposed humans have provided only equivocal evidence for respiratory tract cancer. Even so, this does not negate the need to determine human cancer risk estimates, perhaps by employing means other than epidemiological information. The U.S. EPA (1991a) used dose-response data for nasal tumors in rats exposed to high concentrations of formaldehyde to extrapolate to human cancer risk at low exposure concentrations, using the rate of DNA-protein cross links in target tissue as a measure of delivered dose. Estimates of delivered dose and observed rat nasal tumor incidence were modeled with a linearized multistage procedure (i.e., were fit to an exponential polynomial model) to obtain a 95% upper confidence limit on the slope in the low-dose region of the dose-response curve (a rat unit cancer risk estimate of 1.6×10^{-4} per [pmol DNA-protein cross links/mg DNA/day]). Relationships between formaldehyde air concentrations and rates of formation of DNA-protein cross links in nasal epithelial tissue of rats (Casanova et al. 1989) or of Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) and adjustments to continuous exposure were then used to calculate lifetime human cancer unit risk estimates of 3.3×10^{-4} per ppm formaldehyde based on the monkey data, and 2.8×10^{-3} per ppm formaldehyde based on the rat data.

The use of DNA-protein cross link formation as a formaldehyde dosimeter in cancer target tissues is supported by correlative observations of nonlinear (convex) relationships between DNA-protein cross link formation in nasal epithelium of rats and monkeys and formaldehyde air concentrations and similar convex exposure-response relationships for formaldehyde-induced tumors in rats (Casanova et al. 1991; EPA 1991a). The convex nature of these relationships may be explained by a number of mechanisms, including saturation of enzymes involved in metabolism of formaldehyde, a decrease in the functioning of the mucociliary apparatus that may trap and remove formaldehyde before it reaches target tissues, saturation of protein-binding kinetic mechanisms, and saturation of inherent DNA-protein cross link repair mechanisms.

As discussed in Section 2.3.5, The Chemical Industry Institute of Toxicology and the U.S. EPA (CIIT 1998) are currently exploring options in using CFD models of nasal airflow and uptake of formaldehyde,

pharmacokinetic models of nasal disposition of formaldehyde, and two-stage clonal growth cancer models to derive estimates of cancer risk in humans exposed to inhaled formaldehyde based on nasal epithelial responses observed in rats chronically exposed to formaldehyde.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Although formaldehyde is a normal intermediary cellular metabolite involved in the biosynthesis of purines, thymidine, and several amino acids, it is a highly reactive molecule that can be directly irritating to tissues with which it comes into contact. Human and animal studies indicate that formaldehyde, at appropriate exposure levels, can be irritating to the upper respiratory tract and eyes with inhalation exposure, to the skin with dermal exposure, and to the gastrointestinal tract with oral exposure. Reports of allergic dermal sensitization to formaldehyde are widespread and supported by results from animal studies, but the evidence that formaldehyde sensitizes the respiratory tract is less convincing.

Studies of volunteers exposed to airborne formaldehyde for short periods of time (8 hours or less) indicate that eye, nose, and throat irritation occurs at concentrations in the range of 0.4–3 ppm (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Weber-Tschopp et al. 1977; Witek et al. 1986). At the lower end of this range, the irritation is typically described as mild and noted by a lower percentage of exposed subjects than at the upper end of the range. Studies of monkeys, rats, and mice exposed to higher concentrations in the range of 3–9 ppm for acute to intermediate periods of time demonstrate that formaldehyde nonneoplastic toxic effects are restricted to lesions (squamous metaplasia and hyperplasia) in the epithelium of the upper respiratory tract (Chang et al. 1983; Monticello et al. 1989; Morgan et al. 1986a, 1986c; Rusch et al. 1983; Woutersen et al. 1987; Zwart et al. 1988).

Studies of animals exposed for life to formaldehyde in air or drinking water also show that formaldehyde primarily damages tissue at portals-of-entry (i.e., the upper respiratory tract and the gastrointestinal tract); evidence for toxic effects at distant sites is less consistent. Replicated inhalation studies have shown that formaldehyde induced malignant nasal tumors in rats at high exposure concentrations (10–15 ppm) that also induced nasal epithelial necrosis and cellular proliferation, but not at lower concentrations (0.3–2 ppm) that did not markedly damage nasal epithelial tissue (Albert et al. 1982;

Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Exposure-related cancer or noncancer lesions at other sites were not found in these studies. Statistically significant increased incidences of nasal tumors, however, were not found in mice exposed by inhalation for 2 years (Kerns et al. 1983b) or in hamsters exposed for 18 months (Dalbey 1982) at concentrations similar to those producing nasal tumors in rats. Nonneoplastic nasal epithelial damage was found in mice exposed to 14 ppm, but not in mice exposed to 2 ppm (Kerns et al. 1983b). Three lifetime drinking-water exposure studies in rats that found no consistent, exposure-related cancer or noncancer effects at sites distant from the gastrointestinal tract (Soffriti et al. 1989; Til et al. 1989; Tobe et al. 1989) provide support for the expectation that formaldehyde-induced health effects are restricted to portals-of-entry.

More than 40 epidemiology studies (cohort studies of industrial workers, cohort studies of medical specialists and embalmers, and case-control studies) examining the potential for occupational formaldehyde exposure to induce cancer have provided only equivocal evidence of a relationship between formaldehyde and nasopharyngeal cancer in humans, and even less convincing evidence for extra-respiratory cancer.

Occupational and residential exposure to formaldehyde has been associated with reports of symptoms of eye, nose, and throat irritation from exposure to airborne formaldehyde (Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987), and there are numerous reports of skin irritation and contact dermatitis most likely resulting from dermal exposure to formaldehyde in liquids (Fischer et al. 1995; Kiec-Swierczynska 1996; Maibach 1983; Meding and Swanbeck 1990; Menné et al. 1991). Several cross-sectional studies of nasal epithelial tissue specimens from workers exposed to airborne formaldehyde in the approximate average concentration range of 0.2–1 ppm found evidence in some of the workers for mild lesions (stratified squamous epithelium and mild dysplasia) that are indicative of the irritant and reactive properties of formaldehyde (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c).

The apparent restriction of formaldehyde-induced noncancer and cancer effects to portals-of-entry is consistent with the highly reactive nature of formaldehyde and the existence of physiological mechanisms of protection, such as the nasal mucosal barrier and the detoxifying metabolism of formaldehyde in most, if not all, cells. The available weight of evidence indicates that distant site effects from formaldehyde may occur only when the capacity for local disposition of formaldehyde is exceeded.

Issues relevant to children are explicitly discussed in Sections 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Minimal Risk Levels for Formaldehyde.

The details regarding calculations of the MRLs for formaldehyde are described in Appendix A.

Inhalation MRLs

- An MRL of 0.04 ppm has been derived for acute-duration inhalation exposure (14 days or less) to formaldehyde.

The MRL was calculated from a minimal LOAEL of 0.4 ppm for symptoms of increased itching, sneezing, mucosal congestion, and transient burning sensation of the eyes and of the nasal passages, and elevated eosinophil counts and a transient increase in albumin content of nasal lavage fluid in volunteers exposed to formaldehyde for 2 hours (Pazdrak et al. 1993). The LOAEL was divided by an uncertainty factor of nine (three for the use of a minimal LOAEL and three for human variability) as described in Appendix A.

The selection of 0.4 ppm as an acute exposure concentration that produces mild eye, nose, and throat irritation in some human subjects is supported by reports of: nasal irritation, sneezing, and eye irritation in 3/13 subjects with formaldehyde contact dermatitis and eye irritation in 1/5 normal subjects exposed to 0.4 ppm for 2 hours (Gorski et al. 1992); increased eosinophil counts and protein in nasal lavage fluid in other groups of 10 healthy subjects and 10 workers with purported formaldehyde-induced bronchial asthma exposed to 0.4 ppm for 2 hours (Krakowiak et al. 1998); eye and nasal irritation in 3/16 healthy subjects exposed to 0.2 ppm for 4 hours (Andersen and Molhave 1983); and decreased eye irritation response time in 5/12 subjects exposed to 0.35 ppm for 6 minutes (Bender et al. 1983). Several other acute controlled exposure studies with volunteers have noted higher percentages of subjects reporting mild eye, nose, and throat irritation at concentrations between 1 and 2 ppm (Day et al. 1984; Kulle et al. 1987; Weber-Tschopp et al. 1977; Witek et al. 1986). The Anderson and Molhave (1983) study identified an apparent effect level (0.2 ppm) based on subjective reports of irritation that is lower than the effect levels (0.35–0.4 ppm) in the studies by Pazdrak et al. (1993), Krakowiak et al. (1998), and Bender et al. (1983) which used more objective measures of acute irritation. Because of the use of objective measures of toxicity and the general weight of the available data indicating that some people will not

experience eye or upper respiratory tract irritation from formaldehyde even at 1 ppm, the Pazdrak et al. (1993) LOAEL of 0.4 ppm was considered a minimal LOAEL in a group of potentially sensitive individuals (some subjects had dermal hypersensitivity to formaldehyde) and was selected as the basis of the acute MRL.

- An MRL of 0.03 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to formaldehyde.

The MRL is based on a NOAEL of 0.98 ppm for clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia) observed in Cynomolgus monkeys exposed to formaldehyde for 22 hours/day, 5 days/week for 26 weeks (Rusch et al. 1983). The LOAEL was 2.95 ppm. As described in Appendix A, the NOAEL was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Intermediate-duration inhalation studies with several species of animals clearly identify the upper respiratory tract as the critical target tissue for airborne formaldehyde and suggest that degenerative changes to the upper respiratory tract epithelium may not occur with exposure to concentrations #1 ppm. Formaldehyde-induced epithelial damage in the upper respiratory tract similar to that observed in the Cynomolgus monkeys has been observed in: Rhesus monkeys exposed to 6 ppm for 6 hours/day, 5 days/week for 6 weeks (Monticello et al. 1989); several strains of rats subchronically exposed to concentrations greater than 2 ppm (Appelman et al. 1988; Feron et al. 1988; Monticello et al. 1991; Rusch et al. 1983; Woutersen et al. 1987); and mice exposed to concentrations $4 ppm (Chang et al. 1983; Maronpot et al. 1986). Although there are numerous human studies of acute inhalation toxicity from formaldehyde (controlled-exposure and occupational exposure studies) and numerous investigations of toxic effects from chronic occupational exposures, studies of humans strictly exposed for intermediate durations were not located. In contrast, the database for studies of animals (including primates) exposed by inhalation to formaldehyde is rich, providing data describing exposure-response relationships for formaldehyde-induced effects on the upper respiratory tract system in several species (rats, mice, hamsters, and monkeys). The study by Rusch et al. (1983) examined a number of species and identified the lowest effect level among the available sets of data. Given this observation, the absence of suitable human intermediate-duration data, and the putatively greater relevance of monkeys, compared with

rodents, to humans, the monkey NOAEL of 0.98 ppm and LOAEL of 2.95 ppm for clinical signs of nasopharyngeal irritation were selected as the basis of the intermediate-duration MRL.

- An MRL of 0.008 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to formaldehyde.

The MRL is based on a minimal LOAEL of 0.24 ppm for histological changes (loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium) in nasal tissue specimens from a group of 70 workers employed for an average 10.4 years (range 1–36 years) in a chemical plant that produced formaldehyde and formaldehyde resins for impregnating paper (Holmstrom et al. 1989c). The MRL was derived by dividing the LOAEL by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability) as described in Appendix A.

Several cross-sectional studies of groups of formaldehyde-exposed workers chronically exposed to estimated concentrations ranging from about 0.1 to 0.6 ppm (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c) have found histological evidence for mild damage to nasal epithelial tissue such as the damage described for exposed workers in the Holmstrom et al. (1989c) study. The observed effects were consistently mild, but each study reported a statistically significant, albeit small, increase in average histological score (increasing scores indicating increasing severity of change) for exposed groups compared with nonexposed control groups: 2.8 exposed versus 1.8 on an 8-point scale (Edling et al. 1988); 2.16 versus 1.46 on an 8-point scale (Holmstrom et al. 1989c); 1.9 versus 1.4 on a 5-point scale (Boysen et al. 1990); and 2.3 versus 1.6 on a 6-point scale (Ballarin et al. 1992). The Holmstrom et al. (1989c) study was selected as the basis of the MRL from among these four cross-sectional studies (they each examined equivalent end points and are of similar quality of design) primarily because the statistically significant effects were found in a group exposed to formaldehyde in the absence of potentially confounding exposures to wood dust. A full uncertainty factor of 10 was used to account for human variability because the observed mild effects were seen in groups of chronically exposed workers that were otherwise in apparent good health; a healthy worker effect may have operated causing sensitive individuals to avoid employment in the studied workplaces.

Additional supporting evidence for mild histological changes to the nasal epithelium with chronic exposure to concentrations below 1 ppm comes from rat studies. Although several studies of rats exposed for life (generally with an exposure protocol of 6 hours/day, 5 day/week) found no statistically significant increases in incidences of nonneoplastic lesions in the nasal epithelium of rats exposed to

0.1 to 2 ppm (Kerns et al. 1983b [F344 rats]; Monticello et al. 1996 [F344 rats]; Woutersen et al. 1989 [Wistar rats]), Kamata et al. (1997) reported that some F344 rats, after 28 months of exposure, displayed a mild response at 2 ppm and even at 0.3 ppm. A statistically significantly increased incidence for nasal epithelial squamous metaplasia without hyperplasia was observed in rats exposed to 2 ppm compared with control rats (5/32 versus 0/32); the incidence for nasal epithelial cell hyperplasia with squamous metaplasia was also significantly elevated compared with controls (7/32 versus 0/32). In rats exposed to 0.3 ppm, incidences of the same respective nasal epithelial lesions were also greater than control incidences (1/32 versus 0/32 and 4/32 versus 0/32), but not to a statistically significant degree.

Oral MRLs

Case reports of acute poisoning in humans ingesting doses of formaldehyde greater than 200 mg/kg have reported gastrointestinal effects and symptoms that reflect the chemical reactivity of formaldehyde and have reported other effects (e.g., cardiovascular dysfunction, coma, and renal and hepatic dysfunctions) that are consistent with the exceedance of the capacity of local detoxification mechanisms at these high dose levels (Burkhart et al. 1990; Eells et al. 1981; Kochhar et al. 1986). The acute human poisoning data, coupled with the results from studies of animals orally exposed to formaldehyde for intermediate and chronic durations, suggest that gastrointestinal irritation and damage are the most likely critical effects from acute oral exposure. A no-effect level is not identified by the human data, however, and available studies of animals exposed for acute durations provide no dose-response information for this end point. Available acute-exposure animal data are restricted to 2-week, oral administration studies that only examined body weight in rats (Johannsen et al. 1986) and a 10-day gavage administration study of testicular weight and sperm variables in rats (Cassidy et al. 1983). In the absence of dose-response data for gastrointestinal irritation and damage from acute oral exposure, no acute-duration MRL was derived.

- An MRL of 0.3 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to formaldehyde.

The MRL was based on a NOAEL of 25 mg/kg/day for gastrointestinal effects in rats exposed to formaldehyde in drinking water (Til et al. 1988b). The LOAEL was 125 mg/kg/day. An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to derive the MRL. The Til et al. (1988b) study used groups (10 males and 10 females) of weanling Wistar rats that received 0, 5, 25, or 125 mg/kg/day formaldehyde in their drinking water for 4 weeks. Control groups (20 males and 20 females) were given unsupplemented tap water. A water-

restricted group (10 males and 10 females) received the same amount of unsupplemented drinking water as the amount of liquid consumed by the group given the highest dose of formaldehyde. Dosing solutions were prepared fresh every week and fresh drinking water containing a calculated concentration of formaldehyde was provided to the rats every day. The authors did not report if or how often the drinking water was assayed for actual formaldehyde content, so it is not known, due to possible oxidation, polymerization, or evaporation, if the full dose of formaldehyde was received. Histopathology revealed thickening of the limiting ridges, hyperkeratosis in the forestomach, and focal atrophic inflammation in the glandular stomach in animals given a high concentration of formaldehyde. Moderate papillomatous hyperplasia was seen in one female given a high concentration of formaldehyde. Types of lesions in males given 125 mg/kg formaldehyde are as follows: slight-to-moderate focal hyperkeratosis of forestomach, slight-to-moderate focal gastritis, and slight-to-moderate submucosal mononuclear-cell infiltrate. Types of lesions in females given 125 mg/kg formaldehyde are as follows: very slight, slight-to-moderate focal hyperkeratosis of forestomach; very slight, slight-to-moderate focal gastritis; focal papillomatous hyperplasia; and polymorphonuclear leucocytic infiltration. No gastrointestinal effects were noted at the 25 mg/kg/day dose of formaldehyde.

Gastrointestinal irritation and damage have been observed in both humans and animals after ingestion of formaldehyde. In human poisoning studies, effects observed include: ulceration and sloughing of the soft palate and posterior pharyngeal wall; ulceration of the epiglottis, pyriform fossae, and arytenoids; edematous and ulcerated esophageal mucosa with patches of black sloughed tissue along the entire length; hyperemic areas of the stomach; and superficial ulceration in the distal body and antrum after a single dose of 234 mg/kg formaldehyde (Kochhar et al. 1986); abdominal pain and retching; and hard, white, and leathery stomach after a dose of 517 mg/kg (Burkhart et al. 1990); or abdominal pain after a dose of 624 mg/kg (as formalin) (Eells et al. 1981). In human poisoning studies in which the dose of formaldehyde is not known, gastrointestinal symptoms included mucosal damage, ulceration and bleeding of the buccal cavity and tonsils, and dysphagia due to esophageal mucosal damage (Freestone and Bentley 1989); necrosis of the esophagus and stomach, extensive congestion, peptic plaques in esophagus and stomach, colitis, congestion, diffuse necrosis and hemorrhage of gastric and duodenal mucosa, burns in gastrointestinal mucosa, and ileitis (Koppel et al. 1990). In rat studies in which formaldehyde was administered orally for longer periods of time, consistent evidence has been found for gastrointestinal irritation and damage, but the evidence for orally-induced neoplastic lesions is equivocal due to inconsistent findings among the studies (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989).

- An MRL of 0.2 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to formaldehyde.

The MRL was based on a NOAEL of 15 mg/kg/day for gastrointestinal effects in male rats exposed to formaldehyde in drinking water (Til et al. 1989). The LOAEL was 82 mg/kg/day. An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to derive the MRL. The Til et al. (1989) study used groups of Wistar rats that received formaldehyde in their drinking water for 2 years. Estimated formaldehyde doses in this study were 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Dosing solutions were prepared fresh every week and fresh drinking water containing a calculated concentration of formaldehyde was provided to the rats every day. The authors did not report if or how often the drinking water was assayed for actual formaldehyde content, so it is not known, due to possible oxidation, polymerization, or evaporation, if the full dose of formaldehyde was received. Necropsy findings of high-dose rats killed in weeks 53, 79, and 105 revealed a raised and thickened limiting ridge of the forestomach in most male and female rats of the high-dose group and in some males and females of the other groups, including the control group. Also, several rats in the high-dose groups showed irregular mucosal thickenings in the forestomach and/or glandular stomach. These changes were also found in rats of the other groups as well as the control groups. In high-dose animals, histopathological examination revealed gastric changes including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia, in the glandular stomach. There were no gastric tumors observed apart from two benign papillomas, one in the male of the low-dose group and one in a female control rat.

Death. Cases of death in humans acutely exposed to airborne formaldehyde were not located. Death after the ingestion of formaldehyde (or a formalin solution) in humans has been reported in connection with attempted suicides. Metabolic acidosis has been noted prior to death, along with respiratory, cardiac, and renal failure; autopsy revealed corrosive damage to gastrointestinal mucosa (Burkhart et al. 1990; Eells et al. 1981; Koppel et al. 1990). Increased rates of cancer-related mortality associated with occupational exposure to formaldehyde (predominately by inhalation) have been found in some epidemiological studies, but not in others (see Section 2.2.1.8 and Section 2.5). Animal studies indicate that subchronic inhalation exposure to concentrations below 20 ppm are not lethal (Feron et al. 1988; Maronpot et al. 1986; Martin 1990; Rusch et al. 1983; Saillenfait et al. 1989; Woutersen et al. 1987), but lifetime inhalation exposure to formaldehyde has been associated with early mortalities associated with

nasal tumors in rats exposed to concentrations $10 ppm (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Lifetime administration of 5,000 ppm formaldehyde in drinking water (approximate dose of 300 mg/kg/day) to rats resulted in early mortalities associated with degenerative lesions in the epithelium of the forestomach and the glandular stomach (Tobe et al. 1989).

Systemic Effects.

Respiratory Effects. Results from human and animal studies consistently indicate that the upper respiratory tract is a critical target of airborne formaldehyde at concentrations ranging from 0.4 to 20 ppm.

Controlled exposure human studies indicate that short-term exposure to air concentrations ranging from 0.4 to 3 ppm induces eye, nose, and throat irritation that is generally described as mild by most subjects, especially at the lower end of this range, and that is experienced by a greater percentage of subjects at the upper end, compared with the lower end, of the range (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986). Changes in nasal lavage fluid contents (elevated eosinophil counts and protein content), consistent with mild irritation of the nasal epithelium, have been found in several studies of groups of subjects exposed to 0.4 ppm for 4 hours (Gorski et al. 1992; Krakowiak et al. 1998; Pazdrak et al. 1993). The studied groups included healthy subjects, as well as groups of subjects with dermal sensitivity to formaldehyde (Pazdrak et al. 1993) and groups with purported formaldehyde-induced bronchial asthma (Krakowiak et al. 1998).

Formaldehyde effects on pulmonary function variables, such as FVC, FEV_1, and forced expiratory flow rates, have not been found in most studies between 0.4 and 3 ppm, even in studies of subjects with bronchial asthma or with dermal sensitivity to formaldehyde (Andersen and Molhave 1983; Day et al. 1984; Gorski et al. 1992; Harving et al. 1986, 1990; Kulle et al. 1987; Schachter et al. 1986; Witek et al. 1986). A few controlled exposure studies have found only subtle or infrequent effects of formaldehyde on lower respiratory tract function in this concentration range, supporting the hypotheses that the upper respiratory tract is a more likely target of formaldehyde toxicity than the lower respiratory tract and that pulmonary hypersensitivity to formaldehyde is rare (Green et al. 1987; Nordman et al. 1985; Sauder et al. 1986).

In groups of humans who experienced repeated exposure to airborne formaldehyde under occupational or residential conditions, symptoms of eye, nose, and throat irritation were frequently reported (Boysen et al. 1990; Edling et al. 1988; Garry et al. 1980; Holmstrom et al. 1989c; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987). Mild lesions in biopsied nasal epithelium tissue (e.g., stratified squamous epithelium and mild dysplasia) that are indicative of the irritant and reactive properties of formaldehyde were consistently found in four cross-sectional studies of groups of workers exposed to estimated average workplace air concentrations ranging from about 0.1 to 1 ppm (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Some studies assessing pulmonary function variables (e.g., FVC, FEV_1, FEFR) in groups of formaldehyde-exposed workers, generally experiencing average workplace air concentrations below 2 ppm, have found no changes that can be attributed to exposure (Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988). Other studies have presented evidence for formaldehyde-induced changes in pulmonary function variables in groups of subjects exposed in their homes or workplaces, but the changes in these studies were generally small or subtle (Alexandersson and Hedenstierna 1988, 1989; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Krzyzanowski et al. 1990; Malaka and Kodama 1990).

Studies in animals confirm that the upper respiratory tract is a critical target for airborne formaldehyde. Studies of monkeys, rats, and mice exposed to concentrations in the range of 0.3–40 ppm for acute to chronic periods of time demonstrate that formaldehyde nonneoplastic effects are restricted to lesions (squamous metaplasia and hyperplasia) in the epithelium of the upper respiratory tract (Chang et al. 1983; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989, 1991, 1996; Morgan et al. 1986a, 1986c; Rusch et al. 1983; Woutersen et al. 1987, 1989; Zwart et al. 1988). In several lifetime rat studies, exposure to 0.1–2 ppm formaldehyde (6 hours/day, 5 days/week) produced no statistically significant increased incidence of rats with nonneoplastic nasal epithelial lesions (Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Another 28-month study, however, found significantly increased incidence of nasal epithelial lesions (squamous metaplasia without hyperplasia and epithelial cell hyperplasia with squamous metaplasia) in a group of rats exposed to 2 ppm by the same exposure protocol (Kamata et al. 1997). Incidences of the same lesions in rats exposed to 0.3 ppm also were greater than control incidences, but the difference was not statistically significant.

In rats exposed to the lower concentrations in the 2–20 ppm range, formaldehyde-induced lesions (evidence of which could be found after a few days of exposure) occurred in the anterior regions of the nasal epithelium just posterior to the vestibule and progressed to more posterior regions of the upper

respiratory tract epithelium with higher exposure concentrations (Chang et al. 1983; Monticello et al. 1991; Morgan et al. 1986a, 1986c; Zwart et al. 1988). Results from studies in rats comparing nasal lesion severity following intermittent or continuous exposure protocols at varying concentrations suggest that effects are more concentration-dependent than duration-dependent (Wilmer et al. 1987, 1989). Monkeys exposed to 6 ppm formaldehyde for 6 weeks (Monticello et al. 1989) displayed epithelial lesions similar to those displayed by rats exposed to the same concentration for 6 weeks (Monticello et al. 1991), but the lesions in the monkeys showed a different regional distribution that extended into the trachea. Recent analyses using computational fluid dynamics models to predict airflow and regional uptake of formaldehyde in the upper respiratory tract of monkeys and rats found that predicted regions of high airflow were well correlated with epithelial regions with lesions (Kepler et al. 1998; Kimbell et al. 1993, 1997a). These results support the hypothesis that the rat and monkey may be equally susceptible to formaldehyde-induced tissue damage and that airflow patterns, determined by anatomical features, are key determinants of the amount of formaldehyde reaching sites where lesions develop.

Data on effects on the respiratory tract changes after oral exposure to formaldehyde in rats show no changes attributable to formaldehyde with respect to histopathology and/or lung weights in studies of intermediate (Johannsen et al. 1986; Til et al. 1988b; Vargova et al. 1993) and chronic (Til et al. 1989; Tobe et al. 1989) duration.

Cardiovascular Effects. It is unlikely that formaldehyde is responsible for any significant toxicological effects in organs other than the respiratory tract, particularly after inhalation or dermal exposures that might be encountered in the workplace or home. However, effects on the cardiovascular system, such as decreased blood pressure and hypotension (Burkhart et al. 1990; Eells et al. 1981), circulatory collapse (Freestone and Bentley 1989), and sinus tachycardia (Kochhar et al. 1986) due to the ingestion of high doses of formaldehyde in humans have been reported. It is not clear how formaldehyde induced these symptoms or if other existing conditions contributed in whole or in part to these cardiac responses, but is likely related to the large dose of formaldehyde ingested in a very short period of time.

Rats displayed 5–25% increases in blood pressure, compared with resting values, in response to intravenous administration of formaldehyde doses ranging from 0.5 to 5 mg/kg (Egle and Hudgins 1974). In contrast, an intravenous dose of 20 mg/kg significantly decreased blood pressure by about 30% and induced a transient cardiac arrest. The depressor effect at the high dose level was abolished by vagotomy in the neck region, and only the pressor effect was observed in vagotomized rats exposed to 20 mg/kg.

Egle and Hudgins (1974) suggested that the low-dose pressor effects are caused by formaldehyde-induced release of epinephrine from sympathetic nerve endings and catecholamines from the adrenal medulla, and that the vagal nerve is stimulated at high doses leading to bradycardia and decreased blood pressure. Egle and Hudgins (1974) reported that 1-minute exposures to formaldehyde in inspired air at a concentration of 2 mg/L (1,628 ppm) did not significantly affect blood pressure or heart rate in anesthetized rats. This concentration was reported to be 20-times higher than formaldehyde concentrations in inhaled cigarette smoke. These results indicate that acute cardiovascular effects are not expected at environmentally relevant exposure levels.

Results from repeated exposure animal studies suggest that cardiovascular effects due to formaldehyde toxicity after inhalation are negligible, regardless of the duration of exposure at the concentrations tested (#40 ppm). After inhalation exposure, organ weights and/or histopathology remained unchanged from control animals in studies using rats (Appelman et al. 1988; Kerns et al. 1983b; Woutersen et al. 1987, 1989), monkeys (Monticello et al. 1989; Rusch et al. 1983), and mice (Kerns et al. 1983b; Maronpot et al. 1986). Fewer reports were available on cardiovascular toxicity of formaldehyde after oral exposure at doses up to 300 mg/kg/day; however, the findings of no significant effects (weight or histopathology) on this system were consistent in both rats (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989; Vargova et al. 1993) and dogs (Johannsen et al. 1986).

Gastrointestinal Effects. Formaldehyde did not have a detectable effect on the gastrointestinal tract after inhalation exposure of animals (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987) and only nonspecific effects, such as intestinal cramps, and flatus, were reported in four patients that had been exposed occupationally to formalin or phenol-formaldehyde resins (Kilburn 1994). Formaldehyde acts as a contact irritant and corrosive agent after oral exposures of acute, intermediate, and chronic durations. After large doses taken by mouth (acute exposure), lesions can be found in the oropharynx, consisting of ulceration and/or necrosis of the soft palate and phalangeal structures, ulceration of the epiglottis, and esophageal lesions (which may result in dysphagia) (Freestone and Bentley 1989; Kochhar et al. 1986). More vague clinical signs of emesis (with or without hematoemesis) and abdominal pain or cramping were also present in some cases (Burkhart et al. 1990; Eells et al. 1981); these are due, at least in part, to a contact irritant effect, but may also be attributable to corrosive lesions found in the stomach after the ingestion of formaldehyde. In cases which afforded an examination of the duodenum and other portions of the intestinal tract after the stomach, no lesions attributable to formaldehyde intoxication were noted, indicating that the oral cavity

and the stomach share the brunt of the toxicity of formaldehyde after ingestion. Similar findings in the stomachs of Wistar rats noted in one intermediate-duration study (Til et al. 1988b) consisted of hyperkeratosis of the forestomach (indicative of chronic irritation) and focal atrophic inflammation of the glandular stomach at doses of 125 mg/kg/day. Another study by Til and coworkers (1989) found gastric anomalies, consisting of hyperplasia/hyperkeratosis, atrophic gastritis, and ulcerations in Wistar rats at doses ranging from 82 to 109 mg/kg/day in drinking water. Similar effects were also observed in Wistar rats at doses of 50–300 mg/kg/day for up to 2 years (Tobe et al. 1989) and in Wistar rats, exposed to 250 mg/kg/day in drinking water for up to 32 weeks (Takahashi et al. 1986a). Other studies found no significant effect on the gastrointestinal system in both Sprague-Dawley rats (Johannsen et al. 1986; Vargova et al. 1993) and dogs (Johannsen et al. 1986) at doses ranging from 80 to 300 mg/kg/day. The data suggest that formaldehyde has a strong potential to cause damage to the upper gastrointestinal tract (oral cavity, esophagus, and stomach) after oral exposure, and although laboratory animal data are similar to human data, species differences may account for slight differences in the dose required to initiate the damage to the gastrointestinal tract. Evidence for oral exposure to formaldehyde causing tumors of the gastrointestinal tract is discussed below under Cancer Effects.

Hematological Effects. Intravascular coagulopathy was reported in one man who ingested a large dose of formaldehyde (Burkhart et al. 1990); however, the other reports of human ingestion of lower doses suggest no effects on the blood and blood-forming organs (Eells et al. 1981; Freestone and Bentley 1989; Kochhar et al. 1986; Koppel et al. 1990). No consistently significant hematological effects were noted in several studies using the inhalation (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Woustersen et al. 1987) and oral (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989) routes of exposure in laboratory animals. The oral studies with rats used drinking water as the vehicle, with doses ranging from 82 to 150 mg/kg/day, with no hematological effects noted. The lack of toxicity is likely related to rapid metabolism prior to the formaldehyde reaching the blood and blood-forming components (bone marrow). Some evidence suggests, however, that the rapid metabolic capabilities can be overwhelmed to some degree (Vargova et al. 1993), resulting in some minor alterations in blood parameters. In that study, affected male rats received a gavage dose level of 80 mg/kg/day formaldehyde for 4 weeks. This dosing method may have resulted in large doses of formaldehyde being absorbed over a shorter period of time than in the drinking water studies. In this situation, some unmetabolized formaldehyde may have been responsible for the alterations in erythrocyte count and hemoglobin and mean cellular hemoglobin values.

Musculoskeletal Effects. The only reports available that described some manifestations of adverse musculoskeletal effects in humans included vague signs of muscle and joint stiffness after chronic-inhalation exposures to formaldehyde (Holness and Nethercott 1989). It is unlikely that inhalation exposure to formaldehyde is responsible for these complaints, and they may represent an effect from a confounding factor in that study. The lack of human data and the lack of musculoskeletal effects in animal studies (Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Til et al. 1989), coupled with the available toxicokinetic data, suggest that formaldehyde has no adverse effects on the musculoskeletal system.

Hepatic Effects. Hepatic effects (e.g., congestion of hepatic parenchyma and increased serum enzymes associated with liver damage) have been reported for some human cases of acute poisoning from ingestion (e.g., Freestone and Bentley 1989; Koppel et al. 1990), but not reported for other cases (e.g., Burkhart et al. 1990; Eells et al. 1981). Increased incidence of hepatocellular vacuolization was found in rats exposed to gavage dose level of 80 mg/kg/day for 4 weeks (Vargova et al. 1993), but other studies found no exposure-related changes in liver weight or histopathology in rats exposed to drinking-water doses as high as 150 mg/kg/day for 90 days (Johannsen et al. 1986), 125 mg/kg/day for 4 weeks (Til et al. 1988b), 82–109 mg/kg/day for 2 years (Til et al. 1989), and 300 mg/kg/day for 2 years (Tobe et al. 1989). Liver weight and histopathology were likewise unaffected in Beagle dogs exposed to up to 100 mg/kg/day in the diet for 90 days (Johannsen et al. 1986), as were serum enzyme activities indicative of liver damage in rats exposed to up to 300 mg/kg/day for up to 2 years (Tobe et al. 1989). Increased activities of enzymes indicative of liver damage have been reported in rats exposed to air concentrations of 35 ppm for 18 hours (Murphy et al. 1964) or 20 ppm 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), but accompanying structural changes in the liver were not detected with light microscopy. Other studies with rats have not found evidence for increased serum liver enzymes in rats exposed to air concentrations up to 15 ppm, 5 days/week for up to 28 months (Appelman et al. 1988; Kamata et al. 1997). Several other inhalation studies of intermediate or chronic duration have found no evidence for formaldehyde-induced histological changes in the livers of monkeys exposed to 6 ppm (Monticello et al. 1989), rats exposed to up to 14.3 ppm (Kerns et al. 1983b), or mice exposed to up to 40 ppm (Kerns et al. 1983b; Maronpot et al. 1986).

In general, the information from reports of acute poisoning in humans ingesting formaldehyde and reports of studies of animals exposed to formaldehyde in air, in drinking water, or in the diet indicate that the liver is not a prime target of formaldehyde toxicity, and that hepatic effects from exposure to

formaldehyde are expected to occur only when the capacity of dispositional processes for formaldehyde are exceeded at portals-of-entry.

Renal Effects. The available data suggest that the renal system is not a major target organ of toxicity for formaldehyde. Renal failure/anuria was noted in three case reports involving people ingesting various large or unknown amounts formaldehyde (Eells et al. 1981; Freestone and Bentley 1989; Koppel et al. 1990); however, the mechanism of action for the induction of renal failure is not known. Data for laboratory animals exposed by inhalation for intermediate- and chronic-duration to formaldehyde concentrations ranging from 0.19 to 40 ppm are fairly consistent in the failure of formaldehyde to elicit gross or histological lesions, alterations in renal weight, or to produce significant changes in urine composition (Appelman et al. 1988; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987). Appelman et al. (1988) did report oliguria in rats exposed to 10 ppm for 52 weeks, but Kerns et al. (1983b) did not report a similar finding in rats and mice exposed to up to 14.3 ppm for 2 years. Similarly, lack of renal effects was also reported after intermediate- and chronic-duration oral exposure in most studies (Johannsen et al. 1986; Til et al. 1988b; Tobe et al. 1989; Vargova et al. 1993), but renal papillary necrosis was reported for rats that received 82–109 mg/kg/day in drinking water for 2 years (Til et al. 1989), and increased blood urea nitrogen was reported in rats that received 300 mg/kg/day in drinking water for up to 12 months (Tobe et al. 1989).

Endocrine Effects. No information was available that reported the effects of formaldehyde on the endocrine system of humans after inhalation, oral, or dermal exposure. Formaldehyde has been reported not to exert adverse effects on organs of the endocrine system in laboratory animals and, hence, is not a major target organ for formaldehyde toxicity after inhalation (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987) or oral (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989; Vargova et al. 1993) exposure. No data regarding endocrine effects in animals after dermal exposure were located.

Dermal Effects. Formaldehyde is a widely recognized skin irritant and dermal sensitization agent in humans (see also Immunological and Lymphoreticular Effects section). Patch testing for dermal sensitization to formaldehyde has been carried out with either 1 or 2% solutions because, for most individuals, acute exposure to such concentrations does not produce signs of nonimmune irritation (e.g., erythema [redness], induration, flaking, and/or blistering). Some earlier patch testing procedures utilized concentrations as high as 5%, a practice that has been largely discontinued, presumably because of the

difficulty in discerning between irritant and immune responses at this exposure level (Maibach 1983). Increased incidences of contact dermatitis or allergic contact dermatitis associated with dermal exposure to formaldehyde solutions have been observed in funeral service workers (Nethercott and Holness 1988) and among medical workers (Rudzki et al. 1989). Allergic contact dermatitis from formaldehyde released from "no-iron" textiles was frequently reported until textile finishing processes were changed (in the mid 1970s) so that only small amounts of formaldehyde were released from clothing made from such textiles (Peters and Hesse 1997). Experiments with guinea pigs (Wahlberg 1993) and mice (Iversen 1986) indicated that repeated exposure of skin to concentrations for acute periods as low as 0.4% can be damaging (i.e., produce erythema, epidermal hyperplasia, or increased skin-fold thickness).

Animal studies with repeated exposure to airborne formaldehyde concentrations between 1 and 40 ppm (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987) and oral doses as high as 109 mg/kg/day (Til et al. 1989) indicate that clinically significant dermal effects are not a concern by these routes of exposure, although mice exposed to the highest air concentration (40 ppm) in these studies showed a "loss of skin elasticity" (Maronpot et al. 1986). Eberlein-Konig et al. (1998) reported that a 4-hour exposure of dermally sensitized human subjects to airborne formaldehyde concentrations as low as 0.08 ppm increased transepidermal water loss compared with nonsensitized subjects, but the clinical significance of this effect is uncertain.

Ocular Effects. Eye irritation is one of the most common complaints among people exposed to airborne formaldehyde. In acute, controlled exposure studies with volunteers, mild to moderate eye irritation has been reported at low-level concentrations in the range of 0.4–4 ppm; at the upper end of this range, greater percentages of subjects experienced eye irritation (Akbar-Khanzadeh and Mlynek 1997; Akbar-Khanzadeh et al. 1994; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Kulle 1993; Kulle et al. 1987; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986, 1987). Other results indicating formaldehyde's eye-irritation potential include reports that average rates of eye-blinking were significantly increased during exposure to 2.1 ppm, but not to 1.2 ppm (Weber-Tschopp et al. 1977), and that percentages of subjects with shortened response times (i.e., the time taken for the subjects to note eye irritation) were significantly increased with exposure to 1 ppm, but not to lower concentrations (Bender et al. 1983). In addition, survey studies have reported increased rates of eye irritation in groups of persons who have been repeatedly exposed to formaldehyde in residences or workplaces, compared with groups of nonexposed persons (Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987).

Histological examinations of eyes from animals repeatedly exposed to airborne formaldehyde concentrations as high as 6–40 ppm have not found formaldehyde-induced changes (Appelman et al. 1988; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Swenberg et al. 1980; Woutersen et al. 1987). Ophthalmoscopic examinations likewise revealed no exposure-related changes in rats or mice examined at several intervals during 2-year exposures to concentrations as high as 14.3 ppm (Kerns et al. 1983b), but clinical signs of eye irritation during exposure to 2–15 ppm have been noted in several animal studies (Dinsdale et al. 1993; Monticello et al. 1989; Morgan et al. 1986c). Chronic exposure of rats to drinking water doses as high as 89–102 mg/kg/day produced no histological changes in eyes or Harderian and exorbital lachrymal glands (Til et al. 1989). Direct application of formaldehyde solutions into eyes is expected to be irritating. Krootila et al. (1986) provided evidence that application of a 1% solution of formaldehyde to the eyes of rats caused a breakdown of the blood-aqueous barrier and that the irritative response of the eye is dependent on the trigeminal sensory nerve.

Body Weight Effects. Whereas no reports of body weight effects in formaldehyde-exposed humans were located, numerous reports are available of biologically significant body weight decreases in animals repeatedly exposed to formaldehyde by the inhalation route (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Rusch et al. 1983; Woutersen et al. 1987, 1989) and by the oral route via drinking water or diet (Johannsen et al. 1986; Til et al. 1989; Tobe et al. 1989). Exposure-related effects on body weight were not found in pregnant hamsters dermally exposed during gestation to 37% formaldehyde solutions (Overman 1985) or in guinea pigs dermally exposed for 9 days to 4% formaldehyde solutions (Wahlberg 1993). Air concentrations associated with decreased body weights in repeatedly exposed animals were mostly at or above exposure levels ($10 ppm) that produced severe upper respiratory tract lesions. Oral dosage levels associated with decreased body weights in repeatedly exposed animals were generally $80–100 mg/kg/day and also associated with the development of gastrointestinal tract lesions and decreases in food and water intake.

Metabolic Effects. Metabolic acidosis has been observed in patients who ingested large (>500 mg/kg) single doses of formaldehyde (Burkhart et al. 1990; Eells et al. 1981; Koppel et al. 1990). The rapid metabolic production of formate at these high dose levels was likely involved in the observed acidosis.

Other Systemic Effects. Decreased food and water consumption have been observed in animals exposed to oral doses generally greater than 100 mg/kg/day (Johannsen et al. 1986; Til et al. 1989; Tobe et al.

1989). The decreased consumption was generally associated with decreases in body weight and with development of gastrointestinal lesions with intermediate or chronic exposure.

Immunological and Lymphoreticular Effects. Allergic contact dermatitis from formaldehyde is commonly reported at dermatological clinics throughout the world. Patch test reporting from clinics indicates that about 1–4% of tested patients with skin problems are dermally sensitive to formaldehyde (Fischer et al. 1995; see also: Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991). Given the widespread use of formaldehyde in cleaning solutions and cosmetics (Flyvhom 1991; Rastogi 1992), it is likely that most patients presenting with formaldehyde contact dermatitis experienced sensitization through dermal contact, but dermal sensitization through contact with airborne formaldehyde cannot be ruled out. Severe allergic responses to formaldehyde appear to be rare, but one case report was located of a severe response to a patch test with a 1% formaldehyde solution in a woman who was sensitized after exposure to a dialyzer sterilized with formaldehyde (Maurice et al. 1986). Twenty-six hours after the application of the patch, the patient developed anaphylactic symptoms of laryngeal edema and bronchospasm that resolved on administration of subcutaneous epinephrine.

Although formaldehyde is widely recognized as a dermal irritant that can sensitize the skin in humans, the evidence for immunologically-mediated sensitization of the respiratory tract is weak. Despite the widespread use of formaldehyde in several occupational exposure scenarios (and the widespread occurrence of formaldehyde in tobacco smoke), there are only a few available case reports of formaldehyde-exposed workers who display marked changes in pulmonary function variables (e.g., FEV_1 and FEFR) in response to acute challenges with inhaled formaldehyde that are consistent with an immunologically-mediated mechanism of response (Burge et al. 1985; Hendrick et al. 1982; Lemiere et al. 1995; Nordman et al. 1985). Other studies found no marked response to challenges of inhaled formaldehyde in previously-exposed subjects who complained of asthma-like symptoms (Day et al. 1984; Krakowiak et al. 1998; Reed and Frigas 1984). Several studies have found no consistent evidence for increased serum levels of formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed subjects including groups with complaints of respiratory symptoms (Dykewicz et al. 1991; Gorski et al. 1992; Grammar et al. 1990; Krakowiak et al. 1998; Kramps et al. 1989; Thrasher et al. 1987, 1990).

The only other suggestive evidence of IgE-mediated sensitization to formaldehyde comes from a study of schoolchildren who were exposed to particleboard-paneled classrooms with estimated formaldehyde air

concentrations of 0.075, 0.069, and 0.043 ppm and reported respiratory tract symptoms consistent with the irritant properties of formaldehyde (Wantke et al. 1996a). Elevated serum levels of formaldehyde-specific IgE antibodies were detected in these children. The investigators noted that the elevated levels were not correlated with the number and severity of symptoms, but decreased serum levels were measured in a subgroup of the children 3 months after they were moved to another school with lower air concentration of formaldehyde (0.023–0.029 ppm). The significance of these findings is uncertain, as the reported symptoms were more typical of an irritant response than of asthma-like symptoms that are expected to be mediated through IgE antibodies.

Animal studies examining the sensitizing properties of formaldehyde present evidence consistent with the hypothesis that, although formaldehyde can sensitize skin, it apparently lacks a potential to sensitize the respiratory tract (Hilton et al. 1996). Strong positive responses to formaldehyde were found in three animal assays indicative of skin-sensitization potential (guinea pig maximization test, Buehler occluded patch test and the murine local lymph node assay). However, in a mouse IgE test and an assessment of cytokine secretion patterns by lymph node cells, formaldehyde was negative, producing responses that were not like those produced by trimellitic anhydride, a well-established respiratory tract allergen in animals and humans (Hilton et al. 1996). Although these results suggest a lack of ability to sensitize the respiratory tract, another animal experiment suggests that exposure to formaldehyde may enhance allergic responses of the respiratory tract to other respiratory allergens (Tarkowski and Gorski 1995). This study found that that the production of ovalbumin-specific IgE antibodies in response to intranasal administration of ovalbumin was four-fold greater in mice preexposed to 1.6 ppm formaldehyde for 10 consecutive days, compared to the response in mice without formaldehyde preexposure. In similar experiments, groups of guinea pigs preexposed to a formaldehyde concentration of 0.25 ppm, 8 hours/day for 5 days followed by inhalation exposure to 0.5% ovalbumin were found to have a higher percentage of ovalbumin-sensitized animals than control groups with no preexposure (10/12 versus 3/12) (Riedel et al. 1996). Further research is necessary to confirm the hypothesis of formaldehyde facilitation of other respiratory allergens and to determine if this is relevant to humans exposed to formaldehyde.

Other animal studies indicate that repeated inhalation exposure to formaldehyde at high concentrations, between 10 and 15 ppm, did not produce significant effects in several assays of immune function including resistance to intravenous or subcutaneous injection of neoplastic cells in mice (Dean et al. 1984), resistance to intravenous injection of bacterial cells in mice (Dean et al. 1984), and IgM response to tetanus immunization and IgG response to tetanus toxoid in rats (Holmstrom et al. 1989b).

Neurological Effects. Few studies have reported neurological effects after exposure to formaldehyde in humans; however, these studies tend to report vague symptoms. For example, men exposed to formaldehyde vapors at concentrations #0.98 ppm for 5.5 hours reported such symptoms as fatigue, headaches, and "heavy head" (Bach et al. 1990). Reaction times also decreased as formaldehyde concentrations increased. After the ingestion of formaldehyde in humans, coma (Koppel et al. 1990), lethargy, seizures (Burkhart et al. 1990), and loss of consciousness (Burkhart et al. 1990; Eells et al. 1981) have been reported. Kilburn and colleagues have reported evidence for neurological symptoms and impaired performance in neurobehavioral tests in groups of formaldehyde-exposed histology technicians, but confounding exposure to other neurotoxic solvents prevents drawing definitive conclusions regarding the neurotoxicity of formaldehyde from this source (Kilburn 1985b; Kilburn et al. 1987; Kilburn and Warshaw 1992; Kilburn 1994).

Male rats exposed to 15 ppm formaldehyde showed restless behavior within the first 10 minutes of exposure (Morgan et al. 1986a). Exposure to 5 ppm formaldehyde for 3 hours in male rats resulted in decreased motor activity within 15 minutes from the beginning of exposure; increased concentrations of 5-hydroxyindoleacetic acid (a 5-hydroxytryptamine metabolite), 3,4-dihydroxyphenylacetic acid (a dopamine metabolite), and dopamine were present in the hypothalamus at the end of the 3-hour exposure (Boja et al. 1985). With repeated exposure, mice developed an increased sensitivity to the acute sensory irritant properties of formaldehyde; the increased sensitivity attributed, at least in part, to a conditioning (i.e., learning) process (Wood and Coleman 1995). No abnormal clinical signs were noted in mice treated with doses #10 ppm formaldehyde for 6 hours/day, 5 days/week for 13 weeks; however, listlessness and hunched posture were observed in the mice exposed to 20 ppm formaldehyde, and these symptoms plus ataxia were observed in the 40-ppm dose group (Maronpot et al. 1986). No obvious signs of neurological effects were noted in rats (Appelman et al. 1988; Kerns et al. 1983b; Woutersen et al. 1987) or mice (Kerns et al. 1983b) in chronic-duration inhalation studies. No obvious neurological effects were observed in rats receiving 150 mg/kg/day for 90 days in drinking water (Johannsen et al. 1986), in rats receiving 125 mg/kg/day for 4 weeks in drinking water (Til et al. 1988b), or in rats exposed to 300 mg/kg/day for 12 months in drinking water (Tobe et al. 1989). Beagle dogs exposed to formaldehyde in drinking water at concentrations #100 mg/kg/day experienced no effect on brain weight or histopathology. Similar negative findings were noted in studies of chronic duration at doses #300 mg/kg/day in drinking water in rats (Til et al. 1989; Tobe et al. 1989). It appears that formaldehyde has major effects on the nervous system only after large doses are ingested; such as low-level and vague symptoms after chronic, low-level exposure.

Reproductive Effects. Studies regarding possible reproductive effects in humans exposed to formaldehyde are restricted to a study that found no evidence for effects on sperm numbers or morphology in a small number of pathologists (Ward et al. 1984) and a study that found no evidence for increased rates of miscarriage among a group of 275 persons with presumed residential exposure to formaldehyde (Garry et al. 1980).

Studies of animals exposed to formaldehyde in air, in drinking water or diet, or applied to the skin indicate that the reproductive organs are not a critical target for formaldehyde toxicity, but comprehensive assessments of reproductive performance (e.g., 2-generation studies) in formaldehyde-exposed animals were not located.

No effects on histology or weight of reproductive organs were found in rats or mice exposed repeatedly to air concentrations as high as 20 ppm (Appelman et al. 1988; Maronpot et al. 1986, Woutersen et al. 1987), in dogs repeatedly exposed to formaldehyde in the diet at doses up to 100 mg/kg/day (Johannsen et al. 1986), or in rats exposed to oral doses up to 300 mg/kg/day (Johannsen et al. 1986; Til et al. 1989; Tobe et al. 1989; Vargova et al. 1993). Ovarian and uterine hypoplasia were observed in female mice exposed to air concentrations of 40 ppm for 13 weeks, but was attributed to the general weight loss and poor health of these animals rather than to a direct effect of formaldehyde (Maronpot et al. 1986). Maternal toxicity, expressed as a marked decrease in weight gain, occurred in pregnant rats exposed during gestation by inhalation to 40 ppm, but reproductive variables (e.g., numbers of implantations or resorptions) were not affected (Saillenfait et al. 1989). At lower air concentrations, no signs of maternal toxicity were observed in this and another rat study of gestational exposure (Martin 1990). Exposure during pregnancy to gavage dose levels of 185 mg/kg/day, but not 145 mg/kg/day, produced severe maternal toxicity in pregnant mice (22/34 dams died), but did not affect reproductive variables such as numbers of implantation sites or resorptions (Marks et al. 1980). No effects on reproductive variables were found in pregnant dogs exposed to 9.4 mg/kg/day in the diet on gestation days 4–56 (Hurni and Ohder 1973). Dermal exposure of pregnant hamsters to 37% solutions of formaldehyde produced a small increase in resorption rate without affecting maternal weight gain, but the authors of this study proposed that the effect may have been caused by stress associated with the applied treatment protocol (Overman 1985). Single gavage dose levels of 200 mg/kg, but not 100 mg/kg/day, produced changes in sperm morphology in rats (Cassidy et al. 1983), but with no tests of reproductive performance, the toxicological significance of this finding is uncertain. In a review of available reproductive and developmental toxicity data, WHO (1989) concluded, “There is no convincing evidence that formaldehyde is a teratogen in either

animals or human beings. Formaldehyde has not produced any adverse effects on reproduction in test animals or human beings." IARC (1995) reached a similar conclusion in a more recent review.

Developmental Effects. Studies of possible developmental effects in humans exposed to formaldehyde are restricted to a study that found no statistically significant difference in incidence of low birth weights among groups of mothers who lived in residential districts with differing ambient air levels (up to 38 ppb) of formaldehyde (Grañulevi…iene et al. 1998). Exposure of pregnant rats to air concentrations up to 10 ppm during gestation days 6–15 produced no distinct effects on fetal development (Martin 1990). In another study with several exposure levels, pregnant rats exposed during gestation days 6–20 to the highest concentration, 40 ppm, showed a 51% reduction in weight gain (Saillenfait et al. 1989). Fetal weights were decreased in male offspring from dams exposed to 20 ppm and in female offspring from dams exposed to 40 ppm, but no effects attributable to formaldehyde were noted in the incidences of pregnancies, number of implantations or resorptions, number of dead or live fetuses, fetal sex ratios, or incidences of skeletal or visceral anomalies (Saillenfait et al. 1989). Similarly, no effects on fetal development were found in studies of pregnant rats exposed during gestation days 6–15 to gavage dose levels as high as 185 mg/kg/day (Marks et al. 1980), pregnant dogs exposed to up to 9.4 mg/kg/day in the diet during gestation days 4–56 (Hurni and Ohder 1973), and pregnant hamsters dermally exposed to a 37% aqueous solution of formaldehyde on gestation day 8, 9, 10, or 11 (Overman 1985).

Genotoxic Effects. Formaldehyde has been demonstrated to have genotoxic properties in human and laboratory animal studies. Peripheral lymphocytes in anatomy students exposed to 0.73–1.95 ppm formaldehyde for 8 weeks showed a small increase in SCE (Yager et al. 1986). Lymphocytes from wood workers chronically exposed to formaldehyde also showed increased levels of chromosomal aberrations; however, there were no significant changes in the rates of SCE (Chebotarev et al. 1986). Increases in micronuclei formation, primarily in nasal passage ciliated cells, were found in wood workers chronically exposed to 0.07–0.08 ppm formaldehyde (Ballarin et al. 1992). An increased incidence in chromosomal abnormalities in pulmonary macrophages was noted in male rats exposed to 15 ppm formaldehyde for 5 days (Dallas et al. 1992). No reports of genotoxicity strictly related to the oral or dermal exposure routes were found in the available literature.

Conversely, a number of studies have failed to demonstrate the genotoxic potential of formaldehyde. Fleig et al. (1982) performed chromosome analyses on 15 exposed and 15 non-exposed employees from

formaldehyde-manufacturing facilities with average exposure concentrations not exceeding 5 ppm prior to 1971 and 1 ppm after 1971. There were no differences between exposed and control groups in the incidence of chromosomal aberrations. Connor et al. (1985b) tested urine obtained from hospital autopsy service workers exposed to formaldehyde who had actual exposures to formaldehyde of 0.1–5.8 ppm, with the TWA exposures to formaldehyde in work areas were estimated to be 0.61–1.32 ppm. Mutagenicity tests using *S. typhimurium* TA 100 and TA 98 were conducted, with or without rat S9 suspension. Increases in mutation rates were not produced by the urine of workers exposed to formaldehyde, compared to control urine, in the presence or absence of S9.

Formaldehyde has been found to be genotoxic in a number of *in vivo* and *in vitro* test systems. Tables 2-6 and 2-7 present a cross-section of some of the genotoxicity data that are available for formaldehyde examined in *in vivo* and *in vitro* test systems. With *in vivo* test systems, the data are mixed. Formaldehyde has been found to induce chromosomal aberrations (Chebotarev et al. 1986; Dallas et al. 1992; Rithidech et al. 1987) and to cause increases in micronucleus formation (Ballarin et al. 1992), SCE (Yager et al. 1986), DNA-protein cross links (Casavova et al. 1989, 1991b, 1992; Lam et al. 1985; Shaham et al. 1996a), sperm head abnormalities (Topham 1980), and p53 suppressor gene mutations (Recio et al. 1992). Other reports present negative genotoxic findings (Kligerman et al. 1984; Natarajan et al. 1983; Thomson et al. 1984).

Formaldehyde has also been found to be genotoxic in *S. typhimurium* in most cases (Connor et al. 1983, 1985a; Donovan et al. 1983; Glass et al. 1986; Haworth et al. 1983; Schmid et al. 1986; Takahashi et al. 1985) and not mutagenic in others (DeFlora 1981; DeFlora et al. 1984). A number of human cell lines have been tested with formaldehyde giving positive results without activation, resulting in mutations, DNA damage, chromosomal aberrations, and SCEs (Dresp and Bauchinger 1988; Garry et al. 1981; Goldmacher and Thilly 1983; Grafstrom et al. 1983, 1984, 1985; Krieger and Garry 1983; Liber et al. 1989; Schmid et al. 1986; Snyder and Van Houten 1986). Laboratory animal models, such as the Chinese hamster cell lines (Basler et al. 1985; Galloway et al. 1985; Grafstrom et al. 1993; Miller and Costa 1989; Natarajan et al. 1983), Golden Syrian hamsters (Hatch et al. 1983), and rodent cell lines (Basler et al. 1985; Blackburn et al. 1991; Cosma and Marchok 1988; Cosma et al. 1988a; Frazelle et al. 1983; Heck and Casanova 1987; Ragan and Boreiko 1981, 1983; Ross and Shipley 1980) have demonstrated similar results.

Table 2-6. Genotoxicity of Formaldehyde *In Vivo*

Species (test system)	End point	Result	Reference
Mammals:			
Mouse (spleen lymphocytes)	Chromosomal aberrations	+	Rithidech et al. 1987
Human (occupational exposure)	Chromosomal aberrations	–	Vasudeva and Anand 1996
Human (occupational exposure/nasal mucosa)	Micronucleus increase	+	Ballarin et al. 1992
Human (occupational exposure/urine)	Mutagenicity	–	Connor et al. 1985b
Human (occupational exposure/lymphocytes)	DNA-protein cross links, not formaldehyde specific	+	Shaham et al. 1996a
Human (occupational exposure/white blood cells)	Chromosome aberrations and sister chromatid exchange	–	Thomson et al. 1984
Human (occupational exposure/lymphocytes)	Sister chromatid exchange	+	Yager et al. 1986
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Cherbaterev et al. 1986
Rat (pulmonary lavage)	Chromosomal aberrations	+	Dallas et al. 1992
Rat (nasal mucosal cells)	DNA-protein cross links	+	Casanova et al. 1989
Rat (nasal mucosal cells)	DNA-protein cross links	+	Lam et al. 1985
Rat (bone marrow)	Chromosomal aberrations	–	Dallas et al. 1992
Rat (lymphocytes)	Mitotic activity, sister chromatid exchange, chromosomal aberration	–	Kligerman et al. 1984
Monkey (respiratory tract)	DNA-protein cross links	+	Casanova et al. 1991b
Non-mammals:			
D. Melanogaster	Mortality and sterility	+	Valencia et al. 1989
D. Melanogaster	Lethal mutation	+	Woodruff et al. 1985

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

Table 2-7. Genotoxicity of Formaldehyde *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, UTH8414, UTH 8413 (Ames test)	Gene mutation	(+)	(+)	Glass et al. 1986
S. typhimurium TA 98, TA 100 (Ames test)	Gene mutation	No data	+	Takahashi et al. 1985
S. typhimurium TA 100 (Ames test)	Gene mutation	+	+	Schmid et al. 1986
Escherichia coli	Gene mutation	No data	+	Takahashi et al. 1985
S. typhimurium TA97, TA98, TA100 (Ames test)	Gene mutation	No data	+	Donovan et al. 1983
S. typhimurium TM677, TA100 (Ames test)	Gene mutation	+	+	Donovan et al. 1983
S. typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 (Ames test)	Gene mutation	−	−	DeFlora et al. 1984
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 (Ames test)	Gene mutation	–[a]	–[a]	DeFlora 1981
S. typhimurium TA98, TA100, UTH8413, UTH8414 (Ames test)	Gene mutation	(+)	(+)	Connor et al. 1985b
S. typhimurium TA98, TA100, UTH8413, UTH8414 (Ames test)	Gene mutation	(+)[a]	(+)[a]	Connor et al. 1983
S. typhimurium TA1535, TA1537, TA98, and TA100	Gene mutation	No data	+	Haworth et al. 1983
Eukaryotic organisms:				
Mammalian cells:	Mutations	No data	+	Grafstrom et al. 1985
Human (bronchial fibroblast culture)				
Human (foreskin fibroblast culture)	DNA damage	No data	+	Snyder and Van Houten 1986
Human (lymphocyte cell culture)	Chromosomal aberrations	No data	+	Dresp and Bauchinger 1988
Human (lymphocyte cell culture)	DNA damage	No data	+	Liber et al. 1989

Table 2-7. Genotoxicity of Formaldehyde *In Vitro* (continued)

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Human (lymphocyte cell culture)	Sister chromatid exchange and chromatid-type aberrations	+	+	Schmid et al. 1986
Rat (tracheal epithelium culture)	DNA damage	No data	+	Cosma et al. 1988a
Rat (tracheal epithelium culture)	DNA damage	No data	+	Cosma and Marchok 1988
Rat (nasal mucosa)	DNA binding	No data	+	Heck and Casanova 1987
Mouse (lymphoma L5178Y TK ±)	Mutagenicitiy	+	+	Blackburn et al. 1991
Chinese hamster (V79 cell culture)	Sister chromatid exchange	–	+	Basler et al. 1985
Chinese hamster (V79 cell culture)	Mutations	No data	+	Grafstrom et al. 1993
Chinese hamster (ovary cell culture)	DNA damage	No data	+	Miller and Costa 1989
Chinese hamster (ovary cell culture)	Chromosomal aberrations; sister chromatid exchange	+	+	Natarajan et al. 1983
Chinese hamster (ovary cell culture)	Chromosomal aberrations; sister chromatid exchange	(+)	(+)	Galloway et al. 1985
Golden Syrian hamster (embryo cell culture)	Viral transformation	No data	+	Hatch et al. 1983
C3H/10T½ mouse embryo fibroblasts	Focus transformations	(+)	–	Frazelle et al. 1983
Rodent (Yoshida sarcoma cells)	DNA cross links	No data	(+)	Bedford and Fox 1981
Calf (thymus chromatin)	Histone redistribution	No data	+	Polacow et al. 1976
C3H/10T½ mouse embryo fibroblasts	Focus transformations	+	–	Ragan and Boreiko 1981
C3H/10T½ mouse embryo fibroblasts	Focus transformations	+	–	Boreiko and Ragan 1983
C3H/10T½ mouse embryo fibroblasts	Focus transformations	+	No data	Frazelle et al. 1983
Mouse leukemia L1210 cells	DNA single strand breaks	No data	(+)	Ross and Shipley 1980
Mouse leukemia L1210 cells	DNA protein cross links	No data	+	Ross and Shipley 1980
Human (lymphocyte cultures)	Sister chromatid exchange	No data	+	Kreiger and Garry 1983

Table 2-7. Genotoxicity of Formaldehyde *In Vitro* (continued)

		Result		
Species (test system)	End point	With activation	Without activation	Reference
Human (bronchoial fibroblast cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1984
Human (bronchoial epithelial cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1984
Human (skin fibroblast cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1984
Human (bronchoial epihtelial cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1983
Human (bronchoial fibroblast cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1983
Human (lymphoblastoid TK6 cells)	DNA mutation	No data	+	Goldmacher and Thilly 1983
Human (cultured lymphocytes)	Sister chromatid exchange	No data	+	Garry et al. 1981

[a]test compound was formalin

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

In summary, no reports of genetic effects in humans were located, but formaldehyde has displayed genotoxic activity in the majority of studies in a variety of *in vivo* tests with organisms ranging from bacteria to rodents and a variety of *in vitro* tests including tests with cultured human cells. The weight of evidence indicates that formaldehyde itself is capable of directly reacting with DNA, and producing genotoxic effects, especially when metabolic capacities are exceeded.

Cancer. As discussed in Section 2.2.1.8, there are more than 40 epidemiology studies (cohort mortality studies of industrial workers, cohort mortality studies of medical specialists and embalmers, and case-control studies) examining the potential for occupational formaldehyde exposure to induce cancer. Two meta analyses of these studies calculated aggregate relative risks (with 95% CIs noted in parentheses) for nasopharyngeal cancer deaths in occupationally exposed workers of 1.2 (0.8–1.7) and 2.0 (1.4–2.90), and noted that an exposure-response relationship for nasopharyngeal cancer could be demonstrated by grouping the studies in exposure categories of "low/medium" and "substantial" (Blair et al. 1990a; Partanen 1993). A third meta analysis (Collins et al. 1997), using the same studies plus additional cohort mortality data not available for the earlier analyses, reported meta relative risks of 1.0 (0.5–1.8) for nasopharyngeal cancer across 14 available cohort studies, 1.2 (0.4–2.5) for six available cohort studies of industrial workers, and 1.3 (0.9–2.1) for seven case-control studies. Collins et al. (1997) concluded that their analysis of the data did not support an exposure-response relationship for formaldehyde exposure and nasopharyngeal cancer.

Other reviewers also have arrived at differing conclusions regarding the evidence from the epidemiological studies. On one side, IARC (1995) and EPA (1991a) judged that there was limited evidence in humans and NTP (1998) judged that formaldehyde was reasonably anticipated to be a human carcinogen; whereas McLaughlin (1994) and ECETOC (1995), on the other side, concluded that a causal relationship was not established by the available data. A more recent collaborative review of the data by EPA and CIIT (1998) appears to take a middle stand concluding that "it appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out".

In contrast to the equivocal, limited, or weak nature of the evidence in humans, replicated inhalation studies have consistently shown that formaldehyde induces nasal tumors in rats exposed to high concentrations (10–15 ppm) that also induce nasal epithelial necrosis and cellular proliferation, but not when exposed to lower concentrations (0.3–2 ppm) that do not markedly damage nasal epithelial tissue (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Sellakumar et al.

1985; Woutersen et al. 1989). Exposure-related cancer or noncancer lesions at sites distant from the portal-of-entry were not found in these studies, consistent with the water solubility and reactivity of formaldehyde and the ubiquity of rapid cellular metabolism of formaldehyde.

No information is available as to whether oral exposure to formaldehyde increases the risk of cancer in humans. The evidence for formaldehyde-induced carcinogenicity from four available rat drinking water studies is equivocal due to inconsistent findings (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989). Two studies reported no increased incidence of gastrointestinal tract tumors in rats exposed for life to formaldehyde in drinking water at doses up to 109 mg/kg/day (Til et al. 1989) or 300 mg/kg/day (Tobe et al. 1989). Another study reported increased incidences of gastrointestinal tumors (papillomas, adenocarcinomas, and leiomyosarcomas) in some groups of rats exposed for life to drinking water doses of 188 mg/kg/day, but not in groups exposed to 313 mg/kg/day (Soffritti et al. 1989). The fourth study reported that benign papillomas were found in the forestomach of 8/10 rats exposed for 32 weeks to drinking water doses of 258 mg/kg/day (Takahashi et al. 1986a), but others (Til et al. 1989) have questioned whether a different histologist would have classified the observed lesions as papillary hyperplasia. The weight of the animal evidence suggests that gastrointestinal tract tumors may occur as portal-of-entry effects in rats chronically exposed to formaldehyde in drinking water only at high doses, and that tumors are not likely to occur at dose levels that do not damage the gastric mucosa. The animal studies suggest that there is little likelihood that chronic exposure to non-irritating levels of formaldehyde in drinking water will increase cancer risks in humans.

No studies were located regarding cancer rates in humans predominantly exposed to formaldehyde via the dermal route. Animal cancer studies of dermal exposure are restricted to two studies that found no statistically significant increased incidences of skin tumors in mice exposed twice weekly for 58–60 weeks to solutions containing up to 4% (Iverson 1988) or 10% formaldehyde (Iverson 1986).

NTP (1998) has determined that formaldehyde may reasonably be anticipated to be a human carcinogen, and IARC (1995) made the overall evaluation that formaldehyde is probably carcinogenic to humans (Group 2A) based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals.

EPA (1991a; IRIS 1999) classified formaldehyde in Group B1 - probable human carcinogen based on an evaluation of limited human evidence and sufficient laboratory animal evidence. EPA (1991a) used dose-

response data for nasal tumors in rats exposed to high concentrations of formaldehyde to extrapolate to human cancer risk at low exposure concentrations, using rates of DNA-protein cross links in target tissue as a measure of delivered dose. Relationships between formaldehyde air concentrations and rates of formation of DNA-protein cross links in nasal epithelial tissue of rats (Casanova et al. 1989) or of Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) and adjustments to continuous exposure were used to calculate lifetime human cancer unit risk estimates of $3.3x10^{-4}$ per ppm formaldehyde based on the monkey data, and $2.8x10^{-3}$ per ppm formaldehyde based on the rat data. EPA (1987d, 1991a; IRIS 1999) did not derive a cancer risk estimate for oral exposure to formaldehyde. EPA and CIIT (CIIT 1998) are currently working on options to derive new estimates of cancer risk in humans exposed by inhalation using CFD models of nasal airflow and uptake of formaldehyde in rats, monkeys, and humans; pharmacokinetic models of nasal tissue disposition of formaldehyde; and two-stage clonal growth cancer models incorporating data on cellular proliferation rates.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates

because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Whereas there are numerous studies of adults occupationally exposed to formaldehyde and exposed under acute controlled conditions, data regarding the toxicological properties of formaldehyde in children are limited. Nevertheless, the same type of effects that occur in adults are expected to occur in children (e.g., damage in portal-of-entry tissues at exposure levels that exceed tissue detoxification mechanisms). Symptoms expected to occur in children include eye, nose, and throat irritation from exposure to airborne concentrations between 0.4 and 3 ppm, and dermal irritation from exposure to dermal contact with liquids containing more than 2% formaldehyde. Given the water-soluble and reactive nature of formaldehyde and the apparent ubiquity of rapid cellular metabolism of formaldehyde, it is expected that the irritant effects of formaldehyde would be restricted in children, as in adults, to portals-of-entry, although no

information was located comparing rates of formaldehyde metabolism in children's tissues with rates in adult tissues, either in humans or animals. However, studies of adult humans or rats exposed for short periods to air concentrations of 1.9 ppm or 14.4 ppm, respectively (Heck et al. 1985), and monkeys exposed to 6 ppm for up to 4 weeks (Casanova et al. 1988) found no appreciable changes in circulating blood levels of formaldehyde; these results are consistent with the protective action of rapid metabolism of formaldehyde in portal-of-entry tissues. The developing fetus or nursing infant would be expected to be protected from exposure to formaldehyde (via inhalation, oral, and dermal contact) by the pregnant or breast-feeding mother. Studies of animals exposed during pregnancy to formaldehyde in air (Martin 1990; Saillenfait et al. 1989), in the diet or by gavage (Hurni and Ohder 1973; Marks et al. 1980), or on the skin (Overman 1985) have found no distinct or consistent effects on fetal development, even at exposure levels that produced severe maternal toxicity (e.g., Marks et al. 1980).

Two studies were available providing suggestive evidence that children may be more sensitive than adults to the irritant properties of airborne formaldehyde (Krzyzanowski et al. 1990; Wantke et al. 1996a). Krzyzanowski et al. (1990) questioned a group of 298 children (aged 6–15 years) and 613 adults concerning respiratory symptoms, measured PEFR during evenings and mornings for up to 14 days, and made measurements of household air concentrations of formaldehyde in several rooms of 202 houses. Preliminary reports of this study were published in an earlier report (Quackenboss et al. 1989). Bedroom air concentrations were #0.040 ppm for more than 80% of the subjects, between 0.04 and 0.06 ppm for about 8–10% of the subjects, and greater than 0.06 ppm in about 3% of children and 6% of adults in the study. A few cases were measured with air concentrations exceeding 0.09 ppm, with a maximum value of 0.14 ppm. Regression analysis found no significant relationship between exposure category of children and prevalence rates of subjectively reported respiratory symptoms, but physician-diagnosed chronic bronchitis or asthma prevalence rates were elevated in children with household air concentrations greater than 0.06 ppm, especially in households with environmental tobacco smoke. In adults, neither respiratory symptoms or physician-diagnosed chronic bronchitis or asthma were significantly related to formaldehyde air concentrations. In children, a statistically significant trend for decreasing PEFR values with increasing formaldehyde exposure concentrations was found; the estimated decrease in PEFR associated with 0.06 ppm was 22% compared with mean values for low-level children. In adults, PEFR values (mornings only) were also related to formaldehyde concentrations, but the effect was relatively small; the estimated decrement in adults associated with 0.10 ppm was about 1%.

School children who attended particleboard-paneled classrooms with estimated formaldehyde air concentrations of 0.075, 0.069, and 0.043 ppm reported respiratory tract symptoms consistent with the irritant properties of formaldehyde including rhinitis, cough, nosebleed, and headache (Wantke et al. 1996a). These concentrations are low compared to workplace air concentrations or exposure chamber concentrations associated with irritant symptoms in adults (0.4–3 ppm). Formaldehyde-specific IgE antibodies were detected in serum of 40% of the children. The investigators noted that the elevated levels were not correlated with the number and severity of symptoms, but serum levels and incidence of symptoms decreased in a subgroup of the children 3 months after they were moved to another school with lower air concentration of formaldehyde (0.023–0.029 ppm). As stated earlier when discussing this study, the significance of these findings is uncertain as the reported symptoms were more typical of an irritant response than of asthma-like symptoms that are expected to be mediated through IgE antibodies.

Additional research is necessary to confirm or discard the hypothesis that children may be more susceptible than adults to the irritant effects of formaldehyde and to understand the mechanistic basis of this possible difference.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the

body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to formaldehyde are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by formaldehyde are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Formaldehyde

Formaldehyde is a simple one-carbon molecule and is rapidly absorbed and metabolized by animals, including humans. A thorough review of the available literature failed to produce any reliable biomarkers of exposure to formaldehyde.

As discussed in Section 2.3, formaldehyde is rapidly absorbed by the inhalation and oral routes of exposure. Once absorbed, there are four major metabolic pathways associated with formaldehyde metabolism, with the metabolism to formate and CO_2 the most heavily used (see Figure 2-3 in Section 2.3.3).

Attempts have been made to determine if either blood or urinary levels of formaldehyde or formate could be used as potential biomarkers of exposure, but with disappointing results. Heck et al. (1985) exposed

four men and two women to a 1.9±0.06 ppm air concentration of formaldehyde in a large walk-in chamber for 40 minutes. Shortly before and shortly after the exposure, venous blood samples were taken from each person (each person served as his/her own control) and the blood was analyzed for formaldehyde content. No significant differences were found between pre- and postexposure blood concentrations of formaldehyde at the concentration tested. In the same study, male Fischer 344 rats were placed in a nose-only inhalation chamber and exposed to a 14.4±2.4 ppm air concentration of formaldehyde for 2 hours; rats were sacrificed, and venous blood samples were collected and analyzed for formaldehyde content. Even by using the higher exposure concentration of formaldehyde, no significant differences in blood formaldehyde concentrations were found between the pre- and postexposure blood samples. In addition, the rapid intravenous injection of formaldehyde in monkeys showed a plasma half-life of only 1.5 minutes, with a corresponding increase in blood formate levels.

Einbrodt et al. (1976) exposed students to 0.26–0.92 ppm formaldehyde vapors for 3 hours, with urine samples collected immediately after exposure and 21 hours after exposure. Urine formaldehyde and urine formic acid (formate) concentrations were found to be higher immediately after exposure compared to 21 hours later; however, no baseline sample was obtained prior to exposure. If historic formaldehyde and formic acid baseline levels were assumed, then a closer examination of these data indicates that more formaldehyde (and metabolite) was excreted in the urine than could have possibly been absorbed by inhalation, indicating another route of exposure (perhaps dermal), or co-exposure to another chemical that also has formate as a metabolite (e.g., methanol), or higher personal exposures than were actually measured. There was also no indication that the urine formate levels were adjusted to compensate for urine specific gravity using urine creatinine levels, which may have markedly influenced the test results.

Gottschling et al. (1984) monitored 35 anatomy laboratory students exposed for 2 hours, once a week for 3 weeks, with exposures ranging from 0.036 to 0.111 ppm. Urine was obtained prior to exposure and during the exposure. Wide variations were noted in the urine formate levels prior to exposure, with large intrapersonal and interpersonal variations; mean postexposure urine formate concentrations were elevated after exposure to formaldehyde vapors, but not significantly. In the study by Einbrodt et al. (1976), urine formate levels were significantly elevated in both anatomy laboratory students and in four factory workers exposed to 1 ppm formaldehyde; however, the mass-balance equations for both groups indicated other factors may have influenced the amount of formate found in the urine. Formate production is not specific to formaldehyde because other chemicals such as methanol, halomethanes (e.g., dichloromethane), and acetone have formate in their metabolic pathways (Ferry et al. 1980;

Kornbrust and Bus 1983; Liesivuori and Savolainen 1987). This indicates that even if blood or urine formate levels were elevated, it may be due to individual variation, formaldehyde exposure, or other chemical exposures that result in formate formation. Thus formate blood and urine levels appear to be equally unreliable as definitive biomarkers for formaldehyde exposure.

Formaldehyde that is not rapidly metabolized to formate can react with a variety of cellular components including nucleotides, proteins, and glutathione, forming adducts, such as N6-hydroxymethyl-deoxyadenosine and N2- hydroxymethyldeoxyguanosine, and DNA-protein cross links. Several of these formaldehyde-induced products have been examined as potential biomarkers of exposure for repeated exposure to formaldehyde. A method for detecting biomarkers such as N^6-hydroxymethyldeoxy-adenosine and N^2-hydroxymethyldeoxyguanosine (the major adducts formed by formaldehyde *in vitro*) had experimental complications and does not appear to provide useful biomarkers of formaldehyde exposures (Fennel 1994). Many studies (Casanova-Schmitz et al. 1984a; Casanova and Heck 1987; Casanova et al. 1989a, 1989b, 1991, 1994) utilized radiolabeled compounds tagged with ^{14}C and/or ^{3}H to facilitate detection of DNA-protein cross links; however, this approach would not work to detect past exposures in humans. The formation of DNA-protein cross links in isolated rat nasal epithelial cells (respiratory and olfactory epithelial cells) incubated with formaldehyde has also been reported (Kuykendall et al. 1995). Utilizing a sensitive technique to detect total DNA-protein cross links, Shaham et al. (1996a) reported that cultured human white blood cells showed increasing quantities of DNA-protein cross links when cultured in media with increasing formaldehyde concentrations and that a small group of formaldehyde-exposed persons had a significantly greater mean amount of DNA-protein cross links in their white blood cells than did a group of nonexposed persons. Although DNA-protein cross links are known to be formed by other agents such as ionizing radiation and alkylating agents, Shaham et al. (1996a) concluded that their results suggested that levels of DNA-protein cross links in white blood cells may provide an indicator of formaldehyde-induced tissue damage and a biomarker of occupational exposure to formaldehyde. Shaham et al. (1996b) noted that a larger study of the potential of DNA-protein cross links in white blood cells as a biomarker of effect and exposure was in progress.

Immunological biomarkers of effect (IgG and IgE antibodies against formaldehyde conjugated to human serum albumin) have been examined as potential biomarkers of exposure to airborne formaldehyde. Some studies have reported that increased serum levels of antibodies against formaldehyde-human serum albumin in groups of human subjects correlated with exposure to airborne formaldehyde and symptoms of respiratory distress (Thrasher et al. 1987, 1988b, 1989, 1990), whereas other studies of human subjects

have not found similar correlations (Dykewicz et al. 1991; Grammer et al. 1990; Patterson et al. 1989; Wantke et al. 1996a, 1996b). The hypothesis, put forth by Nordman et al. (1985), concluded that immunological hypersensitivity of the respiratory tract to airborne formaldehyde is rare, and casts doubt that immunological biomarkers for formaldehyde would have been useful biomarkers to indicate exposure. However, Carraro et al. (1997) recently reported that the presence of IgG antibodies against formaldehyde-human serum albumin was significantly associated with smoking habits, but not with self-reported occupational exposure to formaldehyde, in a group of 219 healthy subjects. When only non-smokers were included in the analysis, a statistically significant association was found between the presence of formaldehyde-specific antibodies and occupational exposure to formaldehyde. An indirect competitive immunoenzyme assay for anti-formaldehyde-human serum albumin antibodies was developed for this study. These results suggest that smoking produces a detectable immunological response to formaldehyde and that the technique employed may be useful to indicate occupational or residential exposure to formaldehyde especially in the absence of exposure to tobacco smoke.

Development of biomarkers for exposure is complicated by the fact that the metabolism of many xenobiotics can result in formaldehyde production *in vivo*. Carbon tetrachloride, endrin, paraquat, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Shara et al. 1992), and dichloromethane (Dekant and Vamvakas 1993) are all known to generate formaldehyde during their metabolism.

2.7.2 Biomarkers Used to Characterize Effects Caused by Formaldehyde

Increased eosinophil concentration and increased levels of albumin and total protein have been found in nasal lavage fluid taken from subjects exposed to 0.4 ppm formaldehyde for 2 hours (Krakowiak et al. 1998; Pazdrak et al. 1993). Although these variables are not expected to be only influenced by formaldehyde, they appear to be promising biomarkers of acute respiratory irritation from airborne formaldehyde.

As discussed in the previous section, DNA-protein cross links in white blood cells (Shaham et al. 1996a) and anti-formaldehyde-human serum albumin IgG antibodies in serum (Carraro et al. 1997) are potential biomarkers of both exposure and effect associated with intermediate- or chronic-exposure to formaldehyde.

Li et al. (1995) evaluated the validity of the modified lymphocyte transformation assay for detecting contact hypersensitivity of formaldehyde. Female Hartley guinea pigs were sensitized to formaldehyde

by receiving subcutaneous injections of 1.85% formaldehyde (6 sites, 0.1 mL per site) followed 7 days later by epicutaneous exposure to 0.5 mL of a 1.85% formaldehyde solution. Cells were collected from lymph nodes tissue. Exposure to increasing concentrations of formaldehyde resulted in significant increases in T-lymphocyte blastogenesis ($p<0.05$). Although further refinement of this assay would be required (i.e., use of peripheral blood lymphocytes in lieu of lymph node samples), it does have potential for providing nonspecific biomarker of effect for formaldehyde sensitization.

Another potentially useful biomarker of effect for repeated inhalation exposure to formaldehyde involves the histological examination of nasal biopsy samples. Histological changes in nasal biopsy tissue samples (e.g., loss of ciliated cells, squamous dysplasia and hyperplasia) have been associated with formaldehyde exposure in several cross-sectional studies of formaldehyde-exposed and nonexposed workers (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Each of these studies used a morphological grading method that assigned an increasing point value for histological changes ranging in severity from loss of ciliated cells to the presence of malignant cells. Prevalence of different types of changes and mean histological scores were compared between exposed and nonexposed groups. The findings from rat studies indicating that the development of formaldehyde-induced nasal cancer is preceded by repeated damage to the upper respiratory tract epithelium suggests that monitoring of formaldehyde-exposed workers for cytological abnormalities in nasal biopsy samples may be useful to prevent the development of upper respiratory tract tissue damage or cancer. Similar findings of epithelial squamous dysplasia and hyperplastic nasal mucosa have been found in chronic occupational exposures to formaldehyde (Boysen et al. 1990; Edling et al. 1988); however, as discussed in Section 2.5, these human studies do not conclusively prove that formaldehyde was the primary toxicant responsible for the observed nasal lesions. The squamous metaplasia and mucosal hyperplastic lesions may be useful indicators of more severe formaldehyde-induced effects; however, its usefulness in human exposures is likely to be limited.

2.8 INTERACTIONS WITH OTHER CHEMICALS

The study by Albert et al. (1982) reported the carcinogenic responses to the combined and separate exposures to formaldehyde and hydrochloric acid in male inbred Sprague-Dawley rats. Rats were exposed for 588 days to formaldehyde alone (14.2 ppm); formaldehyde (14.1 ppm) and hydrogen chloride (HCl) (9.5 ppm) combined but not premixed; formaldehyde (14.3 ppm) and HCl (10.0 ppm) combined and premixed; HCl alone (10.2 ppm); or room air. The data did not indicate a synergistic effect on mortality from combined formaldehyde and HCl exposure; no synergism was noted between combined HCl and formaldehyde exposure and the induction of nasal cancers. Rats exposed to formaldehyde alone experienced about a 9% depression in body weights compared to controls; those exposed to HCl alone experienced no noticeable weight loss; exposure to formaldehyde and HCl combined resulted in a 14% depression in body weight, indicating a synergistic adverse effect on body weight from combined HCl and formaldehyde exposure. Lam et al. (1985) studied the effects of inhalation co-exposure to acrolein and formaldehyde in male Fischer 344 rats. Rats were exposed for 6 hours to room air (controls), 2 ppm acrolein, 6 ppm formaldehyde, or a combination of 2 ppm acrolein and 6 ppm formaldehyde. The animals were sacrificed immediately after completion of exposure and their nasal tissues were harvested. Exposure to formaldehyde significantly increased the percentage of interfacial DNA (a measure of DNA-protein cross linking) compared to rats exposed to room air only (12.5 versus 8.1%, $p<0.05$). Co-exposure to acrolein resulted in further increases in the percentage of interfacial DNA (18.6%) which were significantly greater than the effect of formaldehyde alone ($p<0.05$). The authors concluded that simultaneous exposure to acrolein enhanced formaldehyde-induced DNA-protein cross linking and that depletion of glutathione by acrolein inhibited the metabolism of formaldehyde, thereby increasing formaldehyde-induced DNA-protein cross link formation.

To investigate the possibility of additive or potentiating interactions between inhaled aldehydes, Cassee et al. (1996b) compared responses in nasal epithelial histopathology and cell proliferation in groups of male Wistar rats exposed for 3 days (6 hours/day) to 1.0, 3.2, or 6.4 ppm formaldehyde alone; to 0.25, 0.67, or 1.40 ppm acrolein alone; to 750 or 1,500 ppm acetaldehyde alone; or to several mixtures of these aldehydes. At the concentrations tested, the histological and cell proliferation responses measured in the nasal epithelium of rats exposed to the mixture which produced effects (3.2 ppm formaldehyde; 1,500 ppm acetaldehyde; 0.67 ppm acrolein) were attributed by the investigators to the acrolein alone with no additional effects from the formaldehyde or acetaldehyde. The investigators concluded that

combined exposures to these aldehydes at exposure levels in the vicinity of individual no-effect-levels was not associated with a greater hazard than that associated with exposure to the individual chemicals.

As discussed previously in Sections 2.2 and 2.5, experiments with mice (Tarkowski and Gorski 1995) and guinea pigs (Riedel et al. 1996) indicate that exposure to low levels of formaldehyde enhances allergic responses to intranasal administration of ovalbumin and suggest the possibility of formaldehyde facilitation of allergic responses to other respiratory allergens. Mice pre-exposed to 1.6 ppm, 6 hours/day for 10 consecutive days produced four-fold greater ovalbumin-specific IgE antibodies in response to intranasal administration of ovalbumin mice that were not pre-exposed (Tarkowsi and Gorski 1995). A group of guinea pigs exposed to 0.25 ppm formaldehyde, 8 hours/day for 5 days showed a greater percentage of bronchial, presumably allergic, responses to inhaled ovalbumin than a control group without preexposure to formaldehyde (10/12 versus 3/12) (Riedel et al. 1996).

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to formaldehyde than will most persons exposed to the same level of formaldehyde in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of formaldehyde, or compromised function of target organs affected by formaldehyde. Populations who are at greater risk due to their unusually high exposure to formaldehyde are discussed in Section 5.6.

Two populations of humans have received considerable attention in the literature as being particularly sensitive to formaldehyde exposure following inhalation and/or dermal exposure. The first population is asthmatics, and concern focuses on the changes in lung function parameters that formaldehyde may produce (Harving et al. 1990; Kulle et al. 1987; Pazdrak et al. 1993; Reed and Frigas 1984; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986). Most of these studies concluded that there is no evidence of increased airway reactivity as a result of formaldehyde exposure in either normal or asthmatic individuals. Formaldehyde exposures at the concentrations tested (usually >3 ppm) did not exacerbate existing asthmatic conditions, either at rest or after exercise. However, Nordman et al. (1985), in a human population of 230 persons suffering asthmatic symptoms and exposed to formaldehyde, found that when exposed to 2.04 ppm formaldehyde for 30 minutes, eight subjects demonstrated an immediate bronchial reaction, four subjects demonstrated a delayed reaction, and two subjects demonstrated both an

immediate and a delayed reaction. Peak expiratory flow rates dropped 19–49% in the immediate-reaction group and 21–47% in the delayed-reaction group. In a study of seven subjects with a history of occupational exposure to glutaraldehyde and asthma, peak expiratory flow rates were decreased in 3/7 subjects by 27–33% in response to a bronchial challenge with 1% formaldehyde (Gannon et al. 1995). Gannon et al. (1995) suggested that respiratory sensitivity produced by exposure to glutaraldehyde may have cross-reactivity to formaldehyde in some subjects.

The second population of potential concern is people with dermal sensitization. Several cases have been reported. Formaldehyde liquid, but neither the gaseous phase nor formalin, is considered to be a dermal sensitizer (Hilton et al. 1996). Anaphylactic reactions have been reported in the literature (Maurice et al. 1986), in a description of a case in which anaphylaxis occurred in a patient due to skin contact with adhesives sterilized with formaldehyde prior to her hemodialysis therapy. Dermal allergic reactions have also been reported in doctors and nurses exposed to formaldehyde (Rudzki et al. 1989) as well as in fiberglass workers (Kilburn et al. 1985a).

Data from acute controlled-exposure studies, supported by data from animal studies, generally indicate that formaldehyde does not induce airway hyper-reactivity at concentrations #3 ppm, but further studies with asthmatics may be required because of somewhat conflicting data in this potentially sensitive population. Other persons with dermal sensitization to formaldehyde are not likely to develop signs of respiratory insufficiency. Persons with multiple chemical sensitivities may represent a third potentially sensitive population, but studies linking this syndrome with exposure to formaldehyde were not located.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to formaldehyde. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to formaldehyde. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to formaldehyde:

Aaron, CK and Howland, MA (eds.) (1994). Goldfrank's Toxicologic Emergencies. Appleton and Lange, Norwalk, CT.

Dreisbach, RH and Robertson, WO, (eds.) (1987). Handbook of Poisoning. Appleton and Lange, Norwalk, CT.

Ellenhorn, MJ and Barceloux, DG, (eds.) (1988). Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing, New York, NY.

Gossel, TA and Bricker JD (1994). Principles of Clinical Toxicology. 3rd edition, Raven Press, New York, NY.

Haddad, LM and Winchester, JF, (eds.) (1990). Clinical Management of Poisoning and Drug Overdose (2nd edition). WB Saunders, Philadelphia, PA.

The primary concern after oral intoxication with formaldehyde is correcting the severe acidosis and decreased blood pressure that this chemical induces. Treatment should aimed at increasing the blood pressure to a somewhat normal state (sympathomimetic drugs may be used) as well as treating the acidosis with bicarbonate (Aaron and Howland 1994; Gossel and Bricker 1994). Dialysis may also be used to remove excess formate (as formic acid) in the blood in order to correct the acidosis (Burkhart et al. 1990; Eells et al. 1981).

2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to formaldehyde may occur by inhalation, ingestion, or dermal contact. There are no known antidotes to formaldehyde poisoning in humans, particularly after oral exposure. General recommendations for reducing absorption of formaldehyde include removing the exposed individual from the contaminated area and removing contaminated clothing, if applicable. If the eyes and skin were exposed, they should be flushed with copious amounts of water. Since formaldehyde is highly corrosive, vomiting after oral ingestion should not be induced. The stomach contents can be diluted with milk or water by mouth if the patient is alert and responsive, otherwise gastric lavage may be indicated. A bolus of charcoal and isotonic saline cathartic may also be useful (Aaron and Howland 1994).

2.10.2 Reducing Body Burden

Formaldehyde is not stored to any appreciable extent in the human body and is mostly metabolized to formate and carbon dioxide (see Section 2.3). The half-life of formaldehyde in monkeys has been observed to be about 1.5 minutes following an intravenous injection. Furthermore, an inhalation exposure study found that no formaldehyde was present in the blood after a 1.9 ppm exposure for

40 minutes, indicating formaldehyde is metabolized very quickly either in the respiratory tract tissues or in the blood.

Despite a relatively fast clearance of formaldehyde from the body, toxic effects may develop in exposed individuals, particularly in cases of acute oral poisonings which quickly overwhelm the body's natural mechanisms to metabolize formaldehyde (particularly via formaldehyde dehydrogenase; see Figure 2-3). There is no standard method or practice to enhance the elimination of the absorbed dose of formaldehyde (Aaron and Howland 1994; Ellenhorn and Barceloux 1988).

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Target organs of formaldehyde toxicity while in the gaseous phase are the respiratory tract and eyes. After oral exposure, the tissues that formaldehyde comes into contact with on its way to the stomach and intestines (i.e., lips, oral pharynx, esophagus) are the target tissues; after dermal exposure, the adverse effects of formaldehyde are usually localized to the contact area, although other systemic reactions have been reported (Maurice et al. 1986) (see Section 2.2). Formaldehyde readily combines with free, unprotonated amino groups to yield hydroxymethyl adduct derivatives resulting in proton liberation (Loomis 1979). In higher concentrations (5–10%), formaldehyde will precipitate protein, which is the reason for its use in current histological techniques. The mechanism that causes the primary irritant effects is not presently known, but may involve one of the two mechanisms mentioned above. Currently, there are no procedures or therapies that specifically focus on interfering with the mechanism of action of formaldehyde. Supportive care by trained medical personnel is highly recommended.

2.11 ADEQUACY OF THE DATABASE

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

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

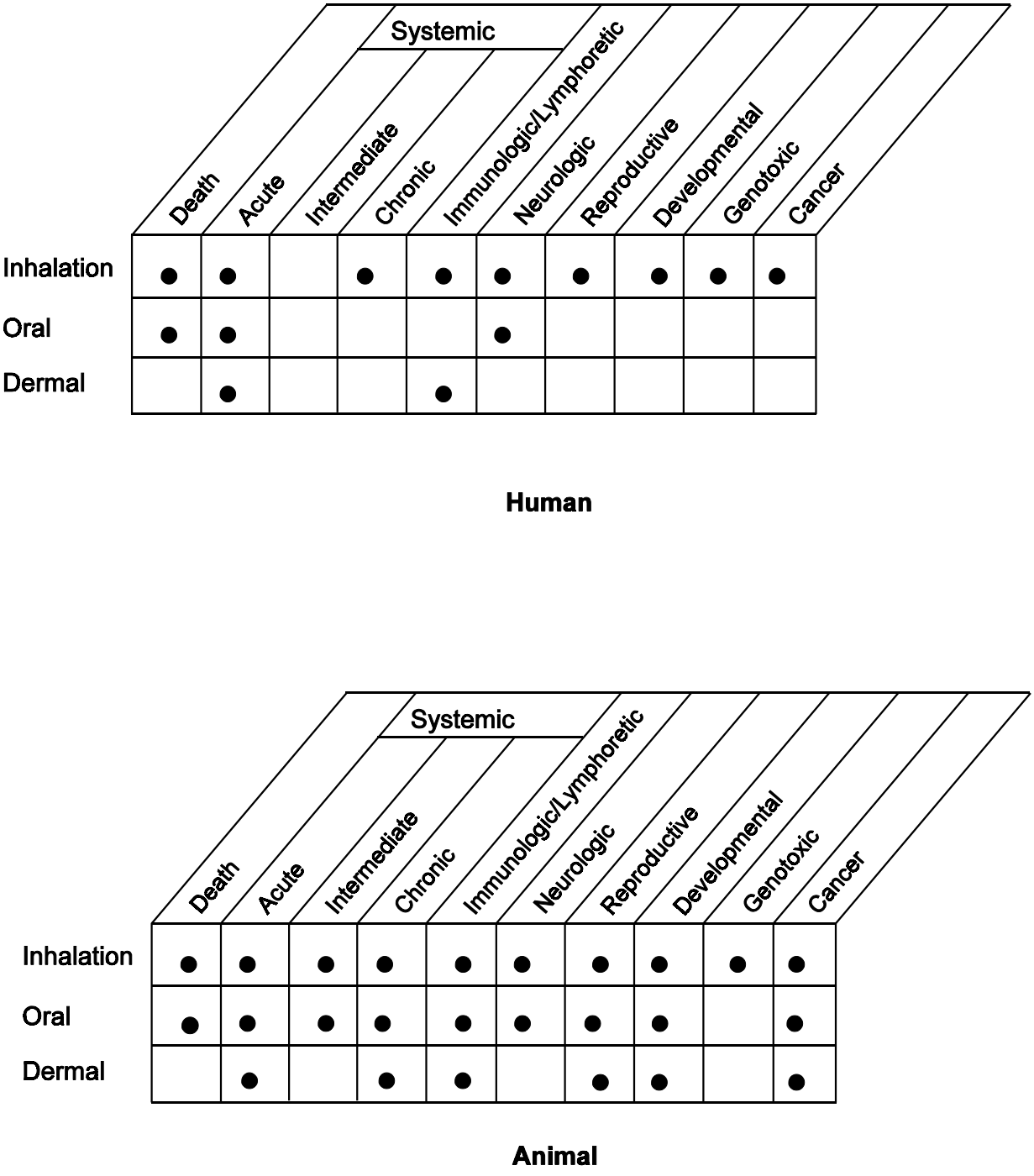
2.11.1 Existing Information on Health Effects of Formaldehyde

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to formaldehyde are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of formaldehyde. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figure 2-5, information is available regarding death, acute and chronic systemic effects, immunological, neurologic, reproductive, developmental, genotoxic, and cancer effects in humans after inhalation exposure to formaldehyde. Lesser amounts of information are available for humans exposed to formaldehyde after oral and dermal exposure. The oral and dermal health effects data are primarily limited to death and acute systemic toxicity data, immunological data (skin sensitization) after dermal exposure, and neurological data after acute oral poisonings.

As also seen in Figure 2-5, significantly more information is available on the inhalation, oral, and dermal effects of formaldehyde in laboratory animals. The information on health effects in animals exposed orally or by inhalation is particularly rich but data regarding dose-response relationships for gastrointestinal effects from acute oral exposure and reproductive effects in multiple generations represent the most notable information gaps (see Section 2.11.2 for further discussion). Information was not located regarding death, systemic effects from intermediate-duration exposure, neurologic effects, and genotoxic effects in animals dermally exposed to formaldehyde.

Figure 2-5. Existing Information of Health Effects of Formaldehyde



2.11.2 Identification of Data Needs

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

Studies of humans under controlled conditions clearly indicate that acute exposures to air concentrations ranging from 0.4 to 3 ppm:

- induce reversible eye, nose, and throat irritation (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle 1993; Kulle et al. 1987; Pazdrak et al. 1993; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986);
- produce changes in nasal lavage fluid contents, indicative of irritation of the nasal epithelium (Gorski et al. 1992; Krakowiak et al. 1998; Pazdrak et al. 1993); and
- do not consistently or markedly affect pulmonary function variables in most individuals (Andersen and Molhave 1983; Day et al. 1984; Gorski et al. 1992; Green et al. 1987; Harving et al. 1986, 1990; Kulle et al. 1987; Nordman et al. 1985; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986).

Acute inhalation animal studies confirm that air concentrations below 10–20 ppm produce damage only in specific regions of the epithelium of the upper respiratory tract in rats, mice, and monkeys and not at distant sites (Bhalla et al. 1991; Cassee and Feron 1994; Chang et al. 1983; Dinsdale et al. 1993; Kamata et al. 1996b; Monticello et al. 1989, 1991; Monteiro-Riviere and Popp 1986; Morgan et al. 1986a, 1986c; Wilmer et al. 1987). An acute inhalation MRL of 0.04 ppm was derived based on the LOAEL of 0.4 ppm for transient symptoms of eye and nose irritation and increased albumin content of nasal lavage fluid in volunteers exposed to formaldehyde for 2 hours (Pazdrak et al. 1993). Confidence is high that this MRL will protect the general public health due to the wealth of data, but confidence may increase with additional information about exposure-response relationships for formaldehyde-induced respiratory effects in potentially susceptible populations of individuals, such as asthmatics.

An acute oral MRL for formaldehyde was not derived because data describing dose-response relationships for gastrointestinal tract irritation in humans or animals after acute oral exposure are lacking. The reports of gastrointestinal effects and symptoms in humans who ingested single large doses (>200 mg/kg) of formaldehyde (Burkhart et al. 1990; Eells et al. 1981; Kochhar et al. 1986), coupled with

data from studies of animals exposed orally for intermediate- and chronic-durations (Til et al. 1988b, 1989; Tobe et al. 1989), indicate that gastrointestinal irritation and damage are the most likely critical effects from acute oral exposure. However, as discussed in Section 2.5, the human data do not identify a no-effect level, and the available animal studies of acute oral exposure (Cassidy et al. 1983; Johannsen et al. 1986) did not examine this end point. At least one comprehensive acute oral toxicity study of at least one animal species exposed to several dosage levels may be needed to generate appropriate data for deriving an acute oral MRL for formaldehyde.

Formaldehyde is a well-known skin irritant and dermal sensitization agent, but systemic distant-site effects from acute dermal exposure are not expected given the reactive nature of formaldehyde, the ability of most cells to rapidly metabolize formaldehyde, and the low rates of formaldehyde absorption through the skin (Jeffcoat et al. 1983). This expectation is additionally supported by the observation that no effects on fetal development were found in pregnant hamsters dermally exposed during pregnancy to a 37% formaldehyde solution (Overman 1985). Exposure-response relationships for dermal effects from acute dermal exposure are well characterized in humans and animals. Experience with various types of formaldehyde solutions in the workplace and results from widespread patch testing in skin clinics indicate that acute dermal exposure to formaldehyde concentrations of 2–5% can evoke a mild to moderate non-allergic skin irritation response in some individuals; concentrations greater than 5% are expected to be irritating to most individuals (Fischer et al. 1995; Maibach 1983). In studies of dermally sensitized individuals, allergic skin reactions to concentrations as low as 0.025–0.05% have been reported (DeGroot et al. 1988; Fischer et al. 1995; Flyvholm et al. 1997). The cases of clothing-induced contact dermatitis that were frequently cited in the literature from the late 1950s until the mid-1970's when newly developed “no-iron’ textiles that released formaldehyde were used (Peters and Heese 1997) further demonstrate the skin irritation potential of formaldehyde. Experiments with guinea pigs given daily non-occluded dermal doses of solutions of formaldehyde indicate that concentrations as low as 0.4% can produce erythema and increased skin thickness within a 10-day period (Wahlberg 1993).

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

Studies of health effects in humans after intermediate-duration inhalation exposure were not located. Studies of humans with predominately chronic inhalation exposure to formaldehyde under occupational

or residential conditions, however, consistently have reported increased incidences of symptoms of upper respiratory tract and/or eye irritation among exposed groups of people (Edling et al. 1988; Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987). Several studies have found nasal epithelial lesions, consistent with the irritant and reactive properties of formaldehyde, in biopsy specimens from workers repeatedly exposed to average concentrations ranging from about 0.2 to 0.5 ppm (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Other studies of similarly exposed groups of workers have either found no, or only small and subtle, exposure-related changes in pulmonary function variables, thus supporting the identification of the upper respiratory tract as the critical target of repeatedly inhaled formaldehyde (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990). Although the persons in these studies are considered to have been exposed for chronic durations, the results, together with the results from the acute controlled inhalation human studies, provide strong evidence that the critical target from intermediate-duration inhalation exposure to formaldehyde will be the upper respiratory tract.

Results from studies of animals exposed by inhalation for intermediate durations provide supporting evidence for the upper respiratory tract as the critical target and describe concentration-response relationships sufficiently well for describing an intermediate-duration inhalation MRL. Data describing intermediate-duration exposure-response relationships for upper respiratory tract lesions and concentrations ranging from 0.2 ppm to as high as 40 ppm are available for rats (Appelman et al. 1988; Casanova et al. 1994; Monticello et al. 1991; Rusch et al. 1983; Woutersen et al. 1987; Zwart et al. 1988), Cynomolgus monkeys (Rusch et al. 1983), hamsters (Rusch et al. 1983), and mice (Maronpot et al. 1986). Comprehensive histological examination of tissues and organs (including the lungs and eyes) in three of these studies (Appelman et al. 1988; Maronpot et al. 1986; Woutersen et al. 1987) and in another study of Rhesus monkeys that included only one exposure concentration (Monticello et al. 1989) found no consistent evidence for lesions outside of the upper respiratory tract. These results confirm the identification of the upper respiratory tract as the target of concern. Other intermediate-duration inhalation exposure studies in rats (Wilmer et al. 1987, 1989) provide evidence that the extent and severity of formaldehyde-induced epithelial lesions in the upper respiratory tract may be more strongly influenced by exposure concentration than duration of exposure.

The intermediate-duration inhalation MRL of 0.03 ppm is based on a NOAEL of 0.98 ppm and a LOAEL of 2.95 ppm for clinical signs of nasopharyngeal irritation and nasal epithelium lesions observed in

Cynomolgus monkeys (Rusch et al. 1983) and an uncertainty factor of 30. Computational fluid dynamic models of airflow and formaldehyde uptake in nasal passages and pharmacokinetic models of tissue disposition of formaldehyde in rats and humans are currently under development (Kimbell et al. 1993, 1997a, 1997b; Subramaniam et al. 1998). The application of these models to the rat intermediate-duration exposure-response data is likely to decrease uncertainty in deriving an intermediate-duration inhalation MRL from animal data. Such models are being developed for Rhesus monkeys (Kepler et al. 1998; Kimbell et al. 1997b), not Cynomolgus monkeys, but the available intermediate-duration data for Rhesus monkeys do not adequately describe concentration-response relationships; therefore a no-effect level cannot presently be estimated. Application of the monkey and human dosimetric models, when they are developed, to data from another Rhesus monkey study that would include multiple exposure levels represents another approach to decreasing uncertainty in the intermediate-duration inhalation MRL.

There is some uncertainty regarding whether or not inhaled formaldehyde can affect the lower respiratory tract by inducing bronchoconstriction or exacerbating asthma in humans, and whether or not repeated exposure may influence these possible, but incompletely understood, effects. As discussed earlier, several acute controlled exposure studies with humans (Andersen and Molhave 1983; Day et al. 1984; Gorski et al. 1992; Green et al. 1987; Harving et al. 1986, 1990; Kulle et al. 1987; Nordman et al. 1985; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986) and studies of chronically exposed persons in workplaces or residences (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990) have found only mild or no changes in pulmonary function variables, except in a few rare cases (see Nordman et al. 1985). However, Amdur (1960) and Swiecichowski et al. (1993) reported that acute inhalation exposure to fairly low levels of formaldehyde (0.3 to 9 ppm) induced bronchoconstriction (i.e., increased pulmonary airway resistance) in guinea pigs. Swiecichowski et al. (1993) further reported that airway reactivity to infused acetylcholine increased after acute exposure to formaldehyde and that when the duration of exposure to formaldehyde was increased from 2 to 8 hours, lower concentrations of formaldehyde were effective in increasing airway reactivity to infused acetylcholine. The mechanism underlying these pulmonary effects is not understood, but Swiecichowski et al. (1993) have hypothesized that formaldehyde may change airway epithelial biochemistry leading to release of mediators of bronchoconstriction. Studies to test this hypothesis were not located. The relevance of the guinea pig findings to the report that a group of children living in homes with 0.06–0.12 ppm formaldehyde showed a greater prevalence of bronchitis and asthma than children living in homes

with less than 0.06 ppm (Krzyzanowski et al. 1990) has been questioned (Swiecichowski et al. 1993), but remains unknown.

Studies of health effects in humans after intermediate-duration oral exposure to formaldehyde were not located. Intermediate-duration oral-exposure toxicity studies in animals that examined a range of tissues and organs are extensive and include a 90-day drinking water rat study that found only weight gain decreases at dosage levels of 100–150 mg/kg/day (Johannsen et al. 1986), a 4-week drinking water rat study that identified a NOAEL of 25 mg/kg/day and a LOAEL of 125 mg/kg/day for forestomach and glandular stomach lesions indicative of irritation (Til et al. 1988b), a 4-week gavage rat study that identified a NOAEL of 40 mg/kg/day and a LOAEL of 80 mg/mg/day for hepatocellular vacuolation and a LOAEL of 20 mg/kg/day for a decrease in IgM and IgG titers and increased relative lymph node weight (Vargova et al. 1993), a 90-day dietary exposure dog study that reported a NOAEL and LOAEL of 75 and 100 mg/kg/day for body weight decreases and no other effects (Johannsen et al. 1986), and a 52-day dietary exposure pregnant dog study that found no evidence of maternal toxicity and no effects on fetal development at doses up to 9.4 mg/kg/day (Hurni and Ohder 1973). In addition, a 32-week drinking water study that focused on the gastrointestinal tract found papillomas in the forestomach and erosions and/or ulcers in the limiting ridge of the fundic mucosa of the glandular stomach in rats exposed to 258 mg/kg/day (Takahashi et al. 1986a).

The findings from the intermediate-duration oral exposure studies by themselves do not consistently identify gastrointestinal tract irritation as the critical effect. However, the weight of evidence from chronic oral administration animal studies (Til et al. 1989; Tobe et al. 1989) and the numerous intermediate inhalation toxicity studies (as previously cited), together with mechanistic understanding of formaldehyde's mode of toxic action, supports the selection of it as the critical effect from intermediate duration. Thus the selection of forestomach and glandular stomach lesions in rats (Til et al. 1988b) as the basis of the intermediate-duration oral MRL of 0.3 mg/kg/day is well-supported. As mentioned in the introduction to Section 2.2.2, there is uncertainty regarding the actual doses that were experienced by animals in the published oral exposure studies because of the lack of reporting regarding how frequently dosing solutions were analyzed for formaldehyde and the well-known instability of aqueous solutions of formaldehyde. Given this uncertainty and the lack of consistency in the findings from the available intermediate-duration oral studies, confidence in the MRL may be improved with additional intermediate-duration dose-response data from another comprehensive dietary or drinking water study of rats that includes frequent monitoring of dosing solutions. Dose-response data for gastrointestinal tract

effects in a primate species may provide an additional means of decreasing uncertainty in the intermediate oral MRL.

Formaldehyde is a well-known skin irritant and skin sensitizer in humans that accounts for about 1–8% of all cases of allergic dermatitis presented at skin clinics (Fischer et al. 1995; Kiec-Swierczynska 1996; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991). Studies of embalmers (Nethercott and Holness 1988) and medical workers (Rudzki et al. 1989) with expected repeated dermal exposure to formaldehyde presented evidence for increased prevalence of formaldehyde-induced skin irritation and dermal allergic reactions. Exposure-response relationships for skin irritation and dermal allergic responses from acute exposure are well characterized (under patch testing conditions) in both normal and sensitized individuals, indicating that 1% solutions are not expected to be irritating to most people, and that allergic dermal reactions in sensitized individuals can occur with concentrations as low as 0.015% (DeGroot et al. 1988; Fischer et al. 1995; Flyvholm et al. 1997; Maibach 1983). No published dose-response data were located for dermal irritation or the development of dermal sensitization in humans for intermediate- or chronic-duration exposure. Given the high reactivity, volatility, and aqueous solubility of formaldehyde and its rapid metabolism by cells, it is likely that dose-response relationships for dermal irritation from acute exposure may not be widely different from relationships for intermediate- and chronic-duration exposures. This hypothesis is supported by the results from inhalation exposure studies in rats indicating that exposure concentration is more important than exposure duration in determining the extent and severity of formaldehyde-induced epithelial lesions in the upper respiratory tract (Wilmer et al. 1987, 1989). Nevertheless, additional animal studies comparing dose-response relationships for skin irritation for acute, intermediate, and chronic exposure durations may be useful in estimating concentrations that will not damage the skin with repeated exposures.

The potency of formaldehyde as a contact allergen is demonstrated by the observation that occluded dermal exposure of guinea pigs to 5% formaldehyde for 3 weeks sensitized 70% of the animals to later dermal challenges with 1% formaldehyde (Hilton et al. 1996). However, published studies that describe dose-response relationship or no-effect levels for the development of dermal sensitization in animals with intermediate- or chronic-duration exposure were not located. Such studies are likely to be useful in estimating concentrations of formaldehyde that would minimize the development of dermal sensitization to formaldehyde in humans.

Chronic-Duration Exposure and Cancer. As with the shorter durations of exposure, the critical targets of chronic inhalation, oral, or dermal exposure to formaldehyde are expected to be portal-of-entry tissues. For the inhalation route, the data are abundant, of good quality, and include both human and animal data. Less health effects data are available for chronic oral and chronic dermal exposure, but the weight of the available data is consistent with this expectation.

Studies of humans chronically exposed to airborne formaldehyde concentrations in the approximate range of 0.1–1 ppm have consistently reported increased incidences of upper respiratory tract and eye irritation (Edling et al. 1988; Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987), evidence for mild histological changes in the nasal epithelium (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c), and either no or only mild changes in pulmonary function variables (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990). Several chronic inhalation studies in rats (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Swenberg et al. 1980; Woutersen et al. 1989) and one study in mice (Kerns et al. 1983b) adequately describe concentration-response relationships for formaldehyde effects on the nasal epithelium and have identified no-effect levels ranging from 0.1 to 2 ppm. No consistent evidence for formaldehyde-induced effects at extra-respiratory sites was found in rats (Kamata et al. 1997; Kerns et al. 1983b) or mice (Kerns et al. 1983b) exposed to concentrations as high as 15 ppm. A chronic inhalation MRL of 0.008 ppm has been derived based on a minimal LOAEL of 0.24 ppm for histological changes in nasal epithelial specimens from a group of workers involved in the production of formaldehyde and formaldehyde resins (Holmstrom et al. 1989c) and an uncertainty factor of 30. Although confidence in this MRL is high due to the wealth of available data, increased confidence may result from additional prospective longitudinal studies of nasal tissue specimens from groups of workers experiencing varying formaldehyde exposure levels to investigate if nasal epithelial damage progresses in incidence or severity with longer duration or higher levels of exposure. Computational fluid dynamics models of airflow and formaldehyde uptake in nasal passages and pharmacokinetic models of tissue disposition of formaldehyde in rats and humans are currently under development (Kimbell et al. 1993, 1997a, 1997b; Subramaniam et al. 1998). Application of these models to chronic rat concentration-response data for nasal lesions represents another research approach to decreasing uncertainty in the chronic inhalation MRL.

No studies were located regarding health effects in humans with chronic oral exposure to formaldehyde. Two chronic drinking water studies with rats (Til et al. 1989; Tobe et al. 1989) provide enough reliable data to identify gastrointestinal tract mucosal damage as the critical target for chronic oral exposure and to describe dose-response relationships and estimates of no-effect levels. Results from the chronic oral studies are supported by results from the intermediate-duration rat studies showing gastrointestinal tract effects and associated no-effect levels (Johannsen et al. 1986; Takahashi et al. 1986a; Til et al. 1988b). The chronic MRL of 0.2 mg/kg/day was based on a NOAEL of 15 mg/kg/day and a LOAEL of 82 mg/kg/day for tissue damage in the forestomach (papillomatous hyperplasia, atrophic gastritis, and ulceration) and glandular stomach (hyperplasia) in male rats (Til et al. 1989) and an uncertainty factor of 100. As with the intermediate-duration data, some uncertainty is associated with the described chronic dose-response relationships due to a lack of reporting of the frequency of analysis of the drinking water for formaldehyde content in the available studies. Results from another intermediate-duration drinking water rat study, rather than a chronic-duration study, that includes frequent monitoring of the drinking water for formaldehyde, may decrease this source of uncertainty in the both the intermediate and chronic oral MRLs, given that the weight of evidence that concentration of formaldehyde at the site of toxic action is likely to be more important in determining cytotoxicity than duration of exposure.

As discussed in the Identification of Data Needs section for intermediate-duration exposure, additional animal studies comparing exposure-response relationships for skin irritation for acute- intermediate- and chronic-exposure durations would be useful in estimating concentrations of formaldehyde solutions that will not damage the skin with repeated exposures. Although no comprehensive toxicity studies in animals were located regarding chronic dermal exposure, understanding of formaldehyde toxicokinetics and mechanism of action suggests that distant-site toxicity is not a concern at environmentally or occupationally relevant dermal exposure levels.

The potential for occupational exposure to formaldehyde to cause cancer in humans has been examined in more than 40 epidemiology studies (cohort mortality and case-control studies). In general, these studies have provided inconsistent evidence for carcinogenicity in humans chronically exposed to low levels of formaldehyde in workplace air. In most studies finding statistically significant associations between occupational formaldehyde and human cancer, the associations have not been strong. The epidemiological studies each have shortcomings, such as limited follow-up, limited exposure information, possible misclassification of disease, presence of confounding risk factors, or small numbers of subjects, that make the establishment of a causal relationship between occupational exposure to

formaldehyde and human cancer difficult. Some of the epidemiological studies have found some scattered evidence for extra-respiratory site cancers in groups of formaldehyde-exposed workers, but the data are not consistent across studies and adjustment for potential confounding factors often has not been possible.

Three meta-analyses of the epidemiologic data are available (Blair et al. 1990a; Collins et al. 1997; Partanen 1993). Each meta-analysis has focused on findings for respiratory cancer deaths based on the premise that the respiratory tract is the most biologically plausible site for cancer from exposure to airborne formaldehyde. Strong support for this premise comes from animal studies showing that chronic inhalation exposure to formaldehyde concentrations between approximately 6 and 15 ppm, but not lower concentrations, induces carcinogenic responses in rats that are restricted to the nasal cavity (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Sellakumar et al. 1985; Swenberg et al. 1980; Woutersen et al. 1989). Similar tumors were found in chronically exposed mice (Kerns et al. 1983b), but were not found in chronically exposed hamsters (Dalbey 1982). The two earlier meta-analyses showed weak overall associations between formaldehyde exposure and nasopharyngeal cancer. Relative risks and associated 95% CIs of 1.2 (0.8–1.7) and 2.0 (1.4–2.9) were reported by Blair et al. (1990a) and Partanen (1993), respectively. The associations were somewhat stronger in studies classified with "substantial" (as opposed to "low/medium") exposure. Relative risks for substantial exposures in the two analyses were 2.1 (1.1–3.5) and 2.7 (1.4–5.6). The meta-analysis by Collins et al. (1997) also showed a weak association across all available studies for relative risks of nasopharyngeal cancer (RR=1.3 [1.2–1.5]), but after adjusting the cohort studies for underreporting of nasopharyngeal cancer (RR=1.0 [0.5–1.8]) and analyzing the case-control studies separately (RR=1.3 [0.9–2.1]), no statistically significant associations were found.

Given that exposure information in case-control studies is generally poor, it seems that additional case-control studies are unlikely to clarify the potential relationship between occupational formaldehyde exposure and human cancer. Future research approaches that may be helpful include establishing prospective cohort mortality studies or updating existing cohort studies focusing on nasal cancer in groups of workers who have experienced high levels of exposure to formaldehyde or who will experience varying levels of formaldehyde exposure and in groups of appropriately matched nonexposed workers. It may be useful to conduct such a prospective study in a country in which occupational exposure levels to formaldehyde are expected to be higher than those in the United States.

Mechanistic studies indicate that the carcinogenic response to inhaled formaldehyde in rats originates in regions of the nasal cavity epithelium that initially show non-neoplastic damage and provide support for the hypothesis that formaldehyde-induced cancer will occur only at exposure levels that extensively damage epithelium tissue (e.g., Monticello et al. 1996). Comparison of the non-neoplastic upper respiratory tract response in rats and monkeys to intermediate-duration formaldehyde exposure has indicated that both monkeys and rats are similarly susceptible to formaldehyde cytotoxicity but display some regional differences in sites of tissue damage within the upper respiratory tract (Casanova et al. 1989, 1991; Heck et al. 1989; Monticello et al. 1989). These observations support the use of data from rodent studies to extrapolatively estimate risks for nasal tissue damage and nasal cancer with human exposure scenarios.

The application of dosimetric models (e.g., CFD models of airflow and uptake in nasal passages and PBPK models of nasal disposition of formaldehyde) currently under development (Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell et al. 1993, 1997a, 1997b; Morgan et al. 1991; Subramaniam et al. 1998) holds promise of reducing uncertainties in estimating human cancer risks from the available rodent data (Morgan 1997). Ongoing efforts (see CIIT 1998; Conolly et al. 1992; Conolly and Andersen 1993) to develop two-stage clonal-growth cancer models (i.e., pharmacodynamic models) incorporating data on formaldehyde-induced cell proliferation rates, numbers of cells at risk, tumor incidence, and site-specific flux of inhaled formaldehyde are also likely to reduce uncertainties in estimating the risks for neoplastic damage to the upper respiratory tract in humans exposed to low levels of airborne formaldehyde.

Results from four drinking water rat studies provide some inconsistent evidence for formaldehyde-induced gastrointestinal tract tumors (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989). As discussed in Section 2.5, the weight of evidence from the rat studies suggests that gastrointestinal tract tumors may occur as late-developing portal-of-entry effects only from repeated exposure to high oral doses that damage the gastric mucosa, and that tumors are not likely to develop at dose levels that do not damage the gastric mucosa. It is unlikely that a human population with high oral exposures to formaldehyde can be identified to study possible relationships to cancer, but better characterization of no-effect levels for gastric mucosal damage in animal species exposed repeatedly to formaldehyde in drinking water may provide additional information to support the hypothesis that low levels of formaldehyde in water samples associated with hazardous waste sites do not present considerable risks for cancer.

No studies were located examining potential relationships between skin cancer in humans and dermal exposure to formaldehyde, but two mouse-skin cancer bioassays found no evidence for increased incidence of skin tumors after 58–60 weeks of twice-weekly exposure to formaldehyde solutions at concentrations of 4% (Iverson 1988) and 10% (Iverson 1986). Additional animal bioassays employing lifetime dermal exposure scenarios would provide more complete assessments of the possible dermal carcinogenicity of formaldehyde.

Genotoxicity. Formaldehyde has been demonstrated to have genotoxic properties in human and laboratory animal studies. Peripheral lymphocytes in anatomy students exposed to 0.73–1.95 ppm formaldehyde for 10 weeks showed a small average increase in SCEs (Yager et al. 1986). Lymphocytes from wood workers chronically exposed to formaldehyde also showed increased levels of chromosomal aberrations; however, there were no significant changes in the rates of SCE (Chebotarev et al. 1986). Other positive findings for genotoxicity include increases in micronuclei formation in wood workers (Ballarin et al. 1992) and an increased incidence in chromosomal abnormalities in pulmonary macrophages in rats (Dallas et al. 1992).

Formaldehyde has been found to be genotoxic in a number of cells and genetic end points. Formaldehyde has been found to induce chromosomal aberrations (Dresp and Bauchinger 1988; Natarajan et al. 1983), increases in micronucleus formation (Ballarin et al. 1992), and SCEs (Yager et al. 1986), as well as numerous other genotoxic end points (Recio et al. 1992; Topham 1980). Formaldehyde has also been found to have genotoxic properties in *S. typhimurium* (Donovan et al. 1983) and in human cell lines (Grafstrom et al. 1985; Snyder and Van Houten 1986). The weight of evidence indicates that formaldehyde is capable of directly reacting with DNA. No reports of genotoxicity strictly related to the oral or dermal exposure routes were found in the available literature. Further cytogenetic analysis of cells from formaldehyde-exposed individuals would possibly provide useful information about the ability and mechanisms by which formaldehyde induces its genotoxic end points.

Reproductive Toxicity. Results from human and animal studies indicate that formaldehyde is not a likely reproductive toxicant at low levels of exposure. No effects on sperm numbers or sperm morphology were found in a group of formaldehyde-exposed pathologists (Ward et al. 1984), and increased rates of miscarriage were not found among persons with presumed residential exposure to formaldehyde (Garry et al. 1980). Studies of reproductive outcomes in groups of formaldehyde-exposed workers may be useful to confirm that the potential for reproductive effects from formaldehyde is low.

Results from such a study will have a better chance of being conclusive if a population is identified that is exposed only to formaldehyde.

Animal studies of inhalation exposure found no direct effects of formaldehyde on reproductive organ histopathology or weight (Appelman et al. 1988; Maronpot et al. 1986; Woutersen et al. 1987) and, with exposure during gestation, no effects on maternal reproductive variables other than decreased body weight gains at high exposure levels (Martin 1990; Saillenfait et al. 1989). Similarly, oral exposure of animals has not been associated with histopathologic or weight changes in reproductive organs (Johannsen et al. 1986; Til et al. 1989; Tobe et al. 1989; Vargova et al. 1993) or with maternal reproductive variables such as numbers of resorptions at non-lethal exposure levels in pregnant animals (Hurni and Ohder 1973; Marks et al. 1980). Changes in sperm morphology were noted in rats given single gavage doses of 200 mg/kg/day, but not 100 mg/kg/day (Cassidy et al. 1983). Overman (1985) reported a small increase in resorption rate in pregnant hamsters dermally exposed to 37% formaldehyde solutions, but attributed this effect to treatment stress rather than to a direct effect of formaldehyde. Assays of reproductive performance in formaldehyde-exposed animals were not located, but may be useful to confirm that formaldehyde is not a reproductive toxicant.

Developmental Toxicity. Results from a human study and several animal studies indicate that formaldehyde is not a likely developmental toxicant at low levels of exposure. No associations were found between incidence of low birth weights and ambient air levels of formaldehyde among groups of mothers living in different residential districts (Grañulevi…iene et al. 1998). No embryolethal or teratogenic effects of formaldehyde were found in gestational-exposure studies of rats exposed to air concentrations up to 40 ppm (Martin 1990; Saillenfait et al. 1989), rats exposed to gavage dose levels up to 185 mg/kg/day (Marks et al. 1980), dogs exposed to dietary doses up to 9.4 mg/kg/day (Hurni and Ohder 1973), and hamsters dermally exposed to 37% formaldehyde solutions (Overman 1985). Formaldehyde was designated as a nonteratogen and nonembryotoxin in the Chernoff/Kavlock developmental toxicity screening test in mice (Seidenberg and Becker 1987). The need for additional developmental toxicity studies may not have a high priority, given the evidence from other repeated-exposure animal toxicity and pharmacokinetic studies indicating that health effects from formaldehyde are likely to be restricted to portals-of-entry.

Immunotoxicity. Dermal sensitization to formaldehyde in humans is well recognized from results of patch testing at dermatological clinics throughout the world (Fischer et al. 1995; Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991) and a few studies of formaldehyde-exposed workers (Nethercott and Holness 1988; Rudzki et al. 1989). Severe allergic responses to dermally applied formaldehyde, however, appear to be rare; only one case of a severe anaphylactic response to formaldehyde was located (Maurice et al. 1986). The potency of formaldehyde as a contact allergen is demonstrated by the observation that occluded dermal exposure of guinea pigs to 5% formaldehyde for 3 weeks sensitized 70% of the animals to later dermal challenges with 1% formaldehyde (Hilton et al. 1996). However, published studies that describe dose-response relationships or no-effect levels for the development of dermal sensitization in animals with intermediate- or chronic-duration dermal exposure were not located. Such studies are likely to be useful in estimating concentrations of formaldehyde that would minimize the development of dermal sensitization to formaldehyde in humans.

Although formaldehyde is widely recognized as a dermal irritant that can sensitize the skin in humans, the evidence for immunologically-mediated sensitization of the respiratory tract from exposure to airborne formaldehyde is weak. There are only a few available case reports of formaldehyde-exposed workers who display marked changes in pulmonary function variables in response to acute challenges with inhaled formaldehyde that are consistent with an immunologically-mediated mechanism of response (Burge et al. 1985; Hendrick et al. 1982; Lemiere et al. 1995). Nordman et al. (1985) reported that, among 230 patients with formaldehyde exposure who reported asthma-like symptoms, only 12 showed marked pulmonary responses to acute formaldehyde challenges. Other studies found no marked response to challenges of inhaled formaldehyde in other groups of previously-exposed subjects who complained of asthma-like symptoms (Day et al. 1984; Krakowiak et al. 1998; Reed and Frigas 1984). Several studies have found no consistent evidence for increased serum levels of formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed subjects including groups with complaints of respiratory symptoms (Dykewicz et al. 1991; Gorski et al. 1992; Grammar et al. 1990; Krakowiak et al. 1998; Kramps et al. 1989; Thrasher et al. 1987, 1990). Elevated serum levels of IgE antibodies and respiratory tract symptoms were found in groups of children exposed to classroom air concentrations of 0.075, 0.069, and 0.043 ppm formaldehyde (Wantke et al. 1996a). However, the relevance of these findings to the possibility of respiratory tract sensitization to formaldehyde is uncertain because the elevated levels of IgE were not correlated with the number and severity of symptoms, and the symptoms were more

indicative of irritant responses than asthma-type responses expected to be mediated through IgE antibodies.

Results from studies with guinea pigs confirm that formaldehyde is a potent skin sensitizer, but does not elicit IgE responses and lymph node cytokine secretion patterns that are typically induced by other potent respiratory tract allergens such as trimellitic anhydride (Hilton et al. 1996). Other animal studies indicate that repeated exposure to formaldehyde at air concentrations between 10 and 15 ppm did not produce significant effects in several assays of immune function including resistance to intravenous or subcutaneous injection of neoplastic cells in mice (Dean et al. 1984), resistance to intravenous injection of bacterial cells in mice (Dean et al. 1984), and IgM response to tetanus immunization and IgG response to tetanus toxoid in rats (Holmstrom et al. 1989b). However, two other studies indicate that exposure to airborne formaldehyde may enhance allergic responses of the respiratory tract to other respiratory allergens (Riedel et al. 1996; Tarkowski and Gorski 1995). Further research is necessary to confirm the hypothesis that exposure to airborne formaldehyde may facilitate immunological responses to other respiratory allergens and to determine if this is relevant to humans exposed to formaldehyde.

Information about immunological and lymphoreticular effects in humans orally exposed to formaldehyde is restricted to a report of splenomegaly in a case of acute poisoning (Koppel et al. 1990). In animal studies, decreased IgM and IgG titers in a hemagluttination assay and increased lymph node weights were found in rats exposed to gavage doses of 20 mg/kg/day and higher, but other measures of IgG and IgM production were not affected by exposure (Vargova et al. 1993). No effects on weights or histopathology of spleen and lymph nodes were found in other studies of orally exposed animals (Til et al. 1988b, 1989; Tobe et al. 1989). The data do not clearly identify immunological effects from oral exposure to formaldehyde as effects of concern. Further research on the possible immunotoxicity of ingested formaldehyde may not be warranted given the likelihood that oral exposures to formaldehyde may be low in most groups of people, due to the instability of formaldehyde in aqueous solutions.

Neurotoxicity. The nervous system does not appear to be a major target organ for formaldehyde toxicity; however, some vague neurological symptoms may occur after inhalation exposure in humans. These may include headaches, "heavy head," fatigue, and increased reaction time (Bach et al. 1990). Kilburn and colleagues have reported evidence for neurological symptoms and impaired performance in neurobehavioral tests in groups of formaldehyde-exposed histology technicians, but confounding exposure to other neurotoxic solvents prevents drawing definitive conclusions regarding the

neurotoxicity of formaldehyde from this source (Kilburn 1985b; Kilburn et al. 1987; Kilburn and Warshaw 1992; Kilburn 1994). Restless behavior (Morgan et al. 1986a), increased levels of 5-hydroxy-indoleacetic acid, 3,4-dihydroxyphenylacetic acid, and dopamine in the hypothalamus (Boja et al. 1985), and evidence for the development of a conditioned avoidance behavior (Wood and Coleman 1995) have been reported in rats. The restless behavior may be attributable to the respiratory irritant effects of the formaldehyde vapor; however, the significance of the increased chemical content in the hypothalamus of rats is unclear. Other studies have found no perceptible effects of formaldehyde on the nervous system of rats and mice at #15 ppm (Appelman et al. 1988; Kerns et al. 1983b), although obvious clinical signs of neurological impairment were observed in mice (Maronpot et al. 1986) and rats (Woutersen et al. 1987) exposed to high concentrations ($20 ppm) of airborne formaldehyde.

Reports of neurotoxicity in humans after an oral exposure to formaldehyde are limited to case reports. Coma, lethargy, seizures, and loss of consciousness have been reported in humans after drinking formaldehyde (Burkhart et al. 1990; Eells et al. 1981; Koppel et al. 1990). No consistent effects on the nervous system after oral exposure to formaldehyde were found in several toxicity reports using laboratory animal models (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989). Increased relative brain weights were observed in one group of rats chronically exposed to drinking water doses of 82–109 mg/kg/day (Til et al. 1989), but not in another group exposed to 300 mg/kg/day (Tobe et al. 1989). The data suggest that the nervous system may be affected by formaldehyde exposure, especially if it is ingested in large quantities or if chronically inhaled in low doses in an occupational setting. Additional prospective evaluations of performance on neurobehavioral tests in groups of formaldehyde-exposed workers may be useful in ascertaining if there are subtle neurological effects from chronic inhalation exposure to formaldehyde. Results from such studies would be most useful if the studied workers were not exposed to other neurotoxic airborne agents; this is a condition which may be difficult to find in occupational settings.

Epidemiological and Human Dosimetry Studies. Results from many acute controlled-exposure human studies and cross-sectional studies of groups of persons repeatedly exposed to airborne formaldehyde provide strong evidence that the upper respiratory tract is the critical target of airborne formaldehyde for any duration of exposure, allow reasonable estimates to be made of minimal risk levels for acute and chronic durations of exposure, and provide strong support for deriving intermediate-duration minimal risk levels from animal exposure-response data. There is considerable confidence that adherence to these values will protect persons living near formaldehyde-contaminated hazardous waste

sites from developing upper respiratory tract health problems. Longitudinal studies that examine nasal specimens from groups of workers with varying air exposure levels will provide information that may further increase confidence in the estimated minimal risk levels.

There does not appear to be a pressing need for epidemiology studies of people exposed orally to formaldehyde given the instability of formaldehyde in environmental sources of water and the implausibility of identifying groups of people exposed to oral doses of formaldehyde that are sufficiently high to damage gastrointestinal tract tissue.

The relatively frequent reporting of dermal sensitization to formaldehyde at dermatological clinics (Fischer et al. 1995; see also: Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991) suggests that cross-sectional and longitudinal studies of dermal exposure levels and prevalence of skin problems in groups of workers with expected dermal exposure to cleaning and disinfectant solutions (e.g., janitorial and/or medical personnel) may be useful to better describe exposure-response relationships for the development of formaldehyde-induced skin irritation and contact dermatitis from intermediate- or chronic-duration exposure to formaldehyde.

Epidemiological studies of occupationally exposed groups of persons have not found consistent or strong evidence for an association between occupational exposure to airborne formaldehyde and cancer, although animal studies have found consistent evidence for formaldehyde-induced nasal tumors with chronic exposure to air concentrations in the range of 6–15 ppm. The available epidemiological studies have shortcomings such as limited exposure information or follow-up, presence of confounding risk factors, or small numbers of subjects, but one plausible explanation for the lack of a consistent response across the studies is that workplace air levels often may be below values necessary for formaldehyde to induce upper respiratory tract cancer. Studies in animals have shown that no increased incidences of nasal tumors were found in rats with lifetime exposure to low (0.3–2 ppm) air concentrations (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989), that damaged regions of the nasal epithelium after short-term exposure are correlated with regions that eventually develop tumors with chronic exposure (Monticello et al. 1996), and that regions of the nasal epithelium with epithelial damage correlate with regions of predicted high airflow and uptake of formaldehyde (Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell et al. 1993, 1997a). Further development is needed of human nasal airflow and formaldehyde uptake models, human pharmacokinetic models for formaldehyde disposition, and human pharmacodynamic models for preneoplastic events in upper respiratory tract tissue.

Application of such models, with associated rat dosimetric models, to the available rat exposure-response data for tumors and preneoplastic events will allow better estimations of air levels presenting minimal risks for cancer in humans.

Biomarkers of Exposure and Effect.

Exposure. Attempts have been made to determine if formaldehyde could be used as a potential biomarker of short-term exposure (Heck et al. 1985); however, no significant difference between pre- and postexposure blood concentrations of formaldehyde could be demonstrated at the concentration tested. In the same study, similar findings were noted in male Fischer 344 rats placed in a nose-only inhalation chamber and exposed to 14.4 ppm formaldehyde for 2 hours. Monitoring blood or urine formate levels has also been considered. Rapid intravenous injection of formaldehyde in monkeys showed a plasma half-life of only 1.5 minutes, with a corresponding increase in blood formate levels; however, formate production is not specific to formaldehyde metabolism (Ferry et al. 1980; Kornbrust and Bus 1983; Liesivuori and Savolainen 1987). Urine formate levels were examined by Einbrodt et al. (1976) and urine formaldehyde and urine formic acid (formate) concentrations were found to be higher immediately after exposure; however, study design posed interpretation concerns. Gottschling et al. (1984) monitored anatomy students exposed to low levels of formaldehyde vapor; wide variations were noted in the urine formate levels prior to exposure, with large intrapersonal and interpersonal variations. Mean postexposure urine formate concentrations were not significantly elevated after exposure. Based on the available data, it appears that the detection of the intact formaldehyde molecule in the blood and tissues, as well as blood and urine formate, are unreliable and poor indicators of formaldehyde exposure in humans and laboratory animals.

Studies of animals have used radiolabeling techniques to measure DNA-protein cross links in nasal epithelium tissue (Casanova-Schmitz et al. 1984a; Casanova and Heck 1987; Casanova et al. 1989a, 1989b, 1991, 1994) and described relationships between exposure levels and the amounts of DNA-protein cross links in regions of the nasal epithelium. Such a technique is impractical for monitoring humans exposed to formaldehyde, but Shaham et al. (1996a) proposed that measurement of total DNA-protein cross links by a different technique in white blood cells may be useful as a biomarker of repeated exposure to formaldehyde. In support of this proposal, it was reported that white blood cells from 12 formaldehyde-exposed anatomists and pathologists had significantly higher average levels of DNA-protein cross links than those from eight subjects without known occupational exposure to formaldehyde

(Shaham et al. 1996a). Additional research to apply these methods to larger groups of occupationally exposed and nonexposed persons may help to determine the reliability of this variable as a biomarker of exposure and to determine the extent to which individuals vary in this response to formaldehyde. Additional research to apply the DNA-protein cross link methods to nasal biopsy specimens may lead to an increased sensitivity of this potential biomarker of exposure and effect. Shaham et al. (1996b) reported that a larger scale study was in progress, but results are not available.

Antibodies (IgG and IgE) against formaldehyde conjugated to human serum albumin have been found to be elevated in some people, but not in others, exposed to formaldehyde (Dykewicz et al. 1991; Grammer et al. 1990; Patterson et al. 1986; Thrasher et al. 1988b, 1989, 1990; Wantke et al. 1996a). The apparently rare frequency of IgE-mediated allergy responses to airborne formaldehyde (Grammer et al. 1990; Kramps et al. 1989; Nordman et al. 1985) suggests that elevation of antibodies against formaldehyde may be too rare to be useful as a generic biomarker of exposure. However, the findings of significant associations between (1) the presence of IgG antibodies against formaldehyde-human serum albumin and smoking habit in a group of healthy subjects, and (2) the presence of such antibodies in non-smokers and occupational exposure to formaldehyde suggest that this biomarker of immunological response may serve as a qualititative biomarker of exposure (Carraro et al. 1997). Additional studies of formaldehyde-specific IgG antibodies in non-smoking groups of formaldehyde-exposed and nonexposed persons may be useful to determine the reliability of this qualitative biomarker of intermediate or chronic exposure to formaldehyde. Additional research may help to further develop the Carraro et al. (1997) assay so that it might be useful for quantifying exposure levels or exposure durations.

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

As discussed in the previous section, DNA-protein cross links and anti-formaldehyde-human serum albumin IgG antibodies are potential biomarkers of effect and exposure from intermediate- or chronic-

duration of exposure. Another potentially useful biomarker of effect for repeated inhalation exposure to formaldehyde involves the histological examination of nasal biopsy samples (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Whereas detection of these biomarkers can represent biological responses to repeated exposure to formaldehyde, it is uncertain to what degree their detection indicates that adverse health effects will occur. Prospective studies of these end points in formaldehyde-exposed and nonexposed workers may decrease this uncertainty and describe temporal relationships between formaldehyde-induced upper respiratory tract tissue damage and/or dysfunction and exposure-related intensity changes in these variables.

Absorption, Distribution, Metabolism, and Excretion. Results from studies of rats exposed for short periods (6 hours) to airborne radiolabeled formaldehyde concentrations between 0.63 and 13.1 ppm indicate that inhaled formaldehyde is rapidly absorbed and metabolized, primarily in the upper respiratory tract, and that, at these exposure concentrations, very little formaldehyde reaches the blood or is transported to distant-site tissues and organs (Heck et al. 1983). In these studies, radioactivity recovered within 70 hours after exposure was found in the expired air (39-42%), the urine (17%), feces (4-5%), and in tissues and the carcass (35-39%). These results are consistent with rapid oxidative metabolism to formate and CO_2 and rapid incorporation of the carbon from formaldehyde into cellular constituents. Consistent with these studies, another experiment showed that 2-hour exposures to formaldehyde of rats (to 14.4 ppm) and humans (to 1.9 ppm) did not significantly increase formaldehyde concentrations in blood when measured immediately after exposure (Heck et al. 1985). Casanova et al. (1988) also showed that blood concentrations of formaldehyde were not elevated, immediately after exposure, in rhesus monkeys exposed to 6 ppm (6 hours/day, 5 days/week) for 4 weeks. These toxicokinetic results, together with the weight of evidence from inhalation toxicological studies of animals showing effects only in the upper respiratory tract, provide high confidence that the disposition of inhaled formaldehyde by the upper respiratory tract in this concentration range and below is nearly complete. Additional animal studies designed to compare formaldehyde-specific metabolic capacities in nasal mucosal tissues from adult and immature animals may be useful in determining a possible mechanistic basis for possible age-related differences in susceptibility to irritation from airborne formaldehyde (see Children's Susceptibility data needs section below).

Ingested formaldehyde is also expected to be rapidly absorbed, rapidly metabolized to formate and CO_2, and rapidly incorporated into cellular consituents, but descriptive toxicokinetic studies of orally administered formaldehyde in animals were not located. Observations of elevated formate levels and

metabolic acidosis in cases of acute formaldehyde poisoning (Eells et al. 1981; Burkhart et al. 1990) are consistent with rapid absorption and metabolism of ingested formaldehyde. A study is available of the dispositional kinetics of radioactivity in rats and mice after ingestion of a cheese made from milk with added radiolabeled formaldehyde (Galli et al. 1983), but the radioactivity in the material fed to the animals was largely (80%) linked to proteins. Given that the levels of formaldehyde in sources of food and water for humans are expected to be very low due to formaldehyde's high reactivity, additional animal studies to more completely describe the absorption, distribution, metabolism, and elimination of orally administered formaldehyde do not seem to warrant a high priority.

Results from a study of rats, guinea pigs, and monkeys under nonoccluded dermal exposure conditions indicated that evaporation from the skin was a major disposition route (Jeffcoat et al. 1983). Additional animal studies of absorption, distribution, and metabolism under occluded conditions of dermal exposure would provide information regarding maximal rates of dermal absorption and local tissue metabolism, and may help to confirm that distant-site effects from dermal exposure are unlikely.

Comparative Toxicokinetics. Experiments with humans, rats, and monkeys indicate that inhaled formaldehyde is absorbed and metabolized so rapidly that blood concentrations do not vary during short-term exposures (Casanova et al. 1988; Heck et al. 1985). These results are consistent with the upper respiratory tract being the critical target of inhaled formaldehyde in each of these species as indicated by the available health effects data. The marked differences between rodents and primates in breathing habits (i.e., rodents are obligate nose breathers) and nasal anatomy led to some early questions about the human relevance of the well-characterized nonneoplastic and neoplastic responses of nasal epithelium in rats to chronic exposure to airborne formaldehyde. However, observations of similar non-neoplastic changes in upper respiratory tract epithelium in Rhesus and Cynomolgus monkeys exposed for intermediate durations (Monticello et al. 1989; Rusch et al. 1983) and observations of histological changes in nasal tissue from occupationally exposed subjects (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c) have provided support for the relevance of the rat data. These results have led to the ongoing development of, for each of these species, anatomical models of nasal airflow and uptake, pharmacokinetic models for nasal tissue metabolism, and pharmacodynamic models of development of tumors and preneoplastic tissue changes to be applied to the rodent data to better estimate air levels that will present minimal risks for upper respiratory tract damage in humans (CIIT 1998; Cohen Hubal et al. 1997; Conolly et al. 1992; Conolly and Andersen 1993; Kepler et al. 1998; Kimbell et al. 1993, 1997a, 1997b; Morgan 1997; Morgan et al. 1991; Subramaniam et al. 1998).

In contrast, mice and hamsters appear to be less susceptible to upper respiratory tract damage from inhaled formaldehyde. The basis for this apparent species difference in susceptibility is unknown, but may involve, at least partially for the case of the mouse, the greater efficiency of mice, compared with rats, to reduce minute volumes during exposure to formaldehyde (Chang et al. 1981, 1983).

As with exposure to airborne formaldehyde, portal-of-entry tissues are expected to be the critical targets of orally or dermally administered formaldehyde in humans and animals. Gastrointestinal effects from high oral doses are expected based on reports of gastrointestinal tract irritation and symptoms in humans who ingested large doses of formaldehyde, together with results from studies of rats exposed orally to formaldehyde for intermediate- and chronic-durations (e.g., Til et al. 1988b, Til et al. 1989; Tobe et al. 1989). Skin irritation in humans with dermal occupational exposure to formaldehyde concentrations in the range of 2-5% and greater is expected based on occupational experience and clinical experience in patch-testing (Fischer et al. 1995; Maibach 1983); additionally, the development of dermal sensitization to formaldehyde is frequently found among patients presenting skin problems at dermatology clinics. The expectation of skin irritation and dermal sensitization, without systemic distant-site effects, from exposure to formaldehyde is supported by results from dermal-exposure toxicity studies in animals (e.g., Overman 1985; Wahlberg 1993) and toxicokinetic studies with rats, guinea pigs and Cynomolgus monkeys (Jeffcoat et al. 1983); although results from the latter studies indicated that monkey skin may be more permeable to formaldehyde than rat skin. In contrast to inhalation exposure, however, there is no information indicating that species differ in susceptibility to formaldehyde toxicity by these routes of exposure. Thus, additional studies comparing species differences in toxicokinetic variables with oral or dermal exposure to formaldehyde do not appear to have a high priority at this time.

Methods of Reducing Toxic Effects. Due to formaldehyde's high water solubility and reactivity and the rapidity of cellular metabolism of formaldehyde to formate and CO_2, toxic effects from formaldehyde are expected to be principally caused by formaldehyde itself (not metabolites) and to be restricted to portal-of-entry tissues, except at high exposure levels that exceed metabolic capacities of these tissues. Thus, following acute exposures to formaldehyde, treatments that dilute or remove non-absorbed or non-reacted formaldehyde from the site of exposure or that present alternative substrates for reaction (e.g., washing of the skin or eyes or dilution of ingested formaldehyde with milk or water) may prevent the occurrence of toxic effects if applied in a timely manner. Methods that may enhance the capacity of portal-of-entry tissues to metabolize formaldehyde may be expected to act against the toxic action of formaldehyde, but no such methods have been established. There are no established treatment

protocols to repair tissue damage that may have been caused by formaldehyde at portals-of-entry or to enhance natural repair mechanisms.

Children's Susceptibility. Suggestive evidence from two studies is available indicating that children may be more susceptible to the locally-acting irritant properties of formaldehyde (Krzyzanowski et al. 1990; Wantke et al. 1996a). Additional health survey studies of groups of children known to experience indoor air concentrations exceeding 0.05–0.1 ppm may be helpful in confirming or discarding this hypothesis.

Studies of laboratory animals, as well as studies of adult humans under acute controlled exposure or occupational exposure conditions, indicate that the irritant effects of formaldehyde are restricted to tissues at portals-of-entry due to the water-solubility and reactivity of formaldehyde and the ability of cells to rapidly metabolize (and detoxify) formaldehyde. Studies designed to compare formaldehyde-specific metabolic capacities and efficiencies in portal-of-entry tissues (e.g., nasal mucosa, gastrointestinal mucosa) from adult and immature animals of varying ages may be useful in determining a possible mechanistic basis for possible age-related differences in susceptibility to formaldehyde.

2.11.3 Ongoing Studies

Ongoing studies pertaining to formaldehyde have been identified and are shown in Table 2-8.

Table 2-8. Ongoing Studies on Formaldehyde

Investigator	Affiliation	Research description	Sponsor
B.K. Andrews, B. Morrell and N.M. Morris	Southern Regional Res Center, New Orleans, LA	Durable Press Fabrics from No- and De-minimus Level-Formaldehyde Finishes	US Dept. of Agriculture
A.E. Blair	NCI, NIH	Studies of Occupational Cancer	Division of Cancer Etiology
T.P. Brown and G.E. Rottinghaus	University of Georgia College of Vet Medicine, Athens, GA	Poultry Toxicosis: Evaluation and Amelioration	US Dept. of Agriculture
A. Cederbaum	VA Medical Center, New York, NY	Interaction of Pyrazole and Glycerol with Human Microsomes and P-450IIEI	National Institute of Alcohol Abuse and Alcoholism
B.J. Collier	Louisiana State University School of Human Ecology, Baton Rouge, LA	Measurement of Formaldehyde Release from Durable Press Cotton Fabrics & Other Products	US Dept. of Agriculture
J.T. Coyle	Massachusetts General Hospital, Boston, MA	Psychosis and Brain Glutamate	National Institute of Mental Health
J. Cwi	Survey Research Associates, Baltimore, MD	Support Services for Occupational Studies	Division of Cancer Etiology
L.M. Ferrari and F. Catell	State Pollution Control Commission, Sydney, NSW	Indoor Air Quality and Energy Conservation	NERDDP
J.B. Guttenplan	NYU Dental Center, New York, NY	Smokeless Tobacco Carcinogenesis and Oral Tissue	National Institute of Dental Research
G. Hager	NCI, NIH	Chromatin Structure and Gene Expression	Division of Cancer Etiology
A.T. Hastie	Thomas Jefferson University, Philadelphia, PA	Pollutant Interactive Effects on Ciliary Defense	NIEHS
G.A. Jamieson	American Red Cross, Rockville, MD	Characterization and Isolation of Platelet ADP Receptors	National Heart, Lung, and Blood Institute
K. Knapp, D. Pahl and F. Black	Atmospheric Research and Assessment Laboratory, Research Triangle Park, NC	Hazardous Air Pollutant Regulatory Activities	Office of Research and Development
J. Merchant	University of Iowa, Iowa City, IA	Core--Occupational Health Research	NIEHS
S.S. Mirvish	University of Nebraska Medical Center, Omaha, NE	Nitrosamine Metabolism and Esophageal Cancer	National Cancer Institute
R. Monson	Harvard University, Boston, MA	Occupational Health	NIEHS

Table 2-8. Ongoing Studies on Formaldehyde (continued)

Investigator	Affiliation	Research description	Sponsor
T.N. Pappas	Dept. of Veterans Affairs Medical Center, Durham, NC	Animals Models of Inflammatory Bowel Disease: Relationship to Substance P Receptor Up Regulation	Dept. of Veterans Affairs
T. Shibamoto	University of California Environmental Toxicology, Davis, CA	Isolation and Identification of Mutagens and Carcinogens in Foods	US Dept. of Agriculture
G.M. Thiele	Omaha VA Medical Center, Omaha, NE	Alcohol and Liver Endothelial Cells in Immune Responses	National Institute on Alcohol Abuse and Alcoholism
J-P. Von Sattel	Massachusetts General Hospital, Boston, MA	Core--Neuropathology	National Institute of Neurological Disorders and Stroke

NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health; NIH = National Institutes of Health; NERDDP = National Energy Research, Development and Demonstration Program