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TOXICOLOGICAL REVIEW OF FORMALDEHYDE - INHALATION ASSESSMENT

(CAS No. 50-00-0)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

VOLUME III of IV

Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response, and References

June 2, 2010

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U.S. Environmental Protection Agency
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5. QUANTITATIVE ASSESSMENT: INHALATION EXPOSURE

This chapter presents the quantitative assessments conducted by EPA for both cancer and noncancer health effects associated with formaldehyde exposure. The quantitative assessment is focused on the inhalation route of exposure. The current IRIS reference dose (RfD) is not reevaluated in this assessment. Formaldehyde's carcinogenicity via the oral route of exposure is not evaluated herein nor is an oral slope factor considered at this time. Therefore, the following sections address derivation of a reference concentration (RfC) and cancer unit risk estimate for inhalation exposures.

For noncancer effects, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Data from the previous chapters are evaluated to determine the health effects associated with formaldehyde exposure and which studies may best inform the exposure response relationship for RfC derivation. Section 5.1 summarizes the observed noncancer health effects, selecting key studies and critical effects for consideration. Candidate RfCs are derived for each identified key study. Several alternatives are considered for uncertainty factors addressing human variability for key studies and alternatives presented (see Section 5.1.2.3). Options for addressing the overall database uncertainty factor are provided which may modify the final RfC (see Section 5.1.3).

The derivation of the cancer inhalation unit risk estimate considered data regarding both respiratory tract cancers and lymphohematopoietic malignancies. Exposure-response modeling from epidemiologic studies was used to derive a combined unit risk estimate for nasopharyngeal cancer and lymphohematopoietic cancers (see Section 5.2). This unit risk estimate is supported by an analysis of exposure-response modeling of respiratory tract cancer risk using data from experimental animal studies (see Section 5.3). Analysis of the animal bioassays includes an evaluation of a published biologically based dose-response model as well as an appraisal of published dose-response modeling of genomics data and a presentation of benchmark dose modeling approaches. Finally, Section 5.4 provides a summary and conclusions from the cancer exposure-response modeling, presenting the final unit risk estimate based on the combined risk of nasopharyngeal cancer and lymphohematopoietic cancers observed in the epidemiology studies.

5.1. INHALATION REFERENCE CONCENTRATION (RFC)

Prior to the current assessment, the EPA IRIS file for formaldehyde did not provide an inhalation RfC. As presented in the hazard identification in Chapter 4, a number of noncancer health effects are associated with formaldehyde exposure. Section 5.1.1 describes each of the health effect categories considered for RfC derivation and the specific endpoints considered for each category. The identified effect categories are: sensory irritation (eye, nose, and throat); upper respiratory tract (URT) pathology; pulmonary function; increased asthma and atopic sensitization; altered immune function; neurotoxicity and reproductive and developmental toxicity. For each health effect category, studies that may adequately inform the exposure-response relationship for specific critical effects are identified for consideration in RfC derivation.

EPA employed a screening process across the different health effect categories to select key studies that would best support the derivation of an inhalation RfC (as described in Section 5.1.2.1). The following factors were considered in this evaluation: characteristics of the study population, exposure regimen, quality of exposure assessment, quality of exposure-response assessment, exposure levels at which effects were seen and statistical power of the study. Based on this analysis, seven studies were considered for RfC derivation. Candidate RfC derivation from a key study includes the following steps: 1) define the critical effect(s); 2) determine appropriate point(s) of departure (PODs) on the basis of inhaled concentration; 3) adjust each POD by endpoint/study-specific uncertainty factors (UFs), to account for uncertainties in the extrapolation of study results to conditions of human environmental exposure. All of the identified key studies were observational epidemiology studies of people and several studies included potentially susceptible individuals (e.g., children, asthmatics). The uncertainty factor for human variability has sometimes been reduced for studies of susceptible populations or lifestages. However, for five of the seven key studies it was unclear if an uncertainty factor of 3 or 1 for human variability was most appropriate. Therefore, alternatives are presented for consideration. Candidate RfCs (cRfCs) are derived for sensory irritation, decreased pulmonary function in children, increased asthma incidence in children, increased allergic sensitization to common allergens in children, and decreased fecundability density ratio (FDR) in women (increased time to pregnancy) (see Table 5-7). All of these cRfCs are derived from endpoints identified in residential studies, with the exception of decreased FDR (observed in an occupational study of women in the woodworking industry).

The overall literature database of both human and laboratory animal studies examining the health effects from formaldehyde exposure is large; however, the available studies for some types of effects are limited. Limitations in the existing database are discussed in Section 5.1.3,

specifically regarding understanding the reproductive and developmental effects and the exposure-response relationship for the observed neurological and behavioral effects from formaldehyde exposure. EPA considers 3 options for addressing these database uncertainties in the final RfC: (1) providing an RfC derived from studies of respiratory and allergenic responses and protective of sensory irritation effects, without further adjustment for uncertainties in the database (noting the need for further research to elucidate reproductive, developmental and neurotoxic effects); (2) providing an RfC with a database uncertainty factor incorporated to reflect the potential that reproductive, developmental, or neurotoxic effects might occur at lower doses; or (3) provide a range for the RfC which encompasses the above two options for the database uncertainty factor.

5.1.1. Candidate Critical Effects by Health Effect Category

The following subsections describe the best available studies and endpoints for quantitative RfC derivation within each health effect category. These studies are considered representative of the health effects attributed to formaldehyde exposure. For more details on specific studies discussed here, see Sections 4.1.1 and 4.2.1. The identified health effect categories are: sensory irritation (eye, nose, and throat); upper respiratory tract (URT) pathology; pulmonary function; increased asthma and allergic sensitization; altered immune function; neurotoxicity and reproductive and developmental toxicity. Discussions in each subsection below describe the various health effects observed in human and animal studies for each category.

For each health effect category, specific studies that may adequately inform the exposure-response relationship for critical effects are identified for consideration in RfC derivation. In general, studies are included where study quality and ability to define exposures are considered adequate for RfC derivation. Whenever possible, greater consideration is typically given to human data from observational epidemiology studies for derivation of an RfC.

5.1.1.1. *Sensory Irritation of the Eyes, Nose, and Throat*

Eye, nose, and throat irritation are common effects of chemically induced sensory irritation; specific effects include lacrimation, burning of the eyes and nose, rhinitis, burning of the throat, and cough (Feron et al., 2001). Chemical irritants such as formaldehyde bind to protein receptors of the trigeminal nerve, triggering a burning and painful sensation. This process is distinct from taste and smell (Cometto-Muniz and Cain, 1992; Nielsen, 1991). The trigeminal nerve has three branches (ophthalmic, maxillary, and mandibular) and not only acts as an afferent nerve relaying these sensations to the central nervous system but has efferent nerve

activity as well (Meggs, 1993). Stimulation of the trigeminal nerve may result in reflex responses, including lacrimation, coughing, and sneezing. In this assessment, both the reflex responses and the sensations (such as burning, pain, and itching of the eyes, nose, and throat) are considered adverse effects (see Section 4.1 for a full discussion of available human data).

There are studies noting irritant effects in rodents (Sarsilmaz et al., 1999; Holmström et al., 1989; Dubreuil et al., 1976) and monkeys (Monticello et al., 1989; Rusch et al., 1983). These animal studies are supportive of the health effects reported in humans. However, given the uncertainties in extrapolation from responses in laboratory animals to expected responses in humans, the available human studies are preferred.

In human studies, the endpoints for assessing irritation include subjective self reporting of symptoms (e.g., pain, burning, itching, increased cough) via questionnaires or objective measures of irritation that can be assessed during controlled acute exposures (e.g., eye-blink counts, lacrimation). Several acute chamber studies support development of a concentration-response relationship for sensory irritation, identifying an effect level for various exposure durations (Kulle, 1993; Andersen and Mølhave, 1983; Bender et al., 1983; Weber-Tschopp et al., 1977). Arts et al. (2006b) reviewed several studies and performed BMD analyses, reporting 10% extra risk BMCL values for reported eye discomfort of 560 and 240 ppb for 3 and 5 hour exposures, respectively. LOAELs of 1,000 ppb and 1,700 ppb were reported for 1−2 minute exposures (Bender et al., 1983; Weber-Tschopp et al., 1977). These acute studies support a role for both concentration and duration in the effect level for eye irritation. Although exposure concentrations are well-defined in these chamber studies, the chamber studies are not appropriate for RfC derivation because they are of acute duration and the exposure levels used are much higher than those reported for chronic exposure scenarios, both occupational and residential.

A study of industrial workers assessed sensory irritation and provided an average exposure derived from in-plant exposure measurements and the work history of each study participant (Holmström and Wilhelmsson, 1988). Although average daily exposures were estimated for each employee, these data were not used to explore an exposure-response relationship within the worker cohort. The symptom prevalence for sensory irritation (e.g., nasal discomfort, eye discomfort, and airway discomfort) relative to the referent group was reported for the cohort as a whole, where worker exposure ranged from 0.05 to 0.5 mg/m^3 formaldehyde 8-hour time-weighted average (TWA), with a mean of 0.26 mg/m^3 (210 ppb). The daily TWA does not reflect the peak exposures experienced during specific work tasks. Although this study demonstrated marked increases in symptoms of sensory irritation in the workplace due to formaldehyde exposure, it provided little data to inform the exposure-response relationship, especially in the range of environmental exposures.

There are three studies that report sensory irritation in humans from chronic exposures in a residential environment and provide sufficient exposure data to support quantitative assessment (Liu et al., 1991; Ritchie and Lehnen, 1987; Hanrahan et al., 1984). Each study reports site-specific exposure measurements and presents some metric of individual exposure. These residential studies employ in-home measurements for each study participant, either as average exposure level (Ritchie and Lehnen, 1987; Hanrahan et al., 1984) or as calculated cumulative exposure based on the time in the home (Liu et al., 1991). Eye irritation is reported at similar levels of residential formaldehyde exposure in the three studies (see Section 5.1.2.2.4). Each study provides an exposure-response relationship for prevalence of sensory irritation in relation to in-home formaldehyde exposure based on individual-level data. The detailed exposure information and chronic nature of the exposures support the selection of these studies as potential principal studies for RfC derivation. Each of these studies is further evaluated and a cRfC developed for consideration (see Section 5.1.2).

5.1.1.2. *Upper Respiratory Tract Pathology*

Formaldehyde-induced respiratory tract pathology includes inflammation, rhinitis, goblet cell hyperplasia, metaplastic changes, squamous cell hyperplasia, and impaired mucociliary transport. A series of laboratory animal studies assessing formaldehyde-induced changes in the nasal mucosa suggests that these changes may be a protective or adaptive response and that increased mucus flow and metaplastic changes will progress in relation to the concentration and duration of exposure to protect the underlying tissue (Swenberg et al., 1983). The degree of inflammation, hyperplasia, and metaplastic change that is due to sensory irritation-induced inflammatory responses versus inflammation and tissue remodeling from formaldehyde-induced direct cell damage cannot be distinguished. These changes have been noted as sensitive indicators of formaldehyde-induced effects, occurring before gross cellular damage and focal lesions (Monticello et al., 1989). These responses are considered for RfC derivation, especially for exposure concentrations where gross damage of the underlying tissue is not expected. Although well-documented studies demonstrating formaldehyde-induced upper respiratory tract (URT) pathology have been performed in laboratory animals, including the rat (Zwart et al., 1988; Woutersen et al., 1987; Morgan et al., 1986a, b, 1983; Swenberg et al., 1986, 1983) and monkey (Rusch et al., 1983), robust human data from epidemiologic studies are available, and these human data are preferred for RfC derivation.

Six epidemiology studies examined the effects of formaldehyde exposure on URT pathology (Pazdrak et al., 1993; Boysen et al., 1990; Holmström et al., 1989; Edling et al., 1988; Holmström and Wilhelmsson, 1988; Andersen and Mølhave, 1983). Of these studies,

Holmström and Wilhelmsson (1988) and Holmström et al. (1989) were identified as the most robust and sensitive and are included as candidate studies for RfC derivation. Both studies address the same cohort and, thus, were considered together. The Holmström and Wilhelmsson (1988) study is discussed above under sensory irritation effects. In this study of 70 factory workers exposed to a TWA formaldehyde concentration of 210 ppb, impaired mucociliary clearance was reported in 20% of the exposed workers and 3% of the 36 nonexposed workers. Using rhinomanometry, Holmström and Wilhelmsson (1988) also found an increase in nasal resistance due to mucosal swelling, though this increase was not statistically significant. In Holmström et al. (1989), nasal biopsy samples were collected from 62 of the 70 formaldehyde-exposed factory workers (these 62 had been exposed to a TWA formaldehyde concentration of 240 ppb) and also from 32 of the nonexposed workers. A pathologist scored each sample by using a scale of 0 (normal respiratory epithelium) to 8 (carcinoma). Biopsy scores for both the exposed and control groups ranged from 0 (normal respiratory epithelium) to 4 (stratified squamous epithelium with marked horny layer). Although the mean biopsy scores for the two groups were similar—2.16 for the formaldehyde-exposed workers and 1.56 for the unexposed workers—the difference was statistically significant and the authors reported that the loss of cilia, goblet cell hyperplasia, and the incidence of cuboidal and squamous cell metaplasia replacing the columnar epithelium were more frequent in the group exposed to formaldehyde. There was no correlation between the duration of exposure and histologic changes or between smoking habits and biopsy scores. The URT effects, taken together (decreased mucous flow, increased inflammation, decreased nasal flow, and degradation of the respiratory epithelium), demonstrate a range of formaldehyde-induced URT pathology consistent with effects observed in controlled animal studies.

5.1.1.3. *Pulmonary Function Effects*

A synthesis of the literature evaluating formaldehyde exposure and pulmonary function is provided in Section 4.4.2. The potential effects of formaldehyde exposure on pulmonary function in humans can be examined on several time-scales of interest. There are reports examining effects from acute exposures among naively exposed anatomy graduate students (Kriebel et al., 1993; 2001), anatomy graduate students with several weeks of episodic exposure (Kriebel et al., 1993), as well as postshift versus preshift differences in pulmonary function in

workers with regular occupational exposure (Malaka and Kodama, 1990; Herbert et al., 1994; Alexandersson et al., 1982; Alexandersson and Hedenstierna, 1989). Depending on whether the exposures are naïve, the epidemiologic studies that assessed the pulmonary effects of acute exposures to formaldehyde may be assessing different biological responses, namely, the acute effect alone or the acute effect(s) in people who may have already been sensitized to formaldehyde effects.

Pulmonary effects of acute formaldehyde exposure have been studied in both healthy volunteers and sensitive populations under controlled conditions (e.g., acute chamber studies). Although acute chamber studies have the advantage of measured controlled exposures, other factors can limit the usefulness of the studies for RfC derivation including: acute duration, small study populations and lack of statistical power to assess the measured parameters. The acute chamber studies are more fully evaluated in Section 4.1.1 and will not be further considered here for RfC derivation.

The observed effects in the previously unexposed anatomy students provide additional information on acute exposures in two naïve populations (Kriebel et al., 1993; 2001), as well as insight into the intermediate stages of possible sensitization (Kriebel et al., 1993). Kriebel and colleagues (1993) examined the prelaboratory and postlaboratory peak expiratory flow (PEF) in students attending anatomy classes once per week. They found the strongest pulmonary response when examining the average cross-laboratory decrement in peak expiratory flow in the first 2 weeks of the study when formaldehyde concentrations collected in the breathing zones had a geometric average concentration of 0.73 ppm. Overall, the students exhibited a 2% decrement in PEF, while the students with any history of asthma showed a 7.3% decrement in PEF. These findings of acute decreases in PEF following students' initial anatomy sessions were corroborated by the Kriebel et al. (2001) study, which used a similar study design applied to another class of anatomy students.

The first Kriebel et al. (1993) study also shows how the acute effects of formaldehyde exposure were altered following several weeks of episodic exposure. By the 5^{th} week of class, the pre- and post-laboratory measurements of PEF were no longer reflecting a clearly demonstrated acute effect but following the 7^{th} week of episodic exposure, both pre-and post-laboratory PEF continued to drop steadily until the class adjourned after 10 weeks time. While the acute effects of formaldehyde exposure appeared to diminish after several weeks of exposure, the intermediate effect across 10 weeks was a 27 liter/minute drop in PEF that was statistically significant ($p<0.01$) after statistical control for random person effects, asthma, an interaction between time and asthma and eye and nose symptoms of irritation. The Kriebel et al. (1993) study is considered of sufficient quality to support an acute RfC but the quantitative

details on the initial acute effects among the naively exposed students are not adequately provided. The findings of the Kriebel et al. (2001) study may have been influenced by decreased class attendance, which dropped from 37 in the first week to 20 in week 6 and to just 10 students by week 10. While the Kriebel et al. (2001) study could be useful as a supportive study for naively exposed students, the longitudinal component is not strong enough to support RfC development.

Several studies of workers assess both cross-shift and chronic effects of formaldehyde exposure (Malaka and Kodama, 1990; Herbert et al., 1994; Alexandersson et al., 1982; Alexandersson and Hedenstierna, 1989). Since formaldehyde exposure may have cumulative effects over chronic exposures, occupational studies generally showed clinically small but statistically significant decrements in pulmonary function across shifts. In general these studies did not identify, have information on or have appropriate statistical control of, potential confounding coexposures. While these occupational studies provide evidence that is clearly and consistently supportive of an acute effect on pulmonary function, they do not directly support RfC development of an acute effect divorced of the concomitant chronic effects.

Several studies allowed for the examination of potential chronic effects of formaldehyde exposure. These included an occupational study (Malaka and Kodama, 1990) that reported preshift pulmonary function as a percentage of expected among the formaldehyde exposed compared to comparable people not exposed to formaldehyde. Studies that did not report preshift pulmonary function as a percentage of expected function (Herbert et al., 1994; Alexandersson et al., 1982) contribute less to an assessment of potential chronic effects because, post hoc, it is difficult to calibrate for cross-study comparison the multiple pulmonary function data without knowledge of the age, gender, smoking status, height, year of birth, etc. that are important determinants of the pulmonary function metrics of concern. The single study (Malaka and Kodama, 1990) that did report functional measures in relation to expected value, found that an average 8-hour time weighted average formaldehyde exposure of 1.13 ppm from area samples was associated with statistically significant decrements in FEV_1, FEV_1/FVC and $FEF_{25–75}$ compared to a referent population. The strongest response was for $FEF_{25–75,}$ which showed a 12% drop in observed function compared to expected function in the unexposed, but it is unclear how to interpret the potential chronic health effect(s) with just the magnitude of the decrement and the length of the average occupational tenure at this plywood facility (6.5 years), which was not reported by exposure status.

One study reported on the longitudinal follow-up of workers exposed to formaldehyde (Alexandersson and Hedenstierna, 1989). This investigation not only examined the acute effects of exposure across shift, but was able to do so among some of the same workers that had been

studied five years earlier (Alexandersson et al., 1982). Statistically significant decreases in FEV_1/FVC and $FEF_{25–75}$ were noted over the intervening five years in nonsmokers after correction for normal aging. The decrease in FEF_{25-75} was 0.212 liters/s (SD = 0.066 liters/s) for each year of exposure and was highly significant ($p < 0.01$). For comparison with the 12% drop in the same pulmonary metric reported by Malaka and Kodama (1990) over an estimated 6.5 years, EPA computed the extrapolated percentage decrease in FEF_{25-75} for the Alexandersson and Hedenstierna (1989) using the reported yearly decrement applied to the preshift values at the time of the initial study period. EPA calculated that from the predicted value of 4.57 liters/s, a decrease of 0.168 liters/s could be estimated for each year of exposure regardless of smoking status. For 6.5 years of exposure, this would result in a 24% drop in FEF_{25-75}. Formaldehyde concentrations were estimated at 0.42 ppm in the first Alexandersson et al. (1982) study and at 0.50 ppm in the second study, but without better exposure measures, the results of the longitudinal follow-up cannot support quantitative RfC development.

Information is lacking in these studies such as length or tenure of employment associated with the preshift pulmonary function or how long the residents had lived in their homes. Likewise, knowledge of how occupational or residential exposure may have changed over time would have allowed for an examination of the progression of any decrement in function associated with long-term episodic exposure. Among these studies, the best designed and executed of the cross-sectional studies was that of Krzyzanowski and colleagues (1990). Municipal employees and their children (613 adults and 298 children) were randomly sampled and were considered to be representative of a diverse local population. Residential exposures to formaldehyde were based on repeated samples from each individual's kitchen, living area and bedroom. The average formaldehyde concentration was 26 ppb, with a maximum sample value of 140 ppb. The majority of subjects (83%) lived in homes with 2-week average concentrations below 40 ppb. Subjects' peak expiratory flow rates (PEFR) were determined 4 times daily in the morning, at noon, in the early evening and before bed for 2 weeks. A statistically significant linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate was reported in children but not adults. All statistical models controlled for socioeconomic status, tobacco smoking (current active or environmental tobacco smoking) and nitrogen dioxide concentrations. In children, formaldehyde concentrations of 60−140 ppb increased the prevalence of physician-diagnosed asthma and bronchitis. Among adults who smoked, there was a statistically significant nonlinear relationship with decreased morning PEFR for formaldehyde concentration > 40 ppb. This well-conducted study had only minor weaknesses such as non-differential measurement error. However, random measurement error tends to attenuate any true effect and is unlikely to have produced a spurious effect. It is

unlikely that these findings were the product of unmeasured or residual confounding as the analyses controlled for smoking as well as nitrogen dioxide levels and there is no evidence of alternative factors that were temporally correlated with formaldehyde concentrations and more strongly associated with decrements in pulmonary function. This study of a large and representative sample from a diverse study population with a well-quantified concentration-response function and is further considered for RfC derivation.

5.1.1.4. *Asthma and Allergic Sensitization (Atopy)*

Sensitization to inhalational chemical exposure may manifest as an allergic or asthmatic response that is characterized by bronchial constriction (BC) or bronchial hyperresponsiveness (BHR). This sensitization may be a result of immune involvement, as in the case of hypersensitivity, or a neurogenic sensitization, where a chemical may directly stimulate inflammation. Asthma is a specific manifestation of IgE-mediated hypersensitivity, characterized by BHR and airway inflammation, resulting in lower airway obstruction (Fireman, 2003; Kuby, 1991).

A variety of hypersensitivity reactions have been reported following exposure to formaldehyde. Rashes and skin reactions have been reported in some individuals after dermal exposures to formaldehyde. Increased expression of Th-2 cytokines in the lymph nodes of mice given dermal applications of formaldehyde indicates the involvement of an immune component to the observed sensitization (Dearman et al., 2005; Hilton et al., 1998; Arts et al., 1997). However, the response does not appear to be IgE mediated (Arts et al., 1997; Lee et al., 1984). Gorski et al. (1992) observed an increase in formaldehyde-mediated neutrophil burst in dermatitis patients exposed in a controlled chamber study and suggests a putative role of oxidative stress and reactive oxygen species (ROS).

5.1.1.4.1. ***Epidemiologic studies.***

A synthesis of the literature evaluating formaldehyde exposure and asthma and allergic sensitization is provided in Section 4.4.3. Inhalation exposure has been associated with increased asthmatic responses in asthmatics in occupational settings. While few available case reports of bronchial asthma suggest direct respiratory tract sensitization to formaldehyde gas (Lemiere et al., 1995; Burge et al., 1985; Hendrick et al., 1982; Hendrick and Lane, 1977, 1975), a greater body of epidemiological data provides evidence of an association between formaldehyde exposure and exacerbation of asthmatic responses in compromised individuals (Kriebel et al., 1993) and particularly in children (Rumchev et al., 2002; Garrett et al., 1999a,b; Krzyzanowski et al., 1990). Asthma incidence in children increased with in-home exposure to

formaldehyde (Rumchev et al., 2002). Similarly, the frequency of respiratory symptoms associated with asthmatic responses and measures of allergic sensitization in children increased with in-home formaldehyde exposure (Garrett et al., 1999 a,b).

The association between formaldehyde and asthma has been studied by examining occupational exposures (Fransman et al., 2003; Malaka and Kodama, 1990), school-related exposures (Zhao et al., 2008; Smedje and Norback, 2001; Norback et al., 2000) and residential exposures (Matsunaga et al., 2008; Tavernier et al., 2006; Gee et al., 2005; Delfino et al., 2003; Rumchev et al., 2002; Garrett et al., 1999 a,b; Palczynski et al., 1999; Norback et al., 1995; Krzyzanowski et al., 1990). The two occupational studies examined the respiratory health of plywood workers (Fransman et al., 2003; Malaka and Kodama, 1990). The most recent of these was conducted in New Zealand by Fransman et al. (2003). Personal samples of formaldehyde exposure were taken. The mean level of exposure was 0.08 mg/m^3 (65 ppb) and the majority of samples were below the limit of detection which was reported to be 0.03 mg/m^3 (24 ppb). Compared with those with low levels of formaldehyde exposure, workers with high levels of exposure were more likely to report having asthma (OR = 4.3 [95% CI: 0.7–27.7]). The association was not seen when examining formaldehyde exposure and use of asthma medication. The second study of plywood workers was completed in Indonesia. Background levels of formaldehyde ranged from 0.003 to 0.07 ppm. The highest concentration of formaldehyde detected in an air sample was in the particleboard unit (range 1.16 to 3.48 ppm). The occurrence of asthma was found to be positively associated with formaldehyde exposure, where asthma was defined as, "Have you ever had an attack of wheezing that made you feel short of breath?", (Malaka and Kodama, 1990).

Studies of exposure to formaldehyde at schools have been performed in China (Zhao et al., 2008) and in Sweden (Smedje and Norback, 2001). In the study from China (Zhao et al., 2008), mean levels of formaldehyde were reported to be 2.3 µg/m^3 (range 1.0–5.0 µg/m^3) indoors and 5.8 µg/m^3 (range 5.0–7.0 µg/m^3) outdoors. Cumulative asthma (i.e., physician-diagnosed asthma since birth) and daytime attacks of breathlessness were found to be associated with outdoor formaldehyde levels. Neither of these outcomes was associated with indoor concentrations of formaldehyde; however, indoor levels were found to be associated with nocturnal attacks of breathlessness. In Sweden (Smedje and Norback, 2001), the levels of formaldehyde measured indoors were higher (arithmetic mean 8 µg/m^3, geometric mean 4 µg/m^3, range <5.0–72 µg/m^3). One difference between the Swedish study and the study conducted in China is that the Swedish study examined the incidence of asthma over a 4-year period and did not report an association between formaldehyde exposure and the incidence of asthma (OR 1.2 [95% CI: 0.8–1.7]) among the whole study population. However, when the

investigators stratified based on history of atopy, they reported that among children without a history of atopy, a new diagnosis of asthma was significantly more likely at higher concentrations of formaldehyde (OR 1.7 per 10 μg/m^3 [95% CI: 1.1–2.6]) and at higher total concentrations of mold (OR = 4.7 per 10-fold increased in total molds [95% CI: 1.2–18.4] in the classroom air. The finding in increase health effects due to formaldehyde and mold exposures did not appear to control for the other exposure and no information on the potential correlation between the two exposures was provided. In order to evaluate the potential for confounding of the reported formaldehyde association by the reported mold association, the magnitude of effects must be compared on an appropriate scale since the magnitude of an odds ratio depends on the magnitude of the change in exposure level that is expected to produce increased risk. After standardizing the units to the reported geometric standard deviation (GSD), the results for formaldehyde is OR[1] = 1.13 per GSD increase in formaldehyde concentration and the results for mold is OR[2]=1.02 per GSD increase in mold exposure (based on a 10-fold increase from the mean mold exposure) or alternatively, OR[3] = 1.06 per GSD increase in mold exposure (based on a 10-fold increase from the minimum mold exposure). As it appears that the magnitude of the formaldehyde effect is stronger than that of the mold effect (following standardization of exposure increment), it can be concluded that the reported formaldehyde effect could not have been due to uncontrolled confounding by mold.

The results of studies measuring residential exposure to formaldehyde and asthma are varied, with some demonstrating an association and others finding no relationship. A recent study (Matsunaga et al., 2008) found no association between 24-hour formaldehyde and prevalence of asthma when pregnant women with an exposure to ≥47 ppb were compared to those with exposure to <18 ppb. However, they reported an increased risk of atopic eczema. This study did not assess the risk of incident asthma. A study utilizing self-reported asthma prevalence as an outcome also found no association with levels of formaldehyde (mean 25.9 μg/m^3, range 2.0–66.8 μg/m^3) (Palczynski et al., 1999), although they noted the incidence of allergic diseases was greatest in the highest formaldehyde exposure group but that the groups were too small for statistical evaluation.

A study performed by Tuthill (1984) measured formaldehyde exposure for children grades K through 6 by using a combination of proxy variables. Overall, there was no association, but some individual variables showed an increased risk. For example, the reported risk ratio for having new construction or remodeling performed in the house in the past 4 months

[1] OR per GSD of formaldehyde = xp[ln(OR per μg/m^3)/10 μg/m^3 * 2.3 μg/^{3}] = exp[ln(1.7)/10*2.3] = 1.13
[2] OR per GSD of mold = xp[ln(OR per 10-fold increase)/ (9*Geo. Mean)*1.6 μg/^{3}] = exp[ln(4.7)/162*1.6] = 1.02
[3] OR per GSD of mold = xp[ln(OR per 10-fold increase)/ (9*Minimum)*1.6 μg/^{3}] = exp[ln(4.7)/45*1.6] = 1.06

was 2.5 (95% CI: 1.7–3.9). The risk ratio for having new or upholstered furniture in the house (within the past 4 months) was 2.2 (95% CI: 1.2–3.9).

The study by Delfino et al. (2003) assessed whether the ambient formaldehyde concentration measured at a central monitoring site was associated with asthma symptoms. The study examined 22 10–15 year olds with at least 1 year of physician-diagnosed asthma and living in a nonsmoking household. The mean levels of formaldehyde were measured to be 7.21 ppb (range 4.27–14.02 ppb). There was a positive association between asthma symptom scores (comparing children who report symptoms interfering with their daily activities versus those with no symptoms or symptoms not great enough to affect their daily activities) and high current levels of formaldehyde (OR 1.90 [95% CI: 1.13–3.19]).

Three studies (Tavernier et al., 2006; Gee et al., 2005; Garrett et al., 1999 a,b) were performed by matching children with and without asthma and comparing the levels of formaldehyde in their homes. Gee et al. (2005) reported median formaldehyde levels of 0.03 ppm in living rooms and 0.04 ppm in bedrooms. Analyses were limited to univariate comparisons of formaldehyde levels for cases of existing asthma and controls without asthma. The concentrations did not differ in a statistically significant manner. The study by Gee et al (2005) was followed up with a more sophisticated analysis of the same children in the same home. Tavernier et al. (2006) reiterated the earlier finding by Gee et al. (2005) that formaldehyde was not found to be associated with existing asthma. Tavernier et al. (2006) did not report the measured levels of formaldehyde but gave the OR for the highest tertile of exposure compared with the lowest tertile of exposure as 0.99 (95% CI: 0.39–2.50).

Garrett et al. (1999 a,b) reported on the risk of allergy and asthma-like respiratory symptoms due to formaldehyde exposure in a cross-sectional survey of households with children with (n = 53) or without (n = 88) doctor-diagnosed asthma. Formaldehyde exposure was characterized by 4 seasonal in-home sampling events across the year for bedrooms and 4-day passive samples collected in living rooms, kitchens and outdoors. Statistically significant linear trends for increased risk of having asthma were seen with increasing formaldehyde levels ($p < 0.02$); however, the ORs for the association did not remain statistically significant after controlling for parental allergy and asthma (exact ORs and 95% CIs not given). Garrett et al (1999 a,b) also evaluated the prevalence and severity of allergic sensitization to 12 common allergens and reported increased prevalence with increasing formaldehyde concentration in the home. The respiratory symptom score was also increased and demonstrated a significant effect for formaldehyde in a multiple regression after adjusting for multiple risk factors and interactions. For the atopy and respiratory symptom endpoints, severity/prevalence was increased in the medium (20–50 $\mu g/m^3$) and high (>50 $\mu g/m^3$) exposure groups relative to the

low (<20 μg/m^3) exposure group, based on the highest of four seasonal 4-day formaldehyde measurements in the home. The associations between formaldehyde concentrations and severity of allergic sensitization are clearly shown and further substantiated with multivariate regression controlling for potential confounders which showed that the unadjusted effect estimate was not confounded. In logistic regressions, both the prevalence and severity of allergic sensitization to 12 common allergens increased with increasing formaldehyde concentration in the home. The crude association for atopy with an increase in formaldehyde concentration per 10 μg/m^3 was OR = 1.34 which increased only slightly when adjusted for parental asthma and gender to and odds ratio of 1.42 per 10 μg/m^3 (95% CI: 0.99–2.04). Passive smoking, the presence of pets, indoor nitrogen dioxide concentrations, airborne fungal spores and house-dust-mite allergens did not influence the effect estimates and were unlikely to be confounders. Additionally, a calculated respiratory symptom score was increased and demonstrated a significant relationship to increased formaldehyde concentration in a multiple linear regression after adjusting for multiple risk factors and interactions. For each of these endpoints, severity/prevalence was increased in the medium (20–50 μg/m^3) and high (>50 μg/m^3) exposure groups relative to the low (<20 μg/m^3) exposure group, based on the highest of four seasonal 4-day formaldehyde measurements in the home.

Residential formaldehyde exposure was associated with an increased risk of asthma in a population-based case-control study of 192 children aged 6 months to 3 years (Rumchev et al., 2002). The study, which comprises 88 cases of children discharged from the emergency department of a children's hospital in Perth, Australia, with a primary diagnosis of asthma and 104 controls, provides a positive exposure-response relationship. Seasonal in-home formaldehyde measurements taken in the living room and subject's bedroom were used to assess exposure (8-hour passive sampler). The odds ratios (ORs) for risk of asthma by formaldehyde exposure level category were adjusted for numerous risk factors both familial and environmental including, familial history of asthma, age, sex, smoking, presence of pets, and attributes of the home. Of these, age, allergic sensitization to common allergens, and family history of allergy were independent risk factors for asthma (ORs of 1.09, 2.57, and 2.66, respectively). Categorical analysis of the data indicates the ORs for asthma were increased in the two highest formaldehyde exposure groups, reaching statistical significance for household exposures >60 μg/m^3 (48 ppb) (OR of 1.39). Analysis of the data with formaldehyde as a continuous variable indicated there was a statistically significant increase in the risk of asthma (3 % increase in risk per every 10 ug/m3 increase in formaldehyde level. All analyses controlled for other indoor air pollutants, allergen levels, relative humidity, and indoor temperature as well as other risk factors.

A study of 202 households (mean formaldehyde level of 26 ppb) found that among children aged 6–15 years old and exposed to environmental tobacco smoke, the prevalence of asthma was 45.5% for those with measured levels of formaldehyde in the kitchen >60 ppb. The prevalence of asthma dropped to 15.1% for levels ≤40 ppb and 0% for 41–60 ppb. No trend in asthma prevalence was seen for children who were not exposed to environmental tobacco smoke (Krzyzanowski et al., 1990).

Finally, a study by Norback et al. (1995) reported mean levels of formaldehyde were 29 μg/m^3 (range <5–110 μg/m^3) in the bedrooms of individuals experiencing nocturnal breathlessness compared with formaldehyde levels of 17 μg/m^3 (<5–60 μg/m^3) among those without nocturnal breathlessness. The OR for this association was 12.5 (95% CI: 2.0–77.9) and the effect was substantially stronger in magnitude than the associations observed for toluene, terpenes and volatile organic compounds which makes confounding by those coexposures unlikely.

5.1.1.4.2. ***Supporting animal studies.***

Several animal studies report increased airway resistance and BC due to inhalation exposures to formaldehyde (Nielsen et al., 1999; Swiecichowski et al., 1993; Biagini et al., 1989; Amdur, 1960). Changes in pulmonary resistance were observed as early as 10 minutes after exposure (Biagini et al., 1989), and reported effect levels ranged from 0.3–13 ppm. Other pulmonary effects were reported in conjunction with BHR, such as increased tracheal reactivity and decreased pulmonary elasticity (Swiecichowski et al., 1993; Amdur, 1960). Although BHR is a common result of Type I hypersensitivity reaction to an allergen, the observation of BHR alone is not sufficient to demonstrate that an agent induces Type 1 hypersensitivity.

BHR may be directly induced both pharmacologically and neurogenically (Joos, 2003; Cain, 2001; Meggs, 1995). There is little evidence that formaldehyde itself is an allergen recognized by the immune system, especially via inhalation (Lee et al., 1984). Although formaldehyde exposure has been reported to alter cytokine levels and immunoglobulins in some experimental systems, these immunomodulatory effects do not support a type 1 hypersensitivity. IgE was unchanged (Fujimaki et al., 2004a; Lee et al., 1984), and cytokine profiles were not consistent with the Th-2 cytokines expected in IgE mediated hypersensitivity (Fujimaki et al., 2004a; Ohtsuka et al., 2003).

Formaldehyde-induced dermal sensitization show parallel results. The physical signs of irritation and sensitization are consistently shown (e.g., rashes, edema). Some involvement of the immune response has been demonstrated with positive LLNA assays, indicating proliferation of lymphocytes in lymph nodes draining the affected area (Hilton et al., 1998; Arts et al., 1997).

Increased expression of Th-2 cytokines in the lymph nodes of mice given dermal applications of formaldehyde does indicate an immune component to the observed sensitization. However, the response does not seem to be mediated by IgE (Arts et al., 1997; Lee et al., 1984).

Ito et al. (1996) reported that a tachykinin NK_1 receptor, but not the histamine H_1 or bradykinin B_2 receptors, is involved in formaldehyde-induced vascular permeability. Neuropeptides NGF and substance P were affected in BAL and stimulated splenocytes from formaldehyde-exposed mice, with greater effects seen in OVA-immunized mice. Tachykinins (e.g., substance P and neurokinin A) are produced by nerve cells and can directly stimulate bronchoconstriction (Van Schoor et al., 2000). Substance P is also a mediator of neurogenic inflammation. Therefore, although formaldehyde may induce some of the symptoms of type 1 hypersensitivity, these symptoms are more likely neurogenic than immunogenic in origin.

In contrast, formaldehyde enhances immunogenic hypersensitivity of known allergens (Sadakane et al., 2002; Riedel et al., 1996; Tarkowski and Gorski, 1995). This potentiation varied based on sensitization protocols (respiratory tract versus systemic, frequency and timing of immunization, allergen, etc.) and formaldehyde exposure regimens (concentration, continuous versus intermittent exposures). Taken as a whole, the results support the finding that formaldehyde exposure can aggravate a type 1 hypersensitivity response (see Table 4-53).

The mechanism underlying this response has not been elucidated. Formaldehyde-induced IgE production has been reported in some studies (Vandenplas et al., 2004; Wantke et al., 1996a). Other studies suggest that this effect does not appear to be immunogenic in nature (Fujimaki et al., 2004a; Lee et al., 1984). Although formaldehyde exposure has been reported to alter cytokine levels and immunoglobulins in some experimental systems (Fujimaki et al., 2004a; Ohtsuka et al., 2003), these immunomodulatory effects do not support immunogenically mediated type 1 hypersensitivity.

These decrements may be mediated via neurogenic potentiation (Sadakane et al., 2002; Riedel et al., 1996; Tarkowski and Gorski, 1995). Tarkowski and Gorski (1995) suggest that formaldehyde may increase permeability of respiratory epithelium and destruction of immunologic barriers. Tachykinin NK1 receptor and various neuropeptides (NGF and substance P) have been implicated in formaldehyde-induced sensitization and lend weight of evidence to a neurogenic MOA (Van Schoor et al., 2000; Ito et al. 1996).

5.1.1.5. *Immune Function*

Although there are some indications of formaldehyde-induced immunomodulation in laboratory animal studies (Jakab, 1992; Morgan et al., 1986a, b, c; Leach et al., 1983) and reports of increased upper respiratory tract infections in formaldehyde-exposed workers

(Lyapina et al., 2004; Krzyzanowski et al., 1990; Holness and Nethercott, 1989), the overall database for toxic effects on immune function and competence is very limited. A study of workers using carbamide-formaldehyde glue indicates decreased neutrophil respiratory burst activity (NRBA) (Lyapina et al., 2004). NRBA was reduced in workers with URT inflammation and long-lasting respiratory tract infections, compared with healthy controls, and in formaldehyde-exposed workers with slight or no respiratory infections. The authors hypothesized that the decreased NRBA in symptomatic workers may be an indication of formaldehyde effects in a susceptible population. Since the workers have increased respiratory tract infections as compared with controls, a formaldehyde-specific effect cannot be excluded. These indications of a functional deficit of the immune system are considered adverse and appropriate for consideration as a critical effect. Although this was a small study (n = 29), the exposed workers had increased chronic URT infections and decreased resistance to infections compared with a control population. Additionally, duration of employment was negatively correlated with both erythrocyte count and hematocrit. Measured formaldehyde concentrations for a work shift were 870 ± 390 μg/m^3 (722 ± 324 ppb). This average work-shift concentration is considered to be the LOAEL for increased respiratory tract inflammation and decreased resistance to infections in a worker population.

5.1.1.6. *Neurological and Behavioral Toxicity*

Studies evaluating the effects of formaldehyde on nervous system structure or function are described in detail in Sections 4.1.1.6 and 4.2.6 and summarized in Section 4.4.8 and Table 4-58. Taken together, the animal and human data support the conclusion that formaldehyde exposure results in neurological and behavioral toxicity. Observed health effects include impaired memory and learning, developmental effects seen as both structural changes in the brain and behavioral changes, and a potential for increased mortality from amyotrophic lateral sclerosis (ALS). Although studies appropriate for RfC derivation do not exist for each potential neurological and behavioral health effect, several studies are available that provide information that needs to be considered when selecting the formaldehyde RfC.

Seven of the available neurotoxicity studies were considered as candidates for RfC development (listed in Table 5-1). All seven studies provided reliable documentation of

Table 5-1. Candidate points of departure (PODs) including duration adjustments for nervous system toxicity in key human and animal studies

Reference	Species	POD[a]		Exposure scenario			POD duration adjustments[b]							Ratio[c]	Effect
		Type	ppb	Hours/day	Days/week	Duration	POD	×	Hours/day	×	Days/week	=	ppb		
Developmental neuropathology effects															
Sarsilmaz et al. (2007)	Rat	LOAEL	6,000	6	5	30 days	6,000	×	6/24	×	5/7	=	1,070	5.6	Volume and cell number change in brain regions following neonatal exposure
Aslan et al. (2006)	Rat	LOAEL	6,000	6	5	30 days	6,000	×	6/24	×	5/7	=	1,070	5.6	Volume and cell number change in brain regions following neonatal exposure
Human neurobehavioral outcomes															
Bach et al. (1990)[d]	Human	NOAEL	170	5.5	1	1 day	170[d]	×		×		=	170	1	Changes in short-term memory and ability to concentrate. Single 5.5-hour exposure
Psychomotor effects															
Senichenkova (1991)	Rat	LOAEL	400	4	7	GD 1–19	400	×	4/24	×	7/7	=	67	6	Changes in open field motor activity (exploratory activity and habituation in offspring following in utero exposure

Table 5-1. Points of departure (POD) for nervous system toxicity in key human and animal studies (continued)

Reference	Species	POD[a]		Exposure scenario			POD duration adjustments[b]							Ratio[c]	Effect
		Type	ppb	Hours/day	Days/week	Duration	POD	×	Hours/day	×	Days/week	=	ppb		
Cognitive effects															
Malek et al. (2003c)	Rat	LOAEL	130[e]	2	1	1 day	130	×	2/4[e]	×		=	65	2	Concentration-dependent decreases in activity by a variety of measures following a single exposure
Pitten et al. (2000)[f]	Rat	LOAEL	2,600	0.17	7	90 days	2,600[f]		--		--		--	--	Impaired memory in a spatial maze. Magnitude of effect increased with continued exposure through 12 weeks
Malek et al. (2003a)	Rat	LOAEL	100[e]	2	7	10 days	100	×	2/4[e]	×	7/7	=	50	2	Impaired learning in a water maze. Short-term (10 day) exposure with testing conducted 2 hours following daily exposure.

[a]1 mg/m^3 = 0.813 ppm. All identified PODs were based on statistically significant findings at the study LOAELs. Full study details are provided in Section 4.1.1.6 (Bach et al., 1990) or 4.2.1.6 and Table 4-57 (all other studies).
[b]Both actual levels of experimental exposures, and duration adjusted PODs are shown.
[c]POD unadjusted dose/duration-adjusted dose.
[d]Testing was conducted during or following exposure, duration was not adjusted.
[e]Testing was conducted 2 hours postexposure; duration was adjusted to 4 hours to include the entire period between start of exposure and testing.
[f]Due to the uncertainty in continuous exposure adjustments and the unusually short (10 minutes) exposure in this study, no adjustment to continuous exposure is presented.exposure, study design, and evaluation

procedures, and all demonstrated robust findings of changes in nervous system structure or function following formaldehyde exposure. All but one of the candidate studies present information at multiple exposure levels to provide an understanding of the exposure response relationship. One selected study (Senichenkova, 1991) provided less robust information, with evaluation at only a single exposure level, but was considered useful as supporting the findings of two other studies (Sarsilmaz et al., 2007; Aslan et al., 2006) regarding neurological sequelae of developmental exposure. All of the selected studies using experimental animals were conducted in rats, although several studies in mice demonstrated dose-related neurotoxic effects following formaldehyde exposure. These studies in mice were not considered for RfC development because of the possibility that results might be confounded by reflex bradypnea at the doses tested in each study; selected behavioral studies in rats were not similarly confounded by reflex bradypnea because the effect occurs in rats only at doses above those at which the effects of concern were seen (see Section 4.2.6 for details).

In order to improve transparency and facilitate comparison of health effect levels across study types and health effects, Table 5-1 summarizes the PODs and exposure scenarios for each selected study and describes the effects on which the selected POD is based. Dose conversions used to adjust from actual experimental exposure concentrations to continuous exposure concentrations are detailed. It should be noted that available studies providing dose-response information regarding the effects of formaldehyde exposure on the nervous system were all of short duration, and thus information regarding the relationship between formaldehyde toxicity and exposure duration (i.e., whether toxicity increases with longer exposures at a given exposure level, or is more related to the maximum exposure concentration) is limited. However, the rodent study by Pitten et al. (2000) and the epidemiology study by Weisskopf et al. (2009) provide strong support for an association between increasing neurotoxicity and increasing duration of exposure.

Although chronic human studies are preferred for RfC derivation, no adequate human study of chronic duration is available (see Section 4.1.1.6 for detailed discussion of available human studies). The available human studies were sufficiently strong to raise concern regarding formaldehyde effects on the nervous system; however, most did not provide sufficient exposure information to permit derivation of a POD for use in quantitative dose-response assessment. Available epidemiologic studies (most notably Weisskopf et al. [2009] and Kilburn et al. [1987, 1985]) provided limited exposure information. Weisskopf et al. (2009) reported a non-statistically significant increase in the rate ratio for ALS for ever being exposed to formaldehyde with RR=1.34 (95% CI: 0.93-1.92) among 987,229 people followed by an American Cancer Society study, but no information regarding exposure concentrations was available. However,

when the cohort was restricted to people without missing data on duration of exposure to formaldehyde, a statistically significant association was demonstrated as RR=2.47 (95% CI: 1.59-3.86, p<0.0001). Weisskopf et al. (2009) also demonstrated statistically significant increased exposure-response for risk of mortality from ALS associated with increased duration of formaldehyde exposure (p = 0.0004). Interpretation of the findings of Kilburn et al. (1987, 1985) is complicated by concomitant exposure of many subjects to other solvents. Although the chamber study by Lang et al. (2008) included a concentration-response assessment of changes in reaction time, as previously discussed, the effects detected were difficult to interpret and the study was not considered useful for RfC derivation.

One acute human study, Bach et al. (1990), which evaluated changes in cognitive function following a single formaldehyde exposure, was considered for evaluation of a cRfC as the chamber exposures were well defined and effects at multiple levels of exposure were reported. In that study, concentration-related changes in short-term memory and ability to concentrate were seen during a single 5.5-hour exposure at a range of levels (32, 170, 390, and 890 ppb). The study was designed as a comparison of effects of short-term formaldehyde exposure in previously occupationally exposed individuals with effects in controls without previous occupational exposure. Because occupational exposure levels were not assessed, exposure measurements from the previously exposed workers are not appropriate for use in RfC derivation. The authors reported a statistically significant exposure-response relationship for three related cognitive measures (number of additions completed, number of errors, and reaction time) in the 'addition test' assessment indicating a deficit in performance. Complete data were not presented, but graphical presentations in the article indicated that the effect was seen at all doses tested, with an apparent NOAEL of 170 ppb (see Figure 5-1).

No BMD modeling could be performed on these data because the graphical representation could not be accurately digitized. The statistical analysis indicated no interaction between formaldehyde effect and previous occupational exposure (i.e., the magnitude and direction of the effect were similar in previously exposed and previously unexposed subjects) and separate data were not presented for the two groups; thus, the LOAEL represents effects in the combined study groups. Overall, the published paper lacks detail and it is difficult to evaluate some aspects of the reported findings, in particular where magnitude and direction of effect are not provided. Finally, the authors noted that controls and the high-exposure group were not well matched on two key parameters (age and education level), adding uncertainty to the reported exposure-response relationship (at the high dose). Although this study was considered valuable in documenting neurological effects in humans following exposure to relatively low concentrations of formaldehyde, the above concerns limit its utility for

quantitative human health risk assessment. Therefore, this study is not considered of sufficient quality for RfC derivation.

In the absence of adequate human data, controlled studies in laboratory animals are considered (see Section 4.2.1.6 for detailed discussion of available animal studies). There are no

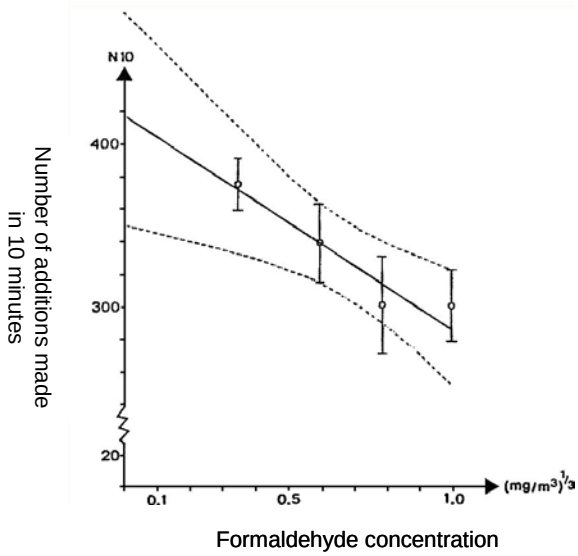


Figure 5-1. Change in number of additions made in 10 minutes following formaldehyde exposure at 0.04, 0.21, 0.48, or 1.1 mg/m^3 (32, 170, 390, or 890 ppb).

Note: Vertical bars are the standard errors of the means, dashed line shows the 95% CI.

Source: Bach et al. (1990).

chronic studies and only one subchronic animal study evaluating neurological and behavioral effects of formaldehyde exposure. Pitten et al. (2000) demonstrated impaired retention of a previously learned task in rats exposed at concentrations of 2,600 or 4,600 ppb, 10 minutes per day, 7 days/week, for 90 days (statistically significant, $p<0.05$). In this study, the magnitude of the impairment increased over time, even though testing was performed 22 hours after exposure, indicating that repeated formaldehyde exposure led to a worsening of effect. The study design, test methods, and reporting of the results are all of adequate quality for both hazard assessment and quantitative risk assessment. However, the short duration (10 minutes) of the repeated daily exposures is a severe limitation to establishing a chronic RfC based on this study, due to uncertainties in extrapolating from 10 minutes to a 24-hour exposure (see Table 5-1). Because

this study as designed indicates an accumulation of effect with repeated exposure, it is useful in documenting the existence of a duration component to the exposure-response relationship. It follows that concentration alone, without an adjustment for duration of exposure, would be inadequate as an exposure metric; however inadequate information is available to inform the appropriate magnitude of the duration effect. Therefore, although Pitten et al. (2000) is a well-conducted study, the data are of limited utility for RfC derivation.

Finally, there are several well-documented acute and subacute animal studies that provide exposure-response information for neurological and behavioral endpoints relevant for RfC derivation. Several laboratory animal studies that evaluate neurological effects following in utero or neonatal exposure address potentially susceptible life stages. Sarsilmaz et al. (2007) and Aslan et al. (2006) observed changes in brain structure (cell number and/or volume changes in specific brain regions) following 30 days of exposure to neonatal rats ($p<0.001$). A related finding by Senichenkova (1991) demonstrated changes in behavior (open field motor activity, including habituation) in young rats following in utero exposure ($p<0.05$). Effects of concern were seen at all doses in these studies, resulting in PODs of 67 ppb following in utero exposure and 1,070 ppb following early postnatal exposure, based on LOAEL values adjusted for continuous exposure (see Table 5-1). These studies support the possibility of neurodevelopmental effects attributable to in utero or early postnatal formaldehyde exposure, at levels similar to or below those causing other types of effects.

The other three studies in Table 5-1 evaluate behavioral changes in rats following exposure to formaldehyde. Malek et al. (2003c) found concentration-related changes in motor activity following a single 2-hour exposure at concentrations from 130–5,180 ppb (with testing 2 hours following cessation of exposure; $p<0.005$)). In a second study, Malek et al. (2003a) found concentrated-related changes in performance on a learning task at similar exposure levels (100–5,400 ppb) when 2-hour exposures were repeated for 10 consecutive days ($p<0.05$); performance was evaluated 2 hours after cessation of exposure, and concentration-related learning deficits were seen at all exposure levels (see Table 5-2 and Figure 5-2).

Although other studies evaluating neurobehavioral effects were available in the formaldehyde database (see Chapter 4), these studies by Malek et al. (2003a, c) were considered to be the most robust, documenting effects at relatively low exposure levels. Both studies also included evaluation at multiple concentrations and showed concentration-related increases in effect. In the Malek et al. (2003a) study with repeated exposures, it is unclear whether or not the measured effect primarily reflects the most recent exposure or cumulative exposure; therefore, the adjustment for continuous exposure was made over the final exposure period and the two hours following exposure (4 hours total), as was done for the single-exposure study (Malek

Table 5-2. Effects of formaldehyde exposure on completion of the labyrinth test by male and female LEW.1K rats

	Swimming time (sec)			Error rate (mean)		
Male rats	**Day 1**	**Day 6**	**Day 10**	**Day 1**	**Day 6**	**Day 10**
Control	105	12.2	6.33	7.4	0.5	0.0
0.1 ppm[a]	100	12.9	6.07	7.7	5.0[c]	3.2[c]
0.5 ppm	97	16.7[c]	7.60[b]	7.6	4.4[c]	1.8[c]
5.4 ppm	105	25.7[c]	10.9[c]	7.7	5.0[c]	2.8[c]
	Swimming time (sec)			**Error rate (mean)**		
Female rats	**Day 1**	**Day 6**	**Day 10**	**Day 1**	**Day 6**	**Day 10**
Control	103	12.5	6.47	7.9	0	0.0
0.1 ppm	96	12.3	7.53	7.1	5.2[c]	3.0[c]
0.5 ppm	97	14.6[c]	7.60[b]	8.0	4.6[c]	2.2[c]
5.4 ppm	98	23.5[c]	9.73[c]	7.9	5.2[c]	2.6[c]

[a]Rats were exposed to formaldehyde for 2 hours/day, for 10 consecutive days.
[b]Different from control, $p < 0.05$.
[c]Different from control, $p < 0.005$.

Source: Malek et al. (2003a).

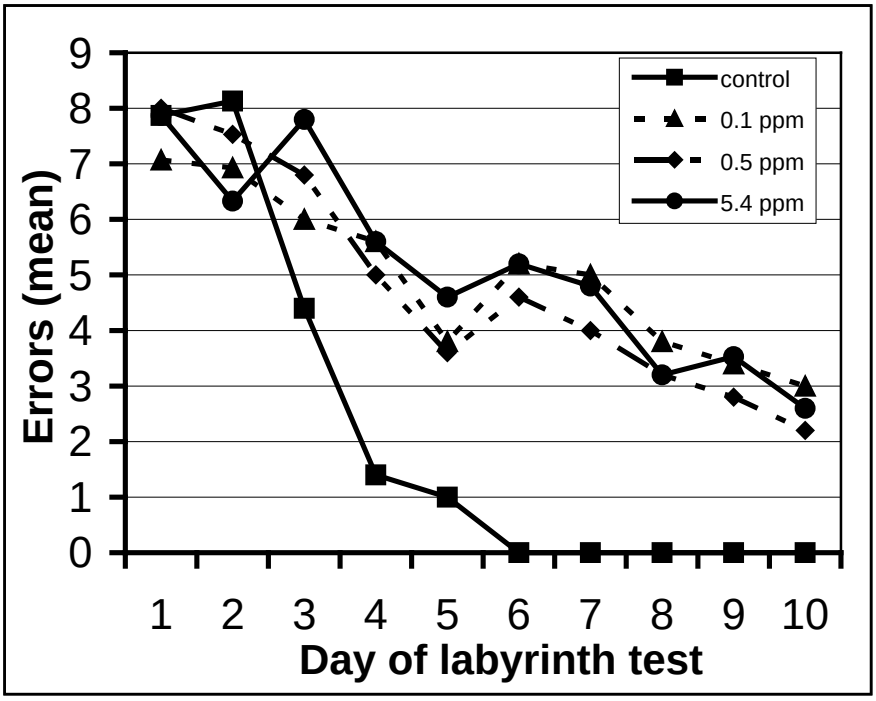


Figure 5-2. Effects of formaldehyde exposure on the error rate of female LEW.1K rats performing the water labyrinth learning test.

Source: Drawn from data reported in Malek et al. (2003a).

et al., 2003c). After appropriate duration adjustments, PODs for these studies range from 50 to 67 ppb (based on LOAELs), and the types of effects seen provide support for the Bach et al. (1990) study that detected cognitive impairments in humans following a single exposure (with a NOAEL of 170 ppb).

Summary of neurological and behavioral effects. In summary, the available studies for formaldehyde and nervous system outcomes have demonstrated that the nervous system is a sensitive target following inhalation of formaldehyde. In experimental animals, changes in nervous system function were seen following acute and subchronic exposures; studies evaluating neurological changes following chronic exposure were unavailable. Available human studies that evaluated nervous system effects following inhalation exposure were found to have many study-specific uncertainties and, thus, were not suitable to serve as the primary basis for a chronic RfC. The Weisskopf et al. (2009) study of ALS, in particular, suggests that humans may be at risk for severe neurological effects from formaldehyde exposure; however, this study

lacked the exposure concentration information necessary to derive an RfC. Neurological findings from the rodent inhalation (acute and subchronic) studies that were judged to be adequate for dose-response assessment identified unadjusted LOAELs ranging from 100 to 6,000 ppb, with LOAELs adjusted for continuous exposure in the range of 50 to 1,070 ppb. Use of these PODs in risk assessment would require addressing uncertainties regarding animal-to-human extrapolation, short study durations, and extrapolation from LOAELs.

Among the adequate studies, EPA considered Malek et al. (2003a) to be the most appropriate for calculation of a cRfC for neurological and behavioral toxicity, based on the exposure level at which effects were seen (100 ppb), the type of effect (impaired learning), which is relevant to humans, and the use of a repeated-exposure paradigm (2 hours/day over a period of 10 days), which addresses different exposure durations. This choice is supported by similar effects seen in other studies (Lu et al., 2008; Pitten et al., 2000; Bach et al., 1990) and by other neurologic effects seen at similar exposure levels (Malek et al., 2003c; Senichenkova, 1991; Sheveleva, 1971).

5.1.1.7. *Developmental and Reproductive Toxicity*

As described in Sections 4.1 and 4.2, both human epidemiologic data (see Section 4.1.1.7) and experimental animal studies (see Section 4.2.7 and Tables 4-70 and 4-73) demonstrate an association between formaldehyde inhalation exposure and adverse developmental and reproductive effects, where adversity is characterized as per EPA risk assessment guidelines (U.S. EPA, 1991a, available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162; 1996, available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2838). Adverse outcomes were observed across the various manifestations of developmental toxicity, including fetal death, structural alterations (including congenital malformations), growth retardation, and functional development. Additionally, in spite of the lack of a comprehensive database of studies for the evaluation of the overall effects of formaldehyde on the reproductive system and its function, the available evidence demonstrates toxicity to the male reproductive system in multiple animal studies, as well as effects on the female reproductive system in both rodents and epidemiologic studies, where an association with impaired fertility and increased spontaneous abortions were noted.

Potential principal studies for specific adverse outcomes are presented and evaluated below including reproductive effects (male and female), fetal death, growth retardation, and structural alterations. The only available evidence for functional alterations is based on developmental neurotoxicity studies which are presented and evaluated in Section 5.1.1.6.

Among the animal studies with developmental and reproductive effects after inhalation exposure (presented in Tables 4-70 ad 4-73), 12 endpoints from nine studies were selected for candidate PODs (see Table 5-3). The criteria for inclusion are that the studies provided reliable documentation of exposure, study design, and positive findings of developmental or reproductive structural, functional or precursor effects. Six of the studies evaluated effects after multiple dose levels, providing dose-response information. The other three studies, with a control and a single FA dose, were included as candidate PODs because effects were observed for endpoints that were either not assessed or observed in the other six studies (e.g., cryptorchidism). Table 5-3 summarizes animal studies deemed suitable for deriving quantitative dose-response information for reproductive and developmental outcomes and their corresponding PODs, adjusted for continuous exposure. Calculations that were used in dose conversions and exposure duration adjustments for the POD values are included. In general, repeated daily exposures of laboratory animals are adjusted from a partial day to a 24-hour exposure and then weighted for the number of days per week the exposures occurred. No chronic animal studies evaluating these endpoints were available, so only subchronic and acute studies are considered.

The human epidemiologic data on developmental and reproductive outcomes are discussed in Section 5.1.1.7.1. below. Exposure duration adjustments to the only suitable human study (Taskinen et al., 1999) are more complex due to uncertainties in the exposure data and the potential for nonoccupational exposures. For this discussion the reported 8-hour TWA exposures will be used for the Taskinen et al. (1999) study. Further duration adjustments to this study are discussed in Section 5.1.2.2.5 for cRfC derivation.

5.1.1.7.1. ***Spontaneous abortion and fetal death.***

Increased risk of spontaneous abortion following maternal occupational formaldehyde exposure was reported in a number of epidemiologic studies (Taskinen et al., 1999, 1994; John et al., 1994; Seitz and Baron, 1990; Axelsson et al., 1984). The studies did not appear to be overtly influenced by common principle biases found in epidemiologic studies. Considered together, the studies are consistent with an adverse effect of formaldehyde exposure on pregnancy loss, where adversity is characterized as per EPA risk assessment guidelines (U.S. EPA, 1991a, 1996). Of these studies, Taskinen et al. (1999) had the higher quality quantitative exposure data reporting reduced fecundity and spontaneous abortion in the exposed workers. Taskinen et al. (1999) is an occupational study with a well-considered study design, including measurements of exposure and outcomes, and relatively high study power. The study population consisted of 602 female workers in Finland who had at least one successful childbirth and first employment in the

Table 5-3. Candidate PODs including duration adjustments for developmental and reproductive toxicity in key animal studies

Reference	Species	POD		Exposure scenario			POD duration adjustments						Ratio[b]	Effect; comments
		Type	ppb[a]	Hours/ day	Days/ week	Duration	POD (ppb)	×	Hours/ day	×	Days/ week	= Adjusted POD (ppb)		
Spontaneous abortion and fetal death														
Kitaev et al. (1984)	Rat	LOAEL	400	4	5	6 months premating	400	×	4/24	×	5/7	= 50	8	Increased (>threefold) embryo degeneration on gestational days 2–3 after 4 months maternal premating treatment
Sheveleva (1971)	Rat	LOAEL	400	4	7	GDs 1-19	400	×	4/24	×	7/7	= 70	5.7	Increased (50%) preimplantation loss[g]
Structural alterations[c]														
Senichenkova (1991)	Rat	LOAEL	400	4	7	GDs 1-19	400	×	4/24	×	7/7	= 70	5.7	Increased (13%) litter incidence of internal organ anomalies, including 20% increase in undescended testes; 9% decreased fetal incidence of hyoid ossification[g]
Senichenkova and Chetobar (1996)	Rat	LOAEL	400	4	7	GDs 1-19	400	×	4/24	×	7/7	= 70	5.7	Increased (21%) fetal and litter incidences of cryptorchidism and increased (6%) fetal incidences of total anomalies[g]
Growth retardation														
Saillenfait et al. (1989)	Rat	BMCL	1,300	6	7	GDs 6-20	1,300	×	6/24	×	5/7	= 325	4	Decreased male fetal body weights[g] (BMR = 5%)

Table 5-3. Candidate PODs including duration adjustments for developmental and reproductive toxicity in key animal studies (continued)

Reference	Species	POD		Exposure scenario			POD duration adjustments						Ratio[b]	Effect; comments
		Type	ppb[a]	Hours/ day	Days/ week	Duration	POD (ppb)	×	Hours/ day	×	Days/ week	= Adjusted POD (ppb)		
Functional development[d]														
Male reproductive toxicity														
Özen et al. (2002)	Rat	LOAEL	10,000	8	5	4 or 13 weeks	10,000	×	8/24	×	5/7	= 2,380	4.2	Decreased testis weight at 4 weeks (2%) and 13 weeks (8%)
Özen et al. (2005)	Rat	LOAEL	5,000	8	5	91 days	5,000	×	8/24	×	5/7	= 1,190	4.2	Decreased (40%) serum testosterone levels at 91 days
Sarsilmaz et al. (1999)	Rat	LOAEL	10,000	8	7	4 weeks	10,000	×	8/24	×	7/7	= 2,380	4.2	Decreased (5%) Leydig cell numbers at 4 weeks
Zhou et al. (2006)	Rat	LOAEL	8,050	12	7	2 weeks	8,050	×	12/24	×	7/7	= 4,025	2	Decreased (~25%) testis weight; alteration of epididymal sperm [decreased (38%) count, decreased (19%) motility, and increased (>3-fold) abnormal morphology] at 2 weeks
Female reproductive toxicity														
Kitaev et al. (1984)	Rat	NOAEL	400	4	5	4 months premating	400	×	4/24	×	5/7	= 50	8	Increased (~66%) follicle-stimulating hormone at 4 months

[a]1 mg/m^3 = 0.813 ppm. All identified PODs were based on statistically significant findings at the study LOAELs. The study details are provided in Section 4.2.1.7. and Tables 4-70 and 4-73. For Saillenfait et al. (1989), the BMCL was calculated (see "effect; comments" column above for details).

[b]POD unadjusted dose/duration-adjusted dose.

[c]Neuropathological alterations following exposures during postnatal development (from the studies by Aslan et al. [2006] and Sarsilmaz et al. [2007]) are addressed in the neurobehavioral toxicity Section 4.2.6 and Table 5-2.

[d]Functional developmental endpoints (from the study by Senichenkova [1991]) are addressed in the neurobehavioral toxicity Section 4.2.6 and Table 5-2.

GDs = Gestation days

wood-working industry beginning at least 6 months prior to the studied pregnancy. Mean daily formaldehyde inhalation exposures during the time-to-pregnancy period were estimated for each worker, based on task-level exposure measurements and work history.

Exposure was reported as a daily exposure index representing the average daily exposure for the time-to-pregnancy period, and three exposure classes were defined as low, medium and high with equivalent mean work-shift TWA exposure of 18, 76 and 219 ppb, respectively. Fecundity density ratio (FDR) was significantly reduced in the high exposure group compared to the referent group (FDR=0.64, 95% CI: 0.43-0.92, p = 0.02) indicating that it took longer for the highly exposed women to become pregnant compared to women who were unexposed. The investigators stratified the 39 women in the high exposure group by glove use. While stratification by glove use reduced the statistical power of each comparison, the magnitude of the effect in each strata was not markedly effected and the 95% confidence intervals of the unstratified and stratified results all overlapped. Figure 5-3 shows the study results stratified by glove use in women in the high-exposure group. While the adverse effect of high exposure to formaldehyde was somewhat more pronounced among the women who did not wear gloves, possibly suggesting that a component of dermal exposure might contribute to the effect, it is unclear what, if any, dermal exposure is expected based on the nature of the work. Regardless, there remains uncertainty as to whether effects are solely due to inhalation exposure. Taskinen et al. (1999) also reported the risk of spontaneous abortions was statistically significantly increased with reported ORs of 3.2 (95% CI: 1.2−8.3), 1.8 (95% CI: 0.8−4) and 2.4 (95% CI: 1.2−4.8) for the high, medium and low exposure groups, respectively. The finding of increased risk of spontaneous abortion is consistent with the finding of delayed conception as measured by the fecundity density ratio.

In some available rodent studies (Kitaev et al., 1984; Sheveleva, 1971), evidence of increased embryo degeneration in early gestation or of preimplantation loss (findings that are generally comparable to spontaneous abortion in humans) was observed. In the Kitaev et al. (1984) study, early implantation losses resulted following treatment of dams prior to mating. This may support a possible contribution of prepregnancy exposures to the spontaneous abortions observed in Taskinen et al. (1999). Quantification of the findings by Kitaev et al. (1984) and Sheveleva (1971) resulted in adjusted PODs of 50 and 70 ppb, respectively, based upon study LOAELs (see Table 5-3).

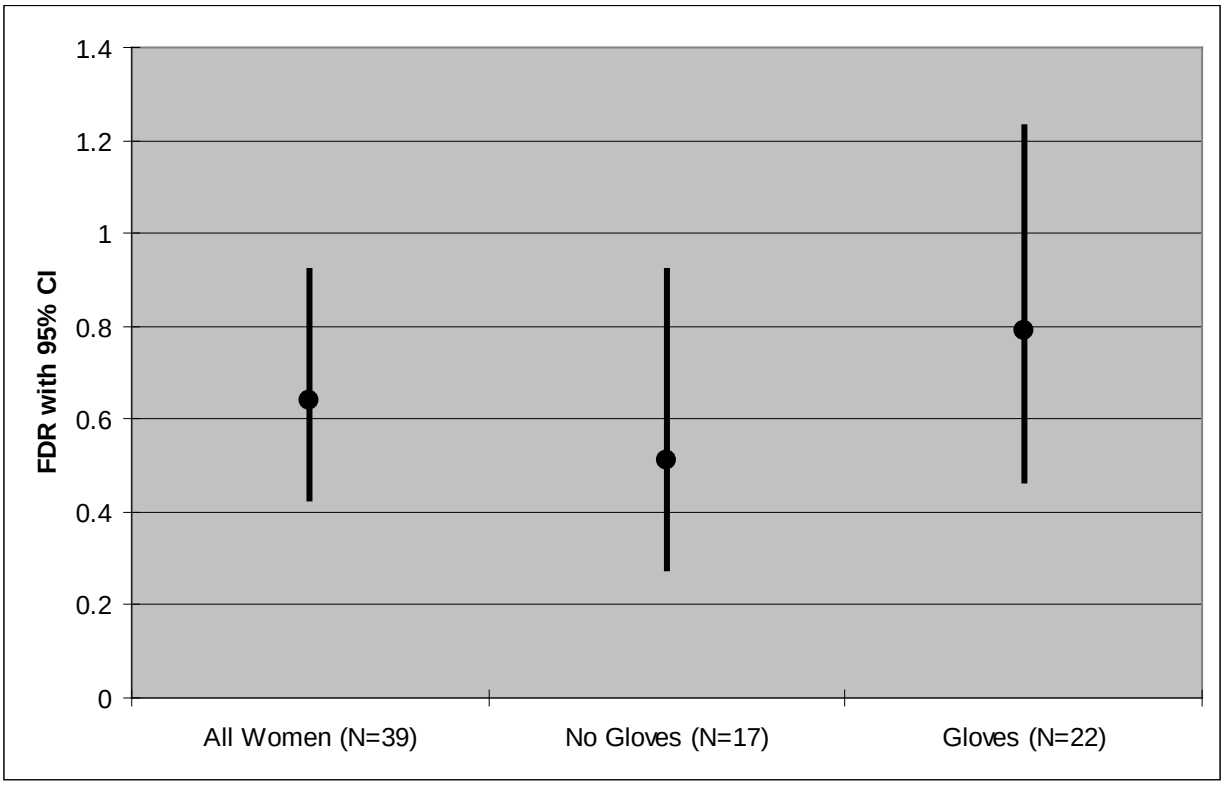


Figure 5-3. Fecundity density ratio among women exposed to formaldehyde in the high exposure index category with 8-hour time-weighted average formaldehyde exposure concentration of 219 ppb (Taskinen et al., 1999)

5.1.1.7.2. ***Structural alterations.***

Studies of occupational exposures to formaldehyde examined the incidence of congenital malformations, but exposure and outcome data were not fully characterized and therefore could not be carried forward to RfC development. Animal studies (Senichenkova and Chetobar, 1996; Senichenkova, 1991) reported increases in internal organ anomalies; the most frequently observed structural anomaly was a delay in fetal testis descent (at times characterized as cryptorchidism in the study reports). For both studies, which exposed rats to formaldehyde for 4 hours/day during gestation, adjusted PODs based upon LOAELs were 70 ppb (see Table 5-3). These studies included only one treatment level, precluding the ability to establish a dose-response relationship, and the observed outcomes were not noted in other developmental toxicity studies with similar exposure scenarios, thus limiting the strength of the studies for use in RfC derivation.

5.1.1.7.3. ***Growth retardation.***

Decreased fetal weight was observed in a number of animal studies that exposed pregnant rats to formaldehyde during gestation. Of these, based on adequacy of dose-response information, Saillenfait et al. (1989) was considered appropriate for consideration for RfC development. In this study, rats were administered formaldehyde 6 hours/day on gestational days (GDs) 6–20. Decreased male fetal body weight (BW) was modeled with a BMR of 5% mean change, a BMCL was established, and, as shown in Table 5-3, the resulting duration-adjusted POD of 325 ppb was derived. The relevance of this finding to human exposures was qualitatively supported by a population-based study by Grazuleviciene et al. (1998) that reported an association between atmospheric formaldehyde exposure and low birth weight; although a dose-response relationship could not be adequately quantified from the information provided.

5.1.1.7.4. ***Male reproductive toxicity.***

Evidence of adverse effects on male reproductive system endpoints following inhalation exposure to formaldehyde was observed in a number of animal studies, where adversity is characterized as per EPA risk assessment guidelines (U.S. EPA, 1991a, 1996). The effects include decreased testes weight, changes in Leydig cell quantity and quality, degeneration of seminiferous tubules, decreased testosterone levels, alterations in biomarkers of toxicity in the testes, and alterations in sperm count, morphology, and/or motility (Golalipour et al., 2007; Xing et al., 2007; Zhou et al., 2006; Özen et al., 2005, 2002; Sarsilmaz et al., 1999; Guseva, 1972). Several of these studies included inhalation exposure of rats to formaldehyde 8 hours/day, 5 days/week for 4 and/or 13 weeks (Özen et al., 2005, 2002; Sarsilmaz et al., 1999) and included exposure-response information that was considered adequate for RfC derivation. In a study by Özen et al. (2002), increased severity of statistically significant testes weight decreases was related to both dose and duration of treatment. Similarly, in the study by Golalipour et al. (2007), seminiferous tubular diameter and epithelial height were reduced in rats following 18 weeks of formaldehyde inhalation exposure, with the severity of outcome positively correlated to the number of hours/week that the animals were exposed. Sarsilmaz et al. (1999) noted dose dependent decreases in Leydig cell quantity after 4 weeks of treatment, while decreased testis weight and atrophy of seminiferous tubules were observed by Zhou et al. (2006) after only 2 weeks of treatment. The reported outcomes in these independent studies illustrate a biologically consistent toxicological profile of treatment-related male reproductive toxicity. PODs, adjusted for continuous exposure, ranged from 1,190 to 4,025 ppb, where the lowest POD was associated with the longest exposure period and vice verse (see Table 5-3).

5.1.1.7.5. ***Female reproductive toxicity.***

Evidence of decreased fecundability was observed in the study by Taskinen et al. (1999), which was described above for spontaneous abortions. Delays in the time to conception that characterized this outcome, as well as increases in the incidence of endometriosis, were statistically significantly associated with occupational exposures to formaldehyde. As these effects were observed in the high exposure group, the unadjusted NOAEL for each of these effects is 76 ppb (8 hour-TWA) based on the next lowest exposure group. Uncertainties included lack of information human variability, as well as on the extrapolation of data from studies of short duration to risk estimates for chronic exposures. As discussed above for spontaneous abortions, the use of these data for cRfC derivation could result in values that would likely be an underestimation of risk because they assume that all the risk was from inhalation exposure and ignore the apparent contribution of dermal exposure (i.e., the dermal-exposure-adjusted candidate inhalation RfCs might be higher). For decreased fecundability, a POD can also be identified based on the data from only the women who wore gloves. The fecundability density ratio (FDR) for the women in the highest exposure group was statistically significantly reduced at FDR=0.64 (95% confidence interval [CI] 0.43–0.92). Evidence of spontaneous abortions in the same study, as described above, may also be indicative of female reproductive toxicity.

In animal studies, assessment of the female reproductive system was quite limited. An increase in the mean follicle-stimulating hormone (FSH) levels in rats, observed at the highest exposure level tested in Kitaev et al. (1984) was found to be sufficient to derive a duration-adjusted POD of 50 ppb (see Table 5-3).

5.1.1.7.6. ***Summary of developmental and reproductive toxicity studies suitable for RfC development.***

A review of the developmental and reproductive toxicity studies in humans and animals that would be suitable for cRfC development demonstrated that the developing organism and the reproductive system are targets for toxicity following formaldehyde exposure by inhalation. In the animal studies, effects during early development were observed following maternal premating or gestational exposures at duration-adjusted PODs ranging from 50−325 ppb. The minimal data available on female reproductive toxicity demonstrated an adjusted POD of 50 ppb with subchronic (4-month) premating exposure, while more extensive evaluation of male reproductive outcomes identified adjusted PODs of 1,190−4,025 for testicular and sperm abnormalities after exposures of from 2 weeks to 3 months in duration. The animal studies demonstrate the broad range of adverse outcomes to the reproductive system and the developing organism following inhalation exposure to formaldehyde and highlight concerns regarding the

inadequacy of the database for the assessment of these outcomes (as described in Chapter 4). These data also support the human relevance of female reproductive and/or embryonic and fetal developmental effects, since some outcomes were similarly observed in both human and animal studies.

The animal study data were not selected for RfC derivation, since a high-quality epidemiology study (Taskinen et al., 1999) was available for the purpose of deriving a chronic RfC. This study, a well-designed population-based case-control study of women who were occupationally exposed to formaldehyde, included a well-defined study population which was adequately selected to allow for meaningful comparisons of health effects among individuals with different levels of exposure to formaldehyde. Potential confounding factors such a selection bias and inaccurate self-reporting were not considered to have had a significant influence on the study findings. The increased risk of spontaneous abortion observed in Taskinen et al. (1999), and perhaps the observed decrease in fecundity, is internally consistent and coherent with other reports of increased risk of pregnancy loss associated with exposure to formaldehyde (John et al., 1994; Taskinen et al., 1994; Seitz and Baron, 1990; Axelsson et al., 1984). It is also supported by similar adverse outcomes observed in the animal data (Kitaev et al., 1984; Sheveleva, 1971).

5.1.2. Summary of Critical Effects and Candidate RfCs

5.1.2.1. *Selection of Studies for Candidate RfC Derivation*

The above reviews of data from both human and animal studies identified health effects associated with formaldehyde exposure. Detailed information on these findings is given in Chapter 4 (see Sections 4.1 and 4.2), and a qualitative summary of the noncancer hazard identification is provided in Section 4.4 for each of the identified health effect categories: sensory irritation, upper respiratory tract pathology, respiratory effects, increased atopic response, immune function, reproductive and developmental toxicity, and neurobehavioral toxicity. In this chapter, results for each health effect category are reviewed and studies are identified which are adequate to inform the exposure-response relationship for health effects from inhalation exposure (see Section 5.1.1). Although the database of published studies that are currently available does not provide adequate quantitative data to derive cRfCs for all qualitatively identified endpoints, at least one adequate study was identified for each of the health effect categories discussed above. For all but one of the categories, at least one study was available that provided epidemiologic (human) data, based on occupational or residential exposures, which was judged adequate to provide a quantitative basis for a cRfC.

In order to select the principal study or studies most appropriate for use as the basis of the RfC for formaldehyde, the relative merits of these studies were evaluated with respect to study quality, characteristics of the study population, the quality and frequency of exposure measurements, and the exposure levels at which effects are observed. The ideal RfC would be derived from a reported exposure level without an appreciable risk of deleterious effects in humans, including sensitive populations, with little uncertainty. Additionally, where possible, the RfC should be derived with consideration of all of the identified health effects. The several factors that were collectively taken into consideration for these studies (in no particular order) included the following:

- Were studies of laboratory animals or humans?
  - Human studies were generally preferred over laboratory animal studies for similar health effects, when both were of good quality, given the uncertainties in interspecies extrapolation.
- What was the study size?
  - Larger studies were generally preferred over smaller studies because they can give more precise estimates of response levels associated with specific exposure levels.
- Among the epidemiologic (human) studies, were exposures from an occupational setting or from a residential setting?
  - Studies of health effects from residential exposures were generally preferred over studies of health effects from occupational exposures because residential exposures tend to have a smaller range of variability and are less prone to large intermittent exposure peaks.
  - Residential exposures are more representative of the exposures of the general population.
- Among the epidemiologic (human) studies, were children among the study population in which health effects were observed?
  - Studies of health effects that assessed the effect of formaldehyde on children's health, representing a potentially more susceptible life-stage for some effects, were given some preference because they provide formaldehyde-specific data relevant to the components of the RfC derivation that address potentially sensitive life-stages and populations.
- Relative to the other studies under consideration for RfC development, how accurately were formaldehyde concentrations measured?
  - Studies based on relatively more accurately measured formaldehyde concentrations were generally preferred over studies that estimated exposures.

- Studies that reported effects at relatively lower formaldehyde concentrations, potentially indicative of more sensitive endpoints, were generally preferred.

Taking all the factors into consideration collectively, the individual studies are presented in Table 5-4.

For sensory irritation, four studies are identified with adequate exposure information for RfC derivation, and all are observational studies of humans (see Table 5-4). Of these, 3 studies were conducted in residential populations, including children and the elderly (Liu et al.,1991; Ritchie and Lehnen, 1987; Hanrahan et al., 1984). Each of these studies includes in-home formaldehyde measurements for each participant. Liu et al. (1991) provide the best exposure measurements, with 7-day in-home passive air samples collected in two seasons. The occupational study by Holmström and Wilhelmsson (1988) provides evidence of sensory irritation in workers; however, only the mean and range of exposures for all workers is given. Furthermore, occupational exposures can include high peak exposures. The residential studies are preferred for development of candidate RfC. Although there are differences in study size and the quality of exposure measurements between the three residential studies, their results are mutually supportive, defining similar effect levels in similar populations, and the use of the three residential studies was considered to provide adequate consideration of the sensory irritation endpoint. Therefore, all 3 studies are selected (Liu et al.,1991; Ritchie and Lehnen, 1987; Hanrahan et al., 1984) and will be evaluated together in the following section.

Histological changes in the upper respiratory tract are well documented in animal studies and have been observed in several worker studies (see Section 4.4). Although the study of resin production workers (Holmström and Wilhelmsson, 1988; Holmström et al., 1989) provides the best documentation of effect level for this health category in humans, it is not carried through for development of a candidate RfC. As with the sensory irritation endpoint reported in these studies, exposure is described for the worker cohort by a simple mean, with a range of exposures given for all workers. Therefore, these data do not provide an exposure-response relationship and the POD would be the mean exposure level of all workers, regardless of effect. This is less exact than other available studies which provide exposure-response relationships. Additionally, animal studies provide a broad database which supports sensory irritation as a more sensitive endpoint than histological changes in the nasal mucosa.

Reduced pulmonary function is associated with formaldehyde exposure in several human studies (students and workers). The best single study demonstrating decreased pulmonary

Table 5-4. Summary of candidate studies for formaldehyde RfC development by health endpoint category

Health endpoint category	Study	Species	Setting	Children	Study size	Formaldehyde measurements	Specific endpoints	Observed effects[a] (ppb)	POD (ppb)
Sensory Irritation	Liu et al. (1991)	Human	Residential	Yes	1,394	Two locations at one time period (winter or summer); 7-day passive monitors	Eye irritation	95	LOAEL=95
	Ritchie and Lehnen (1987)	Human	Residential	Yes	2,007	Two locations at one time period; 30-minute sample	Eye, nose, and throat sensory irritation	200	NOAEL=50
	Hanrahan et al. (1984)	Human	Residential	Yes (teenagers)	61	Two locations at one time period; 60-minute sample	10% increased prevalence of burning eyes	130	$BMCL_{10}$=70
	Holmström and Wilhelmsson (1988)	Human	Occupational	No	106	Several measurements at factory workstations taken over 7 years	Eye irritation	210	NOAEL=70
Upper Respiratory Tract Pathology	Holmström and Wilhelmsson (1988); Holmström et al. (1989)	Human	Occupational	No	132 68 with pathology	Several measurements at factory workstations taken over 7 years	Loss of ciliated epithelium; goblet cell hyperplasia; squamous cell metaplasia	240	LOAEL=240
Sensitization: Asthma and atopy	Garrett et al. (1999 a,b)	Human	Residential	Yes	148	Four locations over up to four time periods; 4-day passive monitors	Increased allergy; increased asthma-like symptoms	28	LOAEL=28

Table 5-4. Summary of candidate studies for formaldehyde RfC development by health endpoint category (continued)

Health endpoint category	Study	Species	Setting	Children	Study size	Formaldehyde measurements	Specific endpoints	Observed effectsa (ppb)	POD (ppb)
Pulmonary Function	Krzyzanowski et al. (1990)	Human	Residential	Yes	208	Four locations over two time periods (opposite seasons); 7-day passive monitors	10% Reduction in PEFR	27	$BMCL_{10}$=17
Neurological	Malek et al. (2003a)	Rat	Laboratory	--	120	Intentional exposures at specific levels	Impaired learning	100	LOAEL=100
Reproductive and Developmental effects	Taskinen et al. (1999) (FDR)	Human	Occupational	No	602	Actual and surrogate measurements estimated by occupational hygienist	Decreased fecundity density ratio (FDR)	226[b]	NOAEL=86
	Taskinen et al. (1999) (SAB)	Human	Occupational	No	602	Actual and surrogate measurements estimated by occupational hygienist	Increased risk of spontaneous abortion (SAB)	26[b]	LOAEL=26
Immune Function	Lyapina et al. (2004)	Human	Occupational	No	29	Average shift concentrations based on measures 8-hour exposures	Increased respiratory tract infections, decreased neutrophil respiratory burst activity	722	LOAEL=722

[a]This is the lowest level of exposure at which adverse effects were observed, the LOAEL, in effect, or the cut-off point for adversity for BMCLs.
[b]See Section 5.1.2.6.2 for methods to adjust exposure levels from Taskinen et al. (1999).

function is the moderate residential study by Krzyzanowski et al. (1990). The study was specifically designed to include homes with children between the ages of 5−15. Results presented for children (n = 208) provide an exposure-response relationship for reduced PEFR. Data quality is considered high for this study, both in terms of the in-home exposure measurements (7-day passive monitors, two time periods) and the contemporaneous in-home measurement of pulmonary function. Sources of potential confounding or bias were considered by the study authors and adequately taken into account in the study. Therefore, this study is retained for derivation of a candidate RfC.

Several studies report increased asthma and/or allergic sensitization in children associated with increased formaldehyde exposure in school or homes (see Section 5.1.4). Of these, two studies are further evaluated here (Garrett et al., 1999 a,b; Rumchev et al., 2002). The study by Rumchev et al. (2002) is a case-control study of asthma incidence in children, and the study by Garrett et al. (1999 a,b) is designed to study several related health effects (asthma, sensitization and respiratory symptoms) in asthmatic and nonasthmatic children. Both studies measure in-home formaldehyde levels with multi-day passive samples. Survey data and health outcome data are considered of high quality in each study. Additionally, sources of potential confounding or bias were considered by the study authors and adequately taken into account in the study. Therefore, both studies are retained for derivation of a candidate RfCs. Although several studies of school children support these findings, the residential studies were considered more appropriate for RfC derivation because individual in-home formaldehyde levels were associated with the health outcome data.

Multiple lines of evidence support the occurrence of neurotoxicity following exposure to formaldehyde, however, none of the available studies in humans were considered to be of adequate quality for derivation of a point of departure for use in quantitative assessment. Of the available neurotoxicity studies, Malek et al. (2003a), in which impaired learning was seen in rats following exposure at 100 ppb, was selected as a potential candidate for RfC development (see Section 5.1.6). A NOAEL was not identified for this effect. In view of the other studies available in the formaldehyde database (including multiple human studies of potentially sensitive populations), and considering the uncertainty in extrapolating from the exposure conditions in the Malek et al. (2003a) study (two hour exposures, repeated on ten consecutive days) to a chronic exposure scenario, this study was not carried forward for derivation of a candidate RfC. It is important to note that the resulting RfC may therefore not fully consider the documented neurotoxic effects of formaldehyde.

Of the various reproductive and developmental effects associated with formaldehyde exposure, reduced fecundity and increased risk of spontaneous abortions are primarily studied in

humans (see Section 5.1.7). Of the available epidemiology studies, only one study provides individual exposure estimates of adequate quality to support RfC development (Taskinen et al., 1999). Exposure-response relationships for decreased fecundability density ratio and increased risk of spontaneous abortions are seen with increased categories of worker exposures. Several potential confounding exposures are evaluated in the study, and the association of decreased fecundability density ratio observed in the study is most convincingly associated with increased formaldehyde exposure (Taskinen et al., 1999). Potential sources of bias were also adequately addressed in the study. This is considered a high quality study and is retained for cRfC derivation.

Although Lyapina et al. (2004) have documented decreased neutrophil respiratory burst activity in exposed workers, the overall weight of evidence for deficit in immune function due to formaldehyde exposure is weak. There is a trend for increased respiratory tract infections in formaldehyde-exposed individuals, but it is a direct result of impaired immune function or, perhaps, increased infection due to direct effects on the protective barriers of the nasal mucosa. Animal studies do not support a finding of a deficit in immune function with formaldehyde exposure. The study by Lyapina et al. (2004) is a small study, and the findings of decreased neutrophil respiratory burst activity were in those individuals with more upper respiratory tract infections, so there is some question of causality. The data evaluation does not provide an exposure-response relationship, but, rather, exposure for the cohort is expressed as a mean exposure of 722 ppb. Although the potential for impairment of immune function is an important health effect, the overall evidence for this effect and this specific study are relatively weak compared to other data available to support RfC derivation for formaldehyde. Therefore, this study is not carried further in the quantitative analysis.

In summary, the best studies evaluated herein for the derivation of an RfC for formaldehyde exposure and the related health effects are: 1) Sensory irritation (Liu et al.,1991; Ritchie and Lehnen, 1987; Hanrahan et al., 1984); 2) reduced pulmonary function (Krzyzanowski et al., 1990); 3) sensitization (atopy and asthma) (Garrett et al., 1999 a,b and Rumchev et al., 2002); and 4) reduced fecundity and increased spontaneous abortion (Taskinen et al., 1999). It is recognized that not all identified health effects are represented in these studies.

5.1.2.2. *Derivation of Candidate RfCs from Key Studies*

5.1.2.2.1. *Candidate RfC derivation for Krzyzanowski et al. (1990) (Pulmonary function).*

The study by Krzyzanowski et al. (1990) is a high quality epidemiology (human) study of health effects in a random sample of residents and their families. The study was specifically designed to include only households that had children 5–15 years of age, a sensitive life-stage for

respiratory effects. The study was of moderate size, when the effects in children were analyzed separately from adults, with the final analysis based on 208 children—a cohort large enough to show statistically significant results. The formaldehyde monitors were prepared by the Lawrence Berkeley Laboratories and were considered to be precise and highly reliable. The 7-day passive formaldehyde monitors generally provide the lowest limit of formaldehyde detection. The investigators specifically tested an a priori hypothesis and conclusively demonstrated to a high level of statistical significance that increased residential formaldehyde exposures were associated with decreased pulmonary function as measured by peak expiratory flow rate (PEFR) in children. This effect was clearly shown at relatively low concentrations of formaldehyde as the mean concentration in the homes was 26 ppb with more than 83% of homes having measured concentration less than 40 ppb. This study also reported specific regression modeling results that allowed EPA to calculate the point of departure for RfC development using a BMCL as the point of departure.

The effects of formaldehyde exposure on pulmonary function represent a sensitive endpoint with a reported 10% reduction in PEFR at 27 ppb. Among children with physician-diagnosed asthma, the observed effects of increased formaldehyde exposure on decreased PEFR were more pronounced—a clear indication of variability in response. The American Thoracic Society (ATS, 2000) considers decreased pulmonary function an adverse health effect, even when it is transient and subclinical. "Assuming that the relationship between the risk factor and the disease is causal, the committee considered that such a shift in the risk factor distribution, and hence the risk profile of the exposed population, should be considered adverse, even in the absence of the immediate occurrence of frank illness" (ATS, 2000). The ATS (2000) stated that individuals in an exposed population experiencing a shift in the distribution of pulmonary function were at potential risk from another agent due to the reduction in their reserve capacity to address additional insults. In the study by Krzyzanowski et al. (1990), the investigators demonstrated statistically significant interaction between formaldehyde exposures, smoking, and chronic cough. That is, a formaldehyde concentration that caused decreased pulmonary function at residential levels also caused chronic cough in the presence of environmental tobacco exposures. Higher prevalence rates of physician-diagnosed asthma and chronic bronchitis were also shown at higher concentrations of formaldehyde (60–140 ppb), an effect that was exacerbated by environmental tobacco exposures.

Figure 5-4 illustrates the reductions in peak expiratory flow rate (PEFR) in children (<15 years of age) in relation to indoor residential formaldehyde concentrations estimated by a random effects model based on 3,021 observations in 208 subjects. Formaldehyde levels in the

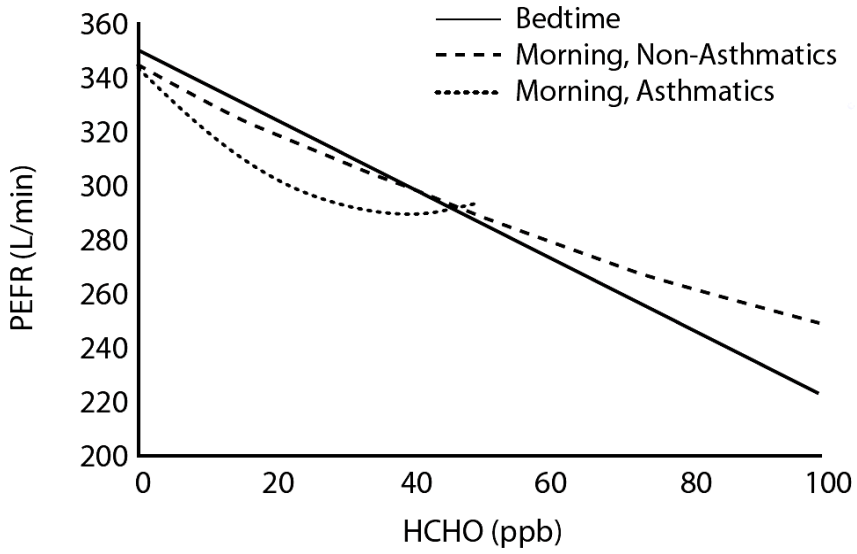


Figure 5-4. Estimated reduction in peak expiratory flow rate (PEFR) in children in relation to indoor residential formaldehyde concentrations.
Source: Krzyzanowski et al. (1990).

home were significantly related to reductions in PEFR in children both at bedtime and in the morning ($p < 0.05$). PEFR measurements in the morning versus at bedtime were significantly different ($p < 0.05$). Formaldehyde-related reductions in PEFR were greater in the morning in asthmatic children than in nonasthmatic children ($p < 0.05$).

Candidate RfC derivation based on Krzyzanowski et al. (1990):

Critical effect: Based on this study, which specifically included a susceptible population, the critical effect is reduction in PEFR in children. PEFR was the most sensitive measure of disease or impaired lung function reported in this population, with decreases in lung function reported in children who lived in homes with average measured formaldehyde concentrations as low as 30 ppb (Krzyzanowski et al. (1990). Children were more sensitive to formaldehyde-associated decreases in PEFR than adults, so the cRfC derived focused on the results in the 208 children.

Point of departure: A BMR of 10% reduction in PEFR was selected as a cut-off point for adversity, based on rationales articulated by the ATS (2000)[4]. Using this BMR and the model coefficient in Table 5 of Krzyzanowski et al. (1990), a $BMCL_{10}$ of 17 ppb (BMC_{10} = 27 ppb) was derived for all children.[5] Although the authors noted that asthmatic children were more sensitive, the necessary data were not provided in the report to calculate a BMCL for asthmatic children alone. Thus, 17 ppb, the BMCL based on all children in the study, was used as the POD.

Application of study-specific Uncertainty Factors (UFs):

Interspecies UF = 1: No interspecies adjustment is needed, as this is a human study.

LOAEL-to-NOAEL UF = 1: Because a BMCL was used for the POD and the BMR of 10% reduction in PEFR was considered to be a cut point for adversity, no LOAEL-to-NOAEL UF was needed (UF_L = 1).

Subchronic-to-chronic UF = 1: The study addresses ongoing residential exposure to formaldehyde. Although information on the duration of exposure for each participant is not provided, the residential nature of the study suggests a longer term exposure than the duration of the study. It was judged that a population-based study of residential exposures is sufficient to derive a chronic RfC without adjusting for a subchronic observation period — at least for adults and older children, and the children in this study were mostly older children (e.g., older than 7 years).

[4] The ATS (2000) recommended that "a small, transient loss of lung function, by itself, should not automatically be designated as adverse" and cited EPA's 1989 review of ozone, which offered a graded classification of lung function changes in persons with asthma as "mild," "moderate," or "severe" for reductions of less than 10, 10–20, and more than 20%, respectively (U.S. EPA, 1989). ATS (2000) concluded that, in evaluating the adverse health effects of air pollution at the level of population health (compared to individual risk), "[a]ssuming that the relationship between the risk factor and the disease is causal, the committee considered that such a shift in the risk factor distribution, and hence the risk profile of the exposed population, should be considered adverse." This was specifically considered by ATS (2000) even when "[e]xposure to air pollution could shift the distribution towards lower levels without bringing any individual child to a level that is associated with clinically relevant consequences." A moderate adverse effect at functional decrements of 10–20% was considered the best indicator of adverse effects in the study population. This criterion had been similarly applied in EPA's *Air Quality Criteria for Ozone and Related Photochemical Oxidants* (U.S. EPA, 2006d) for pulmonary function.

[5] According to the regression model in Table 5 in Krzyzanowski et al. (1990), the coefficient ± standard error for formaldehyde (in ppb) is –1.28 ± 0.46 and the background PEFR is 349.6 L/minute. Thus, a 10% reduction in PEFR is –35 L/minute and the 95% (one-sided) upper bound on the slope for PEFR as a function of formaldehyde exposure is –1.28 – (1.645 × 0.46), or –2.04 L/minute-ppb. Dividing 35 L/minute by 2.04 L/minute-ppb yields 17 ppb as the BMCL.

Human variability UF = 3: The study was designed to include homes with children, and a POD can be established based on reduced PEFR in children, who were more sensitive to the health effects than the adults in the study. Therefore, the POD represents data for a sensitive life stage, an aspect of human (intraindividual) variability. With respect to the human (interindividual) variability UF, although environmental tobacco smoke and socioeconomic status did not affect the formaldehyde results in children, asthmatic children were more sensitive to the effects of formaldehyde exposure on PEFR; thus, asthmatic children represent a population with increased susceptibility for this effect. The prevalence rate for physician-diagnosed asthma in the children was 15.8% in this study, which is higher than the national prevalence of about 5.9% for ages 5 to 17 years.[6] Thus the BMCL based on all children may be influenced by a higher prevalence of susceptible children for the critical effect. The authors do report that the PEFR was reduced to a greater degree in asthmatic children (as shown in Figure 5-4), and a lower BMC of 17 ppb can be calculated in this subgroup versus a BMC of 27 ppb for all children. However, the published regression statistics do not provide sufficient detail to calculate a BMCL specific for asthmatic children. In addition, other potentially sensitive populations (for example, elderly individuals or individuals with respiratory diseases) may not be adequately represented in the study. Therefore, an UF for human variability of 3 is applied to address the observed increased sensitivity of asthmatic children in lieu of a calculated BMCL

$$RfC = \frac{BMCL_{10}}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{17\ ppb}{\left(1 \times 1 \times 1 \times 3\right)} = 5.6\ ppb \qquad (5\text{-}1)$$

UF_A = 1 (interspecies UF)
UF_L = 1 (LOAEL-to-NOAEL UF)
UF_S = 1 (subchronic-to-chronic UF)
UF_H = 3 (human variability UF)

[6] The national prevalence rate of asthma in children ages 5–17 is according to the Centers for Disease Control and Prevention (CDC) (MMWR 49(40):908-911, 2000). Although the Krzyzanowski et al. (1990) study was conducted in the late 1980s, prevalence data from the National Health Interview Survey for 1997 were used for comparison because that is the earliest year for which data are available after a 1997 redesign of the survey. Previously, the survey asthma question was not specific for physician-diagnosed asthma, so the redesigned results were considered to be more comparable to the physician-diagnosed asthma definition in the Krzyzanowski et al. (1990) study.

specific to asthmatic children and to ensure adequate protection for other potentially sensitive populations.

5.1.2.2.2. ***Candidate RfC derivation for Rumchev et al. (2002) (Asthma).***

Residential formaldehyde exposure was associated with an increased risk of asthma in a population-based case-control study of 192 children aged 6 months to 3 years (Rumchev et al., 2002). While it is acknowledged that accurately diagnosing asthma in young children is difficult, as the diagnosing physician was unaware of the formaldehyde level in the children's home, any diagnostic error would be unrelated to formaldehyde concentrations and would not induce a spurious association. It is noted that the endpoint is physician-diagnosed asthma. The study, which comprises 88 cases of children discharged from the emergency department of a children's hospital in Perth, Australia, with a primary diagnosis of asthma and 104 controls, provides a positive exposure-response relationship adequate for RfC derivation. Seasonal in-home formaldehyde measurements taken in the living room and subject's bedroom were used to assess exposure (8-hour passive sampler). The ORs for risk of asthma by formaldehyde exposure level category were adjusted for numerous risk factors, both familial and environmental, including familial history of asthma, age, sex, socioeconomic status, smoking, presence of pets, air conditioning, humidifier, and gas appliances. Of these, age, allergic sensitization to common allergens, and family history of allergy were independent risk factors for asthma (OR = 1.09, 2.57, and 2.66, respectively). Odds ratios were further adjusted for the effects of the measured indoor air pollutants (see Rumchev et al., 2004), indoor allergen levels of dust mites, relative humidity, and indoor temperature. Categorical analysis of the data indicates that the ORs for asthma were increased in the two highest formaldehyde exposure groups, reaching statistical significance for household exposures > 60 $\mu g/m^3$ (48 ppb) (OR = 1.39) (see Figure 5-5). Analysis of the data with formaldehyde as a continuous variable provides a statistically significant increase in the risk of asthma (3% increase in risk per every 10 $\mu g/m^3$ increase in formaldehyde level.)

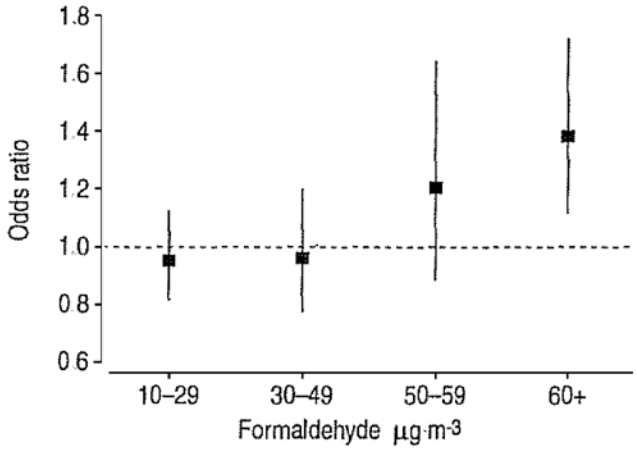


Figure 5-5. Odds ratios for physician-diagnosed asthma in children associated with in-home formaldehyde levels in air.

Source: Rumchev et al. (2002).

Candidate RfC derivation based on Rumchev et al. (2002):

Critical effect: Diagnosis of childhood asthma (case-control study).

Point of departure: A NOAEL of 33 ppb (40 μg/m^3; midpoint of the 30–49 μg/m^3 category) was selected because the OR for asthma in the next highest exposure category was considered to be part of an exposure-related trend of increasing asthma risk and, therefore, biologically significant.

Application of Study-Specific Uncertainty Factors (UFs):

Interspecies UF = 1: No interspecies adjustment is needed as this is a human study.

LOAEL-to-NOAEL UF = 1: No LOAEL-to-NOAEL UF was needed because the POD was a NOAEL (UF_L = 1).

Subchronic to chronic UF = 3: The study addresses ongoing residential exposure to formaldehyde. Although information on the duration of exposure for each participant is not provided, the residential nature of the study suggests a longer term exposure than the duration of the study. Study participants were 3 years or younger, therefore the duration of exposure could not meet the expected definition for a chronic study of one-tenth the lifespan. However, asthma often develops during childhood, indicating a less-than chronic duration of exposure.

Since asthma may develop throughout childhood it is unclear whether a study of children under 3 years of age would be of adequate duration for this developmental window. Therefore, an uncertainty factor of 3 was applied as a subchronic to chronic adjustment.

Human variability UF = 1 or 3: As a case-control study, all new cases of childhood asthma which met the study criteria were eligible for inclusion and the cases likely included children predisposed to asthma. Individuals with a family history of asthma and/or genetic markers for genes believed to predispose individuals to asthma would represent a susceptible population. Therefore, the cases in this study address children as a susceptible population for first diagnosis of asthma. Additionally, there was an association of a familial history of asthma with the diagnosis of children's asthma in this cohort (OR = 2.66). Not all sources of human variability which may contribute to a diagnosis of asthma are known, and there are likely additional sources of interindividual variability among children and among individuals with a family history of asthma, thus it is unlikely that all sources of human variability were adequately represented in the study population.

The two alternatives are described below and cRfCs are derived for each alternative.

Alternative A: Rumchev et al. (2002)
Human variability UF = 3:

To account for potentially susceptible individuals beyond those represented in the study population, an uncertainty factor of 3 for human variability is applied.

$$RfC = \frac{NOAEL}{(UF_A \times UF_L \times UF_S \times UF_H)} = \frac{33\ ppb}{(1 \times 1 \times 3 \times 3)} = 3.3\ ppb$$

UF_A = 1 (interspecies UF)
UF_L = 1 (LOAEL-to-NOAEL UF)
UF_S = 3 (subchronic-to-chronic UF)
UF_H = 3 (human variability UF)

Alternative B: Rumchev et al. (2002)
Human variability UF = 1:

EPA's Technical Report of the RfD and RfC Processes Technical Report (US EPA, 2002a) indicates that UF_H of 1 has been applied in cases where there are data "very specific about the particular vulnerability of infants and children within certain age ranges to an agent." Asthma and allergic sensitization to common allergens develop during childhood and young adulthood defining a developmental window during which individuals are most susceptible to the development of asthma. Since this study includes only children up to 3 years of age, the UF for subchronic exposure is applied above acknowledging that this study does not cover the susceptible developmental window. No additional adjustment is applied for inter-individual variability among children. It is acknowledged that additional sources of human variability are possible—but it is believed that childhood is a key developmental window for initial diagnosis of asthma. The technical report acknowledges that applying a UF_H of 1 may be appropriate where "even within these populations it is possible that some variability still exists.

$$RfC = \frac{NOAEL}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{33\ ppb}{\left(1 \times 1 \times 3 \times 1\right)} = 11\ ppb$$

UF_A = 1 (interspecies UF)
UF_L = 1 (LOAEL-to-NOAEL UF)
UF_S = 3 (subchronic-to-chronic UF)
UF_H = 1 (human variability UF)

5.1.2.2.3. ***Candidate RfC derivation for Garrett et al. (1999 a,b) (Asthma, respiratory symptoms, atopy and severity of allergic sensitization).***

Garrett et al. (1999 a,b) reported on the risk of allergy and asthma-like respiratory symptoms due to formaldehyde exposure in a cross-sectional survey of households with children 7–14 years old with (n = 53) or without (n = 95) doctor-diagnosed asthma. Formaldehyde exposure was characterized by four seasonal in-home sampling events using 4-day passive samples collected in bedrooms, living rooms, kitchens, and outdoors. In logistic regressions, both the prevalence and severity of allergic sensitization to 12 common allergens increased with increasing formaldehyde concentration in the home. Additionally, a calculated respiratory symptom score was increased and demonstrated a significant relationship with increased formaldehyde concentration in a multiple linear regression after adjusting for multiple risk factors and interactions. For each of these endpoints, severity/incidence was increased in the medium (20–50 μg/m^3) and high (>50 μg/m^3) exposure groups relative to the low (<20 μg/m^3)

exposure group, based on the highest of four seasonal 4-day formaldehyde measurements in the home (see Figures 5-6 and 5-7).

The findings of Garrett et al. (1999 a,b) are supported by the observation of an increased bronchial responsiveness to mite allergen in a chamber study of 19 sensitized adult asthmatics exposed to formaldehyde at a concentration of 100 μg/m^3 for 30 minutes (Casset et al., 2006). Additionally, inhalation exposures to formaldehyde have been shown to increase an animal's response to other common allergens via inhalation (Fujimaki et al., 2004b; Sadakane et al., 2002; Riedel et al., 1996; Tarkowski and Gorski, 1995).

Candidate RfC derivation for increased allergic sensitization from Garrett et al. (1999 a,b***):***

Critical effects: ***Allergic sensitization—***Increase in allergic sensitization (proportion of atopic children). Severity of allergic sensitization measured both as number of positive skin tests to common allergens and the recorded allergen wheal ratio for those tests. ***Asthma—***increase in proportion of asthmatic children. ***Respiratory symptoms—***Increased respiratory symptom score.

Point of departure: For all critical effects, categorical analyses are presented that show an increase in the midexposure group (16–40 ppb) and high exposure group (>40 ppb) relative to the low-exposure group (<16 ppb) (see Figures 5-6 and 5-7). However, it is unknown if the findings in the low-exposure group are comparable to the responses that would be observed in an unexposed population. Therefore, the low-exposure group cannot be considered a NOAEL but rather serves as a referent group for the two other exposure groups. Thus, the LOAEL is based on health effects observed in the midexposure group (16−40 ppb) for all three critical effects. As neither the mean or median exposure levels are provided for the exposure categories used to analyze the health effects data, the midpoint of the exposure category is selected for the LOAEL: 28 ppb.

Application of study-specific Uncertainty Factors (UFs)*:*

Interspecies UF = 1: No interspecies adjustment is needed as this is a human study.

LOAEL-to-NOAEL UF = 3: As discussed, the midexposure group is selected as the LOAEL since the low-exposure group is the referent group; there is no true unexposed control. It is unclear whether or not a full LOAEL to NOAEL uncertainty factor is warranted for these data. The authors did provide evidence for increased atopy for every increase of 16 ppb of exposure with borderline statistical significance when adjusted for several potential confounders (OR = 1.4;

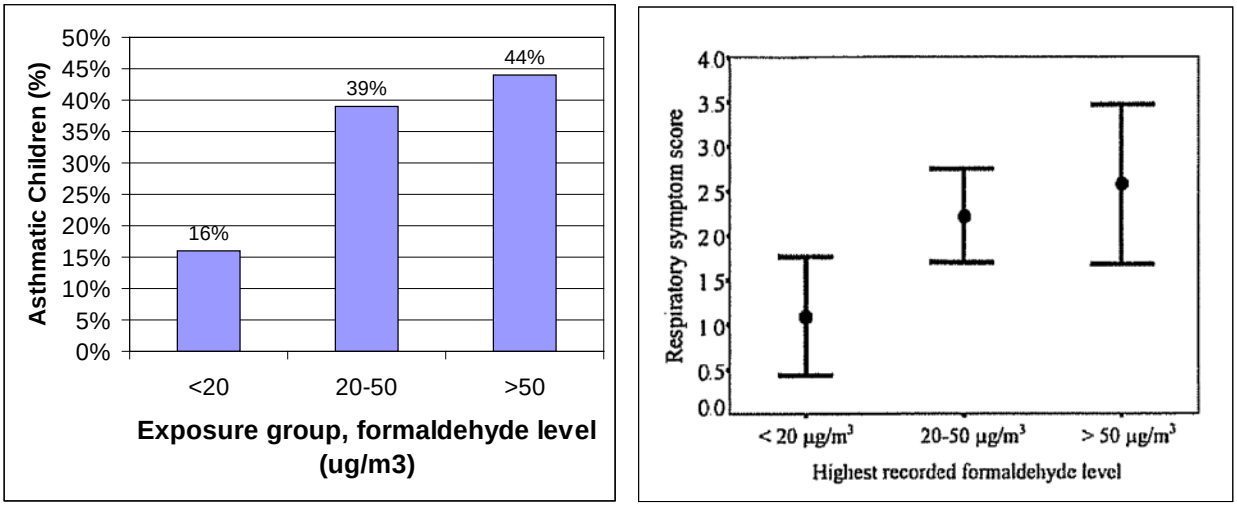


Figure 5-6. Prevalence of asthma and respiratory symptom scores in children associated with in-home formaldehyde levels. Trend analysis indicates statistical significance in these increases {percent asthmatic children, unadjusted (p=0.03) and respiratory symptom score (p=0.03)}.

Source: Garrett et al. (1999a) ; Garrett et al., 1999b (errata).

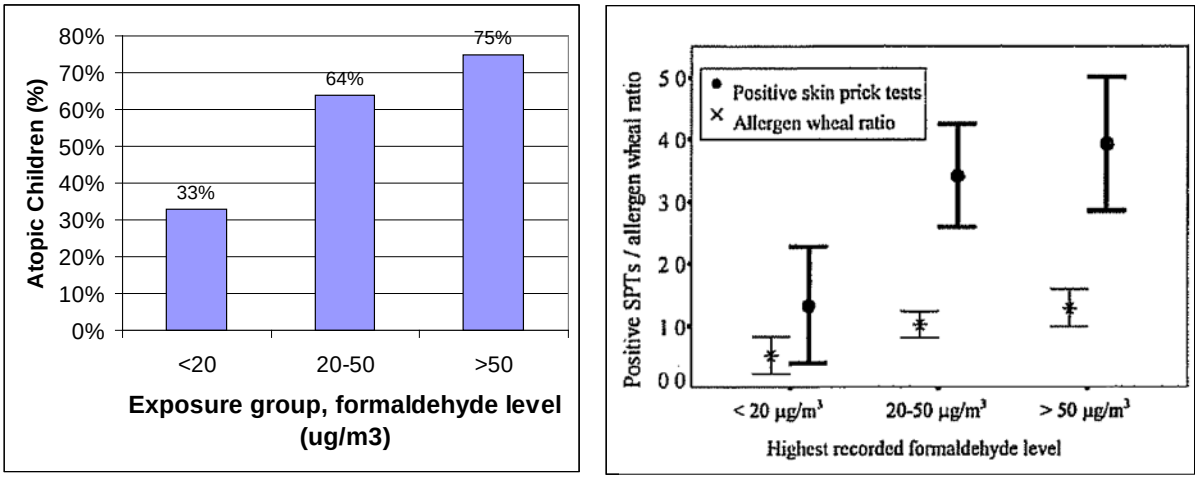


Figure 5-7. Prevalence and severity of allergic sensitization in children associated with in-home formaldehyde levels. Trend analysis indicates statistical significance in these increases {percent atopic children (p = 0.002), positive skin prick tests (p = 0.001) and severity as allergen wheal ratio (p = 0.004)}.

Note: Skin prick tests included 12 environmental allergens (cat, dog, grass [two types], house dust, dust mite [two strains] and fungi [five strains]).
Source: Garrett et al. (1999a) ; Garrett et al., 1999b (errata).

95% CI: 0.98–2.00). An UF of 3 adjusts the LOAEL to a similar range and is consistent with this alternative presentation of the data.

Subchronic to chronic UF = 1: The study addresses ongoing residential exposure to formaldehyde. Although information on the duration of exposure for each participant is not provided, the residential nature of the study suggests a longer term exposure than the duration of the study. It is judged that a population-based study of residential exposures is sufficient for derivation of a chronic RfC without adjusting for a subchronic observation period.

Human variability UF = 1 or 3: This study was designed to assess allergic sensitization, asthma prevalence and respiratory symptoms in children with relation to in-home formaldehyde levels. The recruitment of participants was designed to include households (50%) with asthmatic children, resulting in 43 households with at least one asthmatic child and 37 without asthmatic children for a total of 148 children (35% asthmatic). Parental allergy and asthma were also assessed and included as adjustment variables in the data evaluation. Therefore the study population includes individuals reflecting several key aspects of human variability for asthma and allergic sensitization (age, familial history of disease), and addresses the links between allergic sensitization and asthma. Both asthma and allergic sensitization are risk factors for increased respiratory symptoms.

The two alternatives are described below and cRfCs derived for each alternative

Alternative A: Garrett et al. (1999)

Human variability UF = 3: It is unclear whether the effect levels in the study truly reflect the effect levels in sensitive populations, since study findings controlled for both asthma and family history. Therefore, a value of three was used for the human variability UF.

$$RfC = \frac{LOAEL}{(UF_A \times UF_L \times UF_S \times UF_H)} = \frac{28\ ppb}{(1 \times 3 \times 1 \times 3)} = 2.8\ ppb$$

UF_A = 1 (interspecies UF)
UF_L = 3 (LOAEL-to-NOAEL UF)
UF_S = 1 (subchronic-to-chronic UF)
UF_H = 3 (human variability UF)

Alternative B: Garrett et al. (1999)

Human variability UF = 1:

Individuals with a family history of asthma and/or genetic markers for genes are believed to be predisposed to asthma and this would define a susceptible population within children. In this study parental disease status is a marker for potential genetic susceptibility. Although exposure-response relationships are not provided for individuals with a familial history of disease, analyses provided suggest the results reflect responses from these individuals. Among children with parental allergy, allergic children were exposed to higher formaldehyde levels than non-allergic children (p = 0.02), relating higher formaldehyde exposure to sensitization even among those with a likely genetic susceptibility. As shown in Figure 5-8, formaldehyde levels are related to increased asthma incidence with a significant linear trend (p = 0.02), yet this relationship loses significance when controlling for parental allergy and asthma, suggesting the measured response on which the POD is based is driven by children with a potential for genetic susceptibility.

An EPA Technical Report of the RfD and RfC Processes (US EPA, 2002a) indicates that a UF_H of 1 can be applied in cases where data are "very specific about the particular vulnerability of infants and children within certain age ranges to an agent." Asthma and allergic sensitization to common allergens develop during childhood and young adulthood. Therefore no additional adjustment is applied for human variability. The technical report acknowledges that "even within these populations it is possible that some variability still exists", but that a UF_H of 1 is still applied.

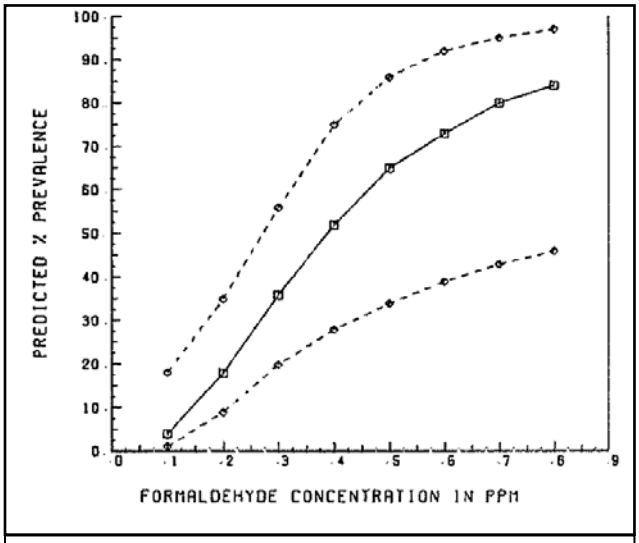
$$RfC = \frac{LOAEL}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{28\ ppb}{\left(1 \times 3 \times 1 \times 1\right)} = 9.3\ ppb$$

UF_A = 1 (interspecies UF)
UF_L = 3 (LOAEL-to-NOAEL UF)
UF_S = 1 (subchronic-to-chronic UF)
UF_H = 1 (human variability UF)

5.1.2.2.4. ***Candidate RfC derivation for Ritchie and Lehnen, 1987; Hanrahan et al., 1984 and Liu et al., 1991 (Sensory irritation).***

There are three studies that report sensory irritation in humans from chronic exposures in a residential environment and provide sufficient exposure data to support quantitative assessment (Liu et al., 1991; Ritchie and Lehnen, 1987; Hanrahan et al., 1984). Each study reports site-specific exposure measurements and presents some metric of individual exposure. These residential studies employ in-home measurements for each study participant, either as average exposure level (Ritchie and Lehnen, 1987; Hanrahan et al., 1984) or as calculated cumulative exposure based on the time in the home (Liu et al., 1991). Eye irritation is reported at similar levels of residential formaldehyde exposure in the three studies (see Figures 5-8 and 5-9). Each

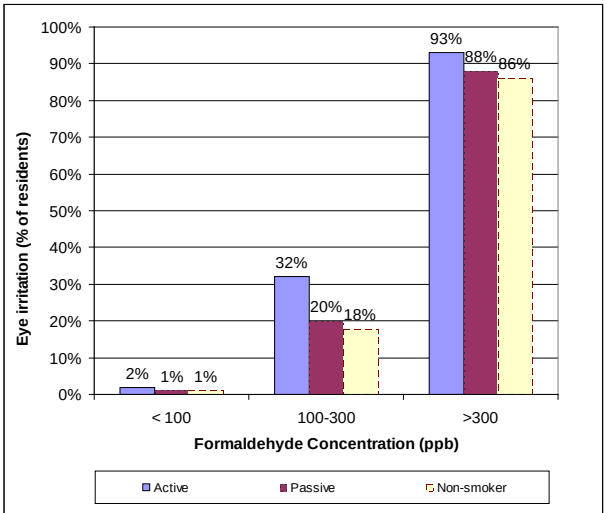
study provides an exposure-response relationship for prevalence of sensory irritation in relation to in-home formaldehyde exposure based on individual level data.



Panel A: Regression of prevalence of eye irritation versus indoor formaldehyde concentration (ppm) in mobile homes (30–60 minute air sample in each home).

Note: Dashed lines show upper and lower 95th percentile confidence intervals on model results. Model based on reported eye irritation from individuals in 42 mobile homes.

Source: Hanrahan et al. (1984).



Panel B: Prevalence of eye irritation in groups defined by in-home formaldehyde exposure (30–60 minute air sample in each mobile home).

Note: Eye irritation rate is given by smoking status: active smokers (n = 143), passive exposure to smoke (n = 133) and nonsmokers (n = 180).

Data source: Ritchie and Lehnen (1987).

Figure 5-8. Positive exposure-response relationships reported for in-home formaldehyde exposures and sensory irritation (eye irritation).

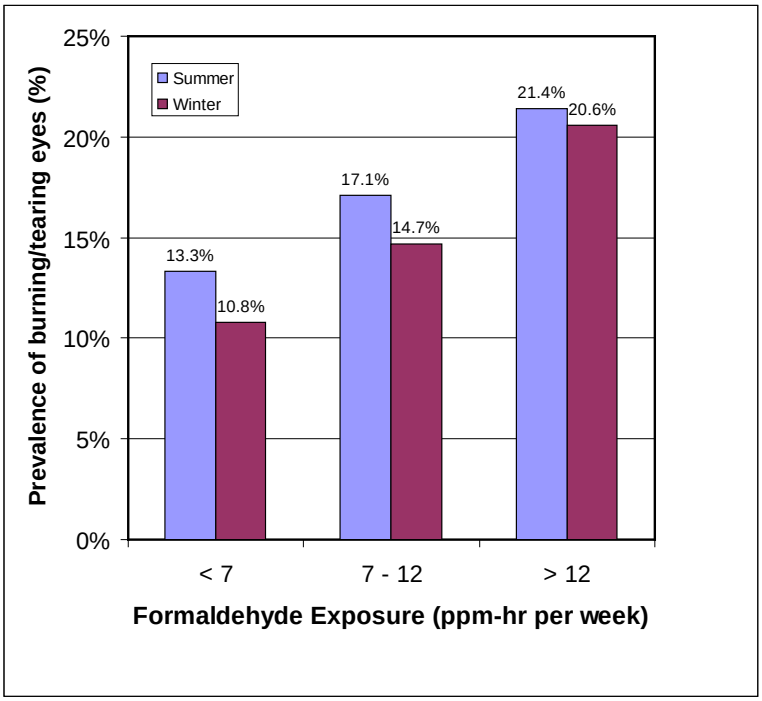


Figure 5-9. Positive exposure-response relationships reported for in-home formaldehyde exposures and sensory irritation (burning eyes).

Note: Cumulative formaldehyde exposure was estimated for each participant from measured in-home formaldehyde levels (7-day passive air sample) and reported hours spent in the home. Prevalence rates are given for both summer (*n* = 1,388) and winter (*n* = 1,093) survey periods.
Data source: Liu et al. (1991).

Ritchie and Lehnen (1987) examined formaldehyde-associated effects on eye, nose, and throat irritation in a large residential study with 2,007 participants from 841 homes. Based on in-home measurements of formaldehyde concentration, participants were categorized into three exposure groups: low (<100 ppb), mid (100–300 ppb) and high (>300 ppb) (average of two 30−60 minute air samples per home). Ritchie and Lehnen (1987) observed clear exposure-response relationships in the percentage of residential occupants reporting eye, nose, and throat irritation. For example, in nonsmoking mobile home residents, incidence scores for eye irritation were 1,–18% and 86%, and for nose/throat irritation were 5–17% and 78%, respectively, for the three exposure groups. The exposure-response relationships were similar regardless of type of home, mobile (*n* = 851) or conventional (*n* = 1,156). Although smoking status was also a predictor of irritation, in-home formaldehyde concentrations were a stronger predictor of health

effects. The study included children and the elderly and results were consistent across age groups. Children <7 years of age were only included in the eye irritation analyses because of concerns about the quality of parental reporting for nose and throat effects in young children. The selection criteria for participants indicate that more sensitive individuals may have been over-represented in the study population.[7] All study participants were self-selected, with a physician's approval, perhaps resulting in a higher proportion of individuals experiencing various irritant and upper respiratory tract symptoms, which may represent a sensitive population for eye, nose, or throat irritation.

Hanrahan et al. (1984) reported an exposure-response relationship for burning eyes and eye irritation in a study of 61 teenage and adult residents of mobile homes. As in the Ritchie and Lehnen (1987) study, in-home formaldehyde measurements were obtained for all participants and measured formaldehyde levels were used to characterize average in-home exposures (30−60 minute air sample). Eye irritation was associated with in-home formaldehyde exposures ($p < 0.05$) (both as "burning eyes" and "eye irritation"), and the authors provided a graphical representation of the best-fitting regression model for exposures between 100 and 800 ppb. From inspection of this graph, the prevalence of eye irritation predicted at 100 ppb is approximately 4% with an upper bound of 18% (95th percentile CI) (see Figure 5-8, Panel A). Because the limit of detection for formaldehyde in indoor air was 100 ppb, data or model results are not provided below 100 ppb.

The third residential study is a random-sample study of over 1,000 mobile home residents (1,394 in the summer; 1,096 in the winter) that included both young children and the elderly (Liu et al., 1991). Cumulative weekly exposures were based on in-home formaldehyde sampling and a participant survey of time spent at home. Air sampling was conducted for a 7-day period using a passive sampler in each home (summer and winter). The resulting estimates of cumulative exposure assumed no formaldehyde exposure outside of the home. Cumulative formaldehyde exposure was a significant predictor of numerous irritant symptoms in a multivariate linear logistic regression, including "burning eyes" ($p < 0.05$). The prevalence of eye irritation increased with increasing cumulative exposure in a categorical analysis of participants 20−64 years old for both summer and winter exposure estimates (see Figure 5-9). Eye irritation was above 10% in the lowest exposure group (0–7.0 ppm-hours/week) and increased to 17.1% and 21.4 % in the mid- and high-exposure group, respectively, for the summer survey time;

[7] Participants in this study were self-selected residents who were concerned about possible formaldehyde exposure and had obtained a written request from a physician to have the Minnesota Department of Health test their homes as part of a free program; thus, people with symptoms may be overrepresented in this study compared with the general population. This potential overrepresentation does not necessarily imply a selection bias because it is unlikely that it was associated with the measured formaldehyde exposure levels in participants' homes.

winter rates were slightly lower but showed a similar increase with increasing cumulative exposure.

Taken together, these three studies report increased eye irritation from residential exposures that are below the BMCLs calculated from acute exposures in the laboratory. Each study has the strength of having individual in-home exposure measurements and demonstrates a positive exposure-response relationship for sensory irritation within a range of residential formaldehyde exposures (both conventional and mobile homes). Potentially confounding factors (such as allergens and some other in-home exposures) have been taken into account and statistical analyses of the data include relevant covariates (e.g., age, sex, smoking status). As such, these studies provide a basis for development of a cRfC for sensory irritation. Additionally, the study populations have been drawn from the general population, including children and the elderly, and have not been limited to those healthy enough for full-time employment (as is often the case in occupational cohorts).

All three studies support a finding of increased eye irritation for exposures above 100 ppb (see Figures 5-8 and 5-9). However, the shape of the exposure-response curve below 100 ppb, or an indication of a no-effect level, is less clear. Two of the studies indicate 1–4% eye irritation in residents where formaldehyde exposures were measured at 100 ppb or less (Ritchie and Lehnen, 1987; Hanrahan et al., 1984). Thus, there is uncertainty in considering 100 ppb as a no-effect level for increased eye irritation for these studies. When modeled, the 95% CIs around the point estimate of 4% eye irritation were 1–18% eye irritation, illustrating the range of response rates at 100 ppb that are consistent with the observed data (Hanrahan et al., 1984). Additionally, the presentation of results by exposure category in Ritchie and Lehnen (1987) is inexact and has individuals with exposures at the low end of the categorical range being grouped with those at higher exposures in the range, obscuring any exposure-response relationship within the categorical range. For these reasons, a POD for RfC derivation from either of these studies should reflect these uncertainties. Therefore, for the NOAEL representing the category of individuals with ≤100 ppb, in which 1–2 % eye irritation was observed, the upper end of this exposure category is not used, but rather the midpoint, 50 ppb (Ritchie and Lehnen, 1987). Although Hanrahan et al. (1984) provided no model results below 100 ppb, an extrapolation of

the graphical results (see Figure 5-8, Panel A) provides an estimated $BMCL_{10}$ of 70 ppb[8]. No additional duration adjustments were made from the in-home exposure measurements to continuous exposure because neither time away from the home, nor potential exposures outside of the home, were characterized in either study.

Of the three studies, only Liu et al. (1991) provides exposure measurements below 100 ppb, with a reported detection limit of 10 ppb formaldehyde for the in-home air monitoring. Additionally, air samples were collected using a 7-day passive sampler which is more representative of average residential exposures than a one-time, 30–60 minute, air sample. Therefore, the data collected by Liu et al. (1991) are more suited to understanding the exposure-response relationship for eye irritation of exposures below 100 ppb. In addition to controlling for age, gender, and smoking status, Liu et al. (1991) controlled for the presence of chronic respiratory disease when assessing the effects of formaldehyde on symptoms of sensory irritation. Finally, this study provides results for both summer and winter survey periods, addressing seasonal variation in both formaldehyde levels and sensory irritation. The use of the cumulative exposure metric considers not only the concentration of formaldehyde but also the number of hours during the week each participant spent in their residence. Linear logistic regression indicates that cumulative formaldehyde exposure was a statistically significant predictor of burning eyes for both winter and summer survey periods. However, no BMCL can be calculated because no regression coefficients were provided in the report. Data were provided for the categorical analysis illustrating a positive exposure-response relationship (redrawn in Figure 5-9). Based on the categorical results, the midexposure group (7−12 ppm-hours/week) demonstrated an increased response compared with the low-exposed group. Since the prevalence rate in the low-exposed group was above 10% for burning eyes, this exposure group does not represent a NOAEL, but rather serves as a referent for the midexposure group. Therefore, the POD is derived from the midpoint of 7−12 ppm-hours/week, 9.5 ppm-hours/week. Using a conversion factor applied by the authors, the cumulative exposure of this midexposure group

[8] Figure 1 of Hanrahan et al. (1984) shows predicted values and 95% confidence intervals (CIs) for the percent prevalence of a burning-eyes response for formaldehyde concentrations ≥100 ppb (See Panel A in Figure 5-9 above). A short extension of the upper 95% CI to the concentration associated with 13% prevalence (i.e., a 10% increased prevalence above an assumed background response rate of 3%; this assumed background rate was chosen to be conservatively high to err on the side of not underestimating the actual value, given that the value was approximated from a visual extension of the upper 95% CI curve) suggests a BMCL of approximately 70 ppb for 10% increased prevalence. The actual value is unknown but is clearly below 100 ppb, which is the minimum exposure concentration depicted in the figure.

corresponds to a continuous home exposure of 70–120 ppb for an individual who spends 60% of the week in the home, with a midpoint of 95 ppb.

Candidate RfC derivation for sensory irritation:

Critical effect: Prevalence of sensory irritation (eye irritation, burning eyes).

Point of departure: Each of the studies discussed above has different strengths and weaknesses for the determination of a POD for sensory irritation. Nevertheless, the effect levels and PODs derived from each study are in relatively close agreement with less than a twofold span from lowest to highest. Therefore each POD is carried through to calculate a cRfC:

NOAEL = 50 ppb (Ritchie and Lehnen, 1987)
$BMCL_{10}$ = 70 ppb (Hanrahan et al., 1984)
LOAEL = 95 ppb (Liu et al., 1991)

Application of Uncertainty Factors (UFs)

Interspecies UF = 1: No interspecies adjustment is needed as this is a human study.

LOAEL-to-NOAEL UF: An uncertainty factor of 1 is applied to the NOAEL and $BMCL_{10}$ established as PODs from Ritchie and Lehnen, (1987) Hanrahan et al. (1984) studies. An uncertainty factor of three is applied to the LOAEL of 95 ppb based on the Liu et al. (1991) study, as the prevalence rates for this exposure level are below 20% for an effect that is of relatively low severity. In addition, the LOAEL is not significantly above the NOAEL and $BMCL_{10}$ from the other studies that evaluated the same endpoint.

Subchronic to chronic UF = 1: These studies address ongoing residential exposure to formaldehyde. Although information on the duration of exposure for each participant is not provided, the residential nature of the study suggests a longer term exposure than the duration of the study. It is judged that a population-based study of residential exposures is sufficient for derivation of a chronic RfC without adjusting for a subchronic observation period.

Human variability UF = 1 or 3: All three studies were population-based and included children, the elderly and both sexes. Sample sizes for two of the studies were

very large (1,394 for Liu et al. [1991]; 2,007 for Ritchie and Lehnen [1987]), increasing the likelihood that sensitive populations were included. Analysis of the data controlled for sex, smoking status, and age group.

The two alternatives are described below and cRfCs derived for each alternative

Alternative A

Sensory irritation studies:

Human variability UF = 3: For all studies, the analysis was based on prevalence rates, decreasing the likelihood that effects on sensitive individuals would be lost due to response averaging. For Ritchie and Lehnen (1987), the prevalence rate in the <100 ppb exposure group (represented by a NOAEL of 50 ppb, the midpoint) was 1−4%. For Hanrahan et al. (1984), the POD is a BMCL corresponding to a 10% response rate. Given these prevalence rates and the fact that the sensory irritation effects assessed are considered minimally adverse, a human variability UF of 3 was considered adequate for this endpoint.

Ritchie and Lehnen (1987):

$$RfC = \frac{NOAEL}{(UF_A \times UF_L \times UF_S \times UF_H)} = \frac{50\ ppb}{(1 \times 1 \times 1 \times 3)} = 17\ ppb$$

Hanrahan et al. (1984):

$$RfC = \frac{BMCL_{10}}{(UF_A \times UF_L \times UF_S \times UF_H)} = \frac{70\ ppb}{(1 \times 1 \times 1 \times 3)} = 23\ ppb$$

Liu et al. (1991):

$$RfC = \frac{LOAEL}{(UF_A \times UF_L \times UF_S \times UF_H)} = \frac{95\ ppb}{(1 \times 3 \times 1 \times 3)} = 9.5\ ppb$$

Alternative B

Sensory irritation studies

Human variability UF = 1: Two studies included a broad age range allowing some assessment of human variability due to life stage. Ritchie and Lehnen (1987) evaluated the influence of age on sensory irritation in the following age groups <1year, 2–6 years, 7–14 years, 15–20 years, 21–54 years, 55–64 years, and ≥65 years. An age effect for eye irritation was not evident in these data and pooled data are presented for this endpoint. Liu et al. (1991) report that greater eye irritation was reported in participants of 20–64 years than in those younger than 20 or older than 65 years. The elderly population (≥65 years) was well-represented in this study (39% of participants in the summer and 34% in the winter). The modeled results on which the $BMCL_{10}$ is based for Hanrahan et al. (1984) are normalized to 48 years of age (the mean age of respondents), which is consistent with the age group considered the most responsive in the Liu et al. (1999) study. Therefore the PODs derived from these studies do account somewhat for human variability across the life stage.

The critical effects of sensory irritation (eye, nose, and throat irritation) are considered minimally adverse health effects. The nominal response rates for eye irritation of 1−4% for in-home exposures below 100 ppb from which the PODs were derived suggest that the PODs are below significant response levels. Additionally, as the data are reported as prevalence rates, there is no masking of effect from sensitive individuals (as may occur when benchmark responses are average values of biometric parameters).

Finally, sensory irritation is a POE effect. Therefore, sources of human variability such as absorption, distribution, and metabolism of a compound are unlikely to influence incidence rates for this endpoint. There may be human variability in the sensitivity of the trigeminal nerve to formaldehyde binding and stimulation.

Taken together, these studies address many potential sources of human variability. Therefore, it is judged that further adjustment to address human variability is not warranted for the minimally adverse health effect of sensory irritation. Thus a UF_H of 1 is applied to all three studies. It is acknowledged that there is the potential for sources of variability not captured in these studies.

Ritchie and Lehnen (1987):

$$RfC = \frac{NOAEL}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{50\ ppb}{\left(1 \times 1 \times 1 \times 1\right)} = 50\ ppb$$

Hanrahan et al. (1984):

$$RfC = \frac{BMCL_{10}}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{70\ ppb}{\left(1 \times 1 \times 1 \times 1\right)} = 70\ ppb$$

Liu et al (1991):

$$RfC = \frac{LOAEL}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{95\ ppb}{\left(1 \times 3 \times 1 \times 1\right)} = 32\ ppb$$

5.1.2.2.5. ***Candidate RfC derivation for Taskinen et al. (1999) (Fecundity density ratio).***

On review of the candidate developmental and reproductive toxicity studies in humans and animals (presented in Section 5.1.3.2.7), the Taskinen et al. (1999) epidemiology study was considered to be the strongest for the purpose of deriving a chronic RfC. This study was a well-designed population-based case-control study of women who were occupationally exposed to formaldehyde. The study population was well defined and adequately selected to allow for meaningful comparisons of health effects among individuals with different levels of exposure to formaldehyde. Potential selection bias and the self-reporting of spontaneous abortion are not considered to have had a significant influence on the study findings. Additionally, the decreased FDR and increased risk of spontaneous abortion observed in Taskinen et al. (1999) are internally consistent and coherent with other reports of increased risk of pregnancy loss associated with exposure to formaldehyde (John et al., 1994; Taskinen et al., 1994; Seitz and Baron, 1990; Axelsson et al., 1984) and is supported by animal data (Kitaev et al., 1984; Sheveleva, 1971).

The Taskinen et al. (1999) study allows the consideration of three potential critical effects: endometriosis, increased spontaneous abortion, and decreased fecundity density ratio (FDR). However, there is little independent support for the finding of increased risk of endometriosis and the ORs for organic solvent exposure within this study (OR = 14.7; 95% CI: 3.1–70) were much greater than for formaldehyde (OR = 4.5, 95% CI: 1.0–20), indicating a reasonable potential for confounding of the formaldehyde association. The finding of increased risk of spontaneous abortions is supported by independent findings in other formaldehyde-exposed cohorts (John et al., 1994; Taskinen et al., 1994; Seitz and Baron, 1990; Axelsson et al., 1984). As this study was designed to examine the effect of workplace formaldehyde exposures on FDR, the study design and data collection best support this finding. The exposure estimates were assessed to represent what the researchers considered the relevant exposures for evaluating risk factors that might influence time-to-pregnancy. Although data on miscarriages were collected to control the time-to-pregnancy findings for potential confounding from formaldehyde-related spontaneous abortions, it is less certain that the exposure measurements coincide with the defined spontaneous abortion cases. Spontaneous abortions were only included in calculations of exposure-specific ORs if a participant indicated that she was employed at the same location when she had the spontaneous abortion and when the time-to-pregnancy exposure assessment was done. The analysis showed that there were statistically significantly increased risks of spontaneous abortion in the lowest exposure group. While this finding was consistent with other studies showing adverse reproductive effects of formaldehyde and appears to be causal, the Taskinen et al. (1999) spontaneous abortion results did not clearly control for all the potential confounders that were controlled for in the FDR analyses (i.e.,

organic solvents and phenols). While the other coexposures were not associated with FDR and therefore not confounders, endometriosis was strongly associated with organic solvents. Therefore, for these endpoints, the study design and strength of results best support the use of decreased FDR in formaldehyde-exposed women as the critical effect for this study.

It is preferable that the critical effect for a specific study be the most sensitive of the effects which is well supported by the study. As spontaneous abortions are significantly increased in the low-exposure group and the response in the midexposure group is considered a no-effect level for decreased FDR, there is uncertainty that an RfC based on the FDR NOAEL would be protective for the more sensitive effect. Although the finding of increased risk of spontaneous abortion is qualitatively convincing, there is more uncertainty in the applicability of the exposure assessment for quantitative risk assessment. Additionally, there is greater uncertainty in the use of the exposure adjustments for the low-exposure group on which the LOAEL for spontaneous abortion is based because the exposure adjustments account for more of the work time in the low-exposure group than the medium and high exposure groups (see Table 5-5).

There are several sources of uncertainty in the exposure estimates for use in RfC derivation. As discussed above, the average exposure estimate for the low exposure group includes a greater proportion of nonassessed background exposures. This is evidenced in part by the reported average exposure being below background levels for these workers, even with exposure measurements as high as 300 ppb. The unaccounted for nontask exposures may represent time during the day spent in the work facility, or time in a different job or work environment. Additionally, task-level exposure measurements were available for only 27% of women in the low exposure group, versus 38% and 69% of women in the medium and high exposure groups, indicating less certainty in exposure classification for the low exposure group.

Duration adjustment for candidate study points of departure. Normally, exposures from occupational studies are adjusted to account for the daily breathing volume appropriate to an environmental (versus occupational) setting and for exposure every day of the year (U.S. EPA, 1993). However, with formaldehyde, there is potential for exposure outside of work from in-home and environmental sources of formaldehyde (Chapter 2). A contemporaneous study of formaldehyde exposures in Finland reports average exposure of 21.4 ppb (measured over 48 hours with a personal monitor) (Jurvelin et al., 2001). Furthermore, both the mean exposure (18 ppb 8hr TWA) and lowest reported exposure (10 ppb 8hr TWA) of the 'low exposed' category are below the reported average ambient exposures for Finland (21.4 ppb). Thus, it is

Table 5-5. Adjustment for nonoccupational exposures to formaldehyde.

Panel A: Proportion of workshift corresponding to the exposure group mean task-level formaldehyde exposure (ppb) and the exposure group daily exposure index (8 hour-TWA).

Exposure group (*n*)	Reported mean exposure (ppb, 8 hr-TWA)		Measured task-level exposures (ppb)		Estimate of time during workday for formaldehyde related tasks assuming mean exposure levels.	
	Mean	Range	Mean	Range	% of worktime[a]	Hours per 8 Hr workshift
Low (119)	18	1–39	70	10–300	26%	2
Medium (77)	76	40–129	140	50–400	54%	4.3
High (39)	219	130–630	330	150–1,000	66%	5.3

[a]Calculated as mean exposure (ppb 8 hour-TWA) divided by mean task-level exposures for the exposure group.

Panel B: Recalculation of daily exposure index (8 hour-TWA) where background formaldehyde exposure is estimated for worktime spent on tasks considered unrelated to occupational use of formaldehyde.

Exposure group (*n*)	Estimate of formaldehyde exposure during formaldehyde-related work tasks		Estimate of formaldehyde exposure from background levels during the workshift		Alternative daily exposure index (ppb, 8 Hr-TWA)
	Mean task level exposure (ppb)	% of worktime in formaldehyde task	Background formaldehyde (ppb)	% of time in nonformaldehyde-related task	
Low (119)	70	26%	21.4	74%	34
Medium (77)	140	54%	21.4	46%	86
High (39)	330	66%	21.4	34%	226

likely that exposure estimates for study participants include time during the workday when women reported no formaldehyde exposure and a zero exposure was assessed for a nonformaldehyde related task. Additionally, participants may have qualified for the study based on employment date but may not have been working with formaldehyde during the entire time-to-pregnancy period. In both cases, the investigators in Taskinen et al. (1999) appear to have

assumed that, while the women were away from their "exposed" workplace, their exposure to formaldehyde was zero, not accounting for background occupational exposures and ambient levels of formaldehyde. This explains why both the mean exposure as well as lower end of workshift exposures for women in the low exposure group were reported at and below expected ambient levels. The women in the low exposure category had task-level workplace exposures of up to 300 ppb in addition to experiencing some work time at background exposure levels. Compared to women who only experienced background exposure levels, those in the low exposure category were at significantly higher risk of spontaneous abortion.

The reported data do not provide information to correct for background formaldehyde exposure during the workday for each participant. However, the published mean exposure values may be used to provide some idea of the impact of including background exposures on the study PODs. Comparison of the values listed in Table 4 of Taskinen et al. (1999) allows for the estimation of the percentage of work time spent performing tasks involving formaldehyde exposure (see Table 5-5, Panel A). For the women in the low exposure category, this percentage is 26% (mean of measured workplace exposures of 70 ppb times 26% equals the mean of the TWA exposure of 18 ppb). Using the same method, the women in the "medium" and "high" exposure category were performing tasks involving formaldehyde exposure approximately 54% and 66% of their work time, respectively. Assuming that the women spent the remainder of their work time at the background concentration of 21.4 ppb (Jurvelin et al., 2001), a more appropriate estimate of the women's 8-hour TWA formaldehyde exposures would be 34 ppb for the low category, 86 ppb for the medium category, and 226 ppb for the high category (see Table 5-5, Panel B).

Candidate RfC derivation for Taskinen et al. (1999):

Critical effect: Decreased FDR.

Point of departure: For decreased FDR, the midexposure level is considered a NOAEL. The mean exposure as an 8-hour TWA for the workday is reported as 76 ppb. EPA has adjusted this POD to account for potential background formaldehyde exposures during the workshift (see Table 5-5) resulting in an adjusted POD of 86 ppb. No further duration adjustment is made to this POD to account for background levels of formaldehyde exposure outside of the workplace.

Application of study-specific Uncertainty Factors (UFs):

Interspecies UF = 1: No interspecies adjustment is needed as this is a human study.

LOAEL-to-NOAEL UF = 1: Selection of an NOAEL as the POD.

Subchronic to chronic UF = 1: The study design represents a study population with a range of exposure durations, including chronic exposures. By drawing the study population from full-time employees and members of the wood-working union, there is an expectation that the study population reflects the demographic of that group as a whole. Although specific summary information is not published for this study group (e.g., average length of employment), the lack of this reporting in itself does not seem to justify an UF for subchronic-to-chronic exposure given the overall study design. As a study adequate for assessing reproductive effects in a chronically exposed cohort, no further adjustment was considered needed.

Human variability UF = 10: The study population included women employed in the wood-working industry who were healthy enough to be gainfully employed. Additionally, study inclusion criteria ensured that all study participants had at least one pregnancy resulting in a live birth during the study period (1985–1995). Therefore, these women were reproductively successful. The authors judged that selective participation did not influence potential confounders such as irregular menstruation or earlier miscarriages, which could impact the time to pregnancy results. Susceptible populations were not addressed and, in fact, the women in the study may be considered healthier than the general population in terms of reproductive health. Therefore, an uncertainty factor of 10 for human variability was applied.

$$RfC = \frac{NOAEL}{\left(UF_A \times UF_L \times UF_S \times UF_H\right)} = \frac{86\ ppb}{\left(1 \times 1 \times 1 \times 10\right)} = 8.6\ ppb \qquad (5\text{-}2)$$

UF_A = 1 (interspecies UF)

UF_L = 1 (LOAEL-to-NOAEL UF)

UF_S = 1 (subchronic to chronic UF)

UF_H = 10 (human variability UF)

5.1.2.3. *Evaluation of the Study-Specific Candidate RfCs*

Seven studies were selected as key studies for consideration in RfC derivation (see Section 5.1.2, Table 5-4). Candidate RfCs from these studies address various health effects including: sensory irritation, respiratory effects, asthma, increased allergic sensitization, and decreased fecundity (see Table 5-6).

Three of the seven studies address sensory irritation of the eye, nose, and throat (Liu et al., 1991; Ritchie and Lehnen, 1987; Hanrahan et al., 1984). The PODs for sensory irritation range from 50 to 95 ppb for a health effect that is considered minimally adverse. Two alternatives are presented for the human variability uncertainty factor in RfC derivation based on these SI studies. Alternative A ($UF_H = 3$) results in cRfCs from 9.5 to 23 ppb. Alternative B ($UF_H = 1$) results in cRfCs from 32 to 70 ppb.

A cRfC of 9 ppb is derived for decreased FDR in an occupational study of women in the wood-working industry (Taskinen et al., 1999). This endpoint is supported by four other epidemiologic studies and is considered a potential health concern for occupationally exposed women (John et al., 1994; Taskinen et al., 1994; Seitz and Baron, 1990; Axelsson et al., 1984). However, there is some uncertainty regarding the influence of peak exposures in the work place on the apparent exposure-response relationship based on average workday exposures calculated for study participants. It is unknown if the observed decreased FDR can be attributed to the average exposures from which the cRfC is derived or if it is a result of the measured exposures (as high as 1,000 ppb). If this were the case the cRfC of 9 ppb, based on the average time-weighted exposures, would be protective for decreased fecundity.

Three studies identify adverse health effects in residential populations including children: increased incidence of asthma, decreased pulmonary function, increase in respiratory symptoms, and increased allergic sensitization (Rumchev et al., 2002; Garrett et al., 1999 a,b; Krzyzanowski et al., 1999). Asthma, allergic sensitization, pulmonary function, and symptoms of respiratory disease are not only clinically related, but etiologically related, and it is reasonable that they are considered together from a public health perspective. These health effects are observed below the exposure levels that result in sensory irritation and the resulting cRfCs are correspondingly lower, in a range between 2.8 and 11 ppb, depending on the study, endpoint considered, and the application of alternative uncertainty factors for human variability (see Table 5-6).

These three studies of related health effects: asthma, allergic sensitization, pulmonary function, and symptoms of respiratory disease in children from in-home exposure to formaldehyde (Rumchev et al., 2002; Garrett et al., 1999 a,b; Krzyzanowski et al., 1999) were chosen as the basis for the derivation of the RfC. These cocritical studies are mutually

Table 5-6. Summary of reference concentration (RfC) derivation from critical study and supporting studies

Endpoint	Study	Study size	Homes	Children	POD (ppb)	Application of study-specific UF			cRfC (ppb)
						UF_L	UF_S	UF_H	
Respiratory effects/asthma and sensitization									
Reduction of PEFR in children (10%)	Krzyzanowski et al. (1990)	208	Yes	Yes	$BMCL_{10}$ = 17	1	1	3	**5.6**
Asthma incidence	Rumchev et al. (2002)	192	Yes	Yes	NOAEL = 33	1	3	**Alternative A**	
								3	**3.3**
								Alternative B	
								1	**11**
Increased asthma; allergic sensitization	Garrett et al. (1999 a,b)	148	Yes	Yes	LOAEL = 28	3	1	**Alternative A**	
								3	**2.8**
								Alternative B	
								1	**9.3**
Sensory Irritation									
Eye irritation, burning eyes	Ritchie and Lehnen (1987)	2,007	Yes	Yes	NOAEL = 50	1	1	**Alternative A**	
								3	**17**
								Alternative B	
								1	**50**
	Hanrahan et al. (1984)	61	Yes	Some teenagers	$BMCL_{10}$ = 70	1	1	**Alternative A**	
								3	**23**
								Alternative B	
								1	**70**

Table 5-6. Summary of reference concentration (RfC) derivation from critical study and supporting studies (continued)

Endpoint	Study	Study size	Homes	Children	POD (ppb)	Application of study-specific UF			cRfC (ppb)
						UF_L	UF_S	UF_H	
Eye irritation, burning eyes (continued)	Liu et al. (1991)	1,394	Yes	Yes	LOAEL = 95	3	1	**Alternative A**	
								3	**9.5**
								Alternative B	
								1	**32**
Reproductive/Developmental									
Decreased fecundability density ratio (FDR)	Taskinen et al., 1999	602	No	No	NOAEL= 86	1	1	10	**8.6**

Notes: 1: The final RfC will be rounded to one significant digit per EPA policy. Since the Candidate RfC is an interim calculation, two-significant digits are retained as common practice in mathematics {i.e., one significant digit more that the final result, to avoid rounding errors compounding across multiple mathematical manipulations}.

supportive and provide similar cRfCs. Therefore, the RfC is taken as the mean of the cRfCs of the cRfCs of the three cocritical studies. For two of these studies (Rumchev et al., 2002; Garrett et al., 1999 a,b), EPA is providing alternatives for the application of the UF addressing human variability. These alternatives result in a threefold difference in cRfCs for each study when considering the critical effects of childhood asthma and allergic sensitization (see Table 5-6). Alternative A, described above for each study, acknowledges that evaluation of these effects in children does address some aspects of human variability, but there remains the potential for additional interindividual variability within the studied population, thus a UF of 3 is warranted. Alternative B, described above for each study, also acknowledges that these studies address human variability and susceptible populations. However in alternative B it is judged that since children are a sensitive lifestage for these effects (asthma and atopy), and are likely the most sensitive population, an UF of 1 may be applied. It is acknowledged that some degree of interindividual variability may remain.

Alternative A: Application of a UF of 3 for human variability

Co-critical studies: Rumchev et al. (2002); Krzyzanowski et al. (1999); Garrett et al. (1999)

Critical endpoints: Asthma, allergic sensitization, pulmonary function, and symptoms of respiratory disease in children.

Candidate RfCs:
cRfC = 5.6 ppb—decreased PEFR (Krzyzanowski et al., 1999)
cRfC = 3.3 ppb—increased physician-diagnosed asthma (Rumchev et al., 2002)
cRfC = 2.8 ppb—increased asthma, atopy and respiratory symptoms (Garrett et al., 1999)

RfC: $$RfC = \frac{5.6\ ppb + 3.3\ ppb + 2.8\ ppb}{3} = \frac{11.7\ ppb}{3} = 4\ ppb$$

Alternative B: Application of a UF of 1 for human variability
(UF_H = 3 remains for Krzyzanowski et al., 1999)

Co-critical studies: Rumchev et al. (2002); Krzyzanowski et al. (1999); Garrett et al. (1999)

Critical endpoints: Asthma, allergic sensitization, pulmonary function, and symptoms of respiratory disease in children.

Candidate RfCs:
cRfC = 5.6 ppb—decreased PEFR (Krzyzanowski et al., 1999)
cRfC = 11 ppb—increased physician diagnosed asthma (Rumchev et al., 2002)
cRfC = 9.3 ppb—increased asthma, atopy and respiratory symptoms (Garrett et al., 1999)

RfC: $$RfC = \frac{5.6\ \text{ppb} + 11\ \text{ppb} + 9.3\ \text{ppb}}{3} = \frac{25.9\ \text{ppb}}{3} = 9\ \text{ppb}$$

5.1.3. Database Uncertainties in the RfC Derivation

The database of available laboratory animal studies, human clinical and epidemiological studies, and supporting mechanistic information for formaldehyde is substantial. Many of the health effects are well studied in animals and humans, especially those endpoints related to sensory irritation and respiratory effects at the POE, such as respiratory tract pathology, asthma and reduced pulmonary function. This is reflected in the number and high quality of human studies presented in Table 5-4 and supporting data summarized in Chapter 4.

The data also indicate effects in other health effect categories, specifically neurotoxic effects, reproductive toxicity, and developmental effects (see Section 5.1.2). These are areas where additional research are needed to reduce uncertainty and better characterize the potential for health effects and the concentrations at which they might occur in humans.

The existing toxicological study database strongly supports the potential for formaldehyde to cause both reproductive and developmental toxicity (see Chapter 4; Tables 4-69 and 4-72). There is, however, no assessment of these endpoints from a satisfactory two-generation toxicity study to fully evaluate the effect of formaldehyde exposure on reproductive and developmental endpoints. Data are adequate to derive a cRfC of 9 ppb for decreased fecundability density ratio (FDR) from a human occupational study (Taskinen et al., 1999). This study also reports an increase in spontaneous abortions, although there is uncertainty on the exposure levels of concern for this endpoint; spontaneous abortions may also contribute to the decreased FDR on which one of the cRfCs is based. The greatest uncertainty in

the cRfC for decreased FDR is the use of a time-weighted exposure metric which does not address possible contributions of peak exposure levels to the observed health effect. As such, it is possible that this cRfC is lower than is needed for protection against decreased FDR. The cRfC for decreased FDR does suggest that the RfC derived from the better studied respiratory effects would be protective of that reproductive/developmental endpoint, but there remain uncertainties as to the full range of potential reproductive and developmental effects. No data exist to sufficiently inform the exposure-response relationship for other reproductive and developmental endpoints as they relate to RfC derivation (see Section 5.1.2.6). For example, male reproductive effects and structural and behavioral developmental effects (including postnatal development) are not addressed by a study of decreased FDR. This is a database deficiency. A survey of the currently available data indicates observed effect levels of 5,000−10,000 ppb for male reproductive endpoints and 400 ppb and above for growth retardation and structural anomalies in animal studies. However, these studies employed only one treatment level, precluding the ability to establish a dose-response relationship, thus limiting the strength of the studies for use in RfC derivation.

Similarly, there is evidence that formaldehyde can cause neurotoxic effects. There is a deficit of studies with appropriate exposure scenarios to support derivation of an RfC reflecting the potential for observed neurotoxicity due to formaldehyde exposure. None of the available human studies that evaluated neurological effects were adequate for use in quantitative risk assessment, although they did identify neurological effects of concern, including changes in memory and concentration (e.g., Bach et al. [1990]; Kilburn et al. [1987, 1985]) and increased risk of mortality from amyotrophic lateral sclerosis (ALS) with increasing duration of exposure to formaldehyde (Weisskopf et al., 2009). The human and animal data indicate the potential for serious neurological and behavioral effects from short-term formaldehyde exposure (see Section 5.1.2.6). Limited studies in humans, as well as controlled studies in established animal models, confirm the neurotoxic effects of formaldehyde at exposure levels of 100–170 ppb (Malek et al., 2003a, c; Bach et al., 1990) (see Table 5-1). For example, an adverse effect level of 100 ppb for impaired learning is reported for short-term exposures (2 hours/day for 10 days) in rats (Malek et al., 2003a). For this effect, appropriate duration adjustment for extrapolation of a 2-hour repeated exposure over a limited number of days is uncertain. Given the nature of these health effects, and the potential for children to be exposed in the home to levels as high as 100 ppb (the level at which effects were seen in animals following a single exposure), this is a significant data gap. Studies are inadequate to determine whether exposure to levels of formaldehyde at or below those that impact children's respiratory health and sensitization will cause neurotoxicity in humans, including endpoints such as impaired learning and memory.

Approaches to the application of a database uncertainty factor:
Options EPA is considering include:

(1) Provide an RfC derived from studies of respiratory and allergenic responses and protective of sensory irritation effects with a database uncertainty factor of one given significant data on formaldehyde, but noting that further research reproductive, developmental and neurotoxic effects would be valuable.

(2) Provide an RfC with a database uncertainty factor of one, with this RfC explicitly identified as being protective of the well-studied effects.

(3) Apply a database UF of 3 to the RfC derived from studies of respiratory and allergenic responses to reflect the potential that reproductive, developmental, or neurotoxic effects might occur at lower doses:

(3) Provide both an RfC identified as protective of the better-studied effects and an RfC with a database uncertainty factor of 3 incorporated to account for limits to the data on reproductive, developmental and neurotoxic effects.

It is unclear what uncertainty factors are appropriate to account for human variability and deficiencies in the overall database. For this reason, several alternatives have been presented.

5.1.4. Uncertainties in the RfC Derivation

By design, the RfC is an estimate of an exposure level at which it is unlikely there would be deleterious effects to the human population (including sensitive subgroups) during a lifetime of exposure. Although the RfC is derived from the best available studies, there are a number of uncertainties that underlie the RfC. Some of these uncertainties are addressed quantitatively by applying UFs on a study-specific a basis for RfCs based on animal studies, less-than-chronic exposures, use of a LOAEL as the POD, and to address human variability for the relevant endpoint (see Section 5.1.3). This section elaborates on some of the sources of uncertainty in the final RfC.

As the RfC is derived from human studies, the majority in a residential setting, study aspects that are often a great source of uncertainty are of no concern (e.g., use of animal studies, study of a worker population). The uncertainties discussed below apply specifically to the database of formaldehyde studies and the process to derive the RfC.

5.1.4.1. *Point of Departure*

Most of the studies considered for RfC derivation did not provide enough data to support BMD modeling, which is generally the preferred approach for obtaining a POD for a given dataset (the preference for a POD based on BMD modeling does not, as a general rule, apply to comparisons across datasets). Rather, the PODs for most studies were LOAELs or NOAELs, which have a number of shortcomings relative to a POD obtained from BMD modeling (i.e., a BMCL or BMDL):

- LOAELs and NOAELs are a reflection of the particular exposure/dose levels used in a study, contributing some inaccuracy to the POD determination.
- LOAELs and NOAELs are often determined based on statistical significance and, thus, reflect the number of study subjects or test animals. Studies are typically dissimilar in detection ability and statistical power, with smaller studies tending to identify higher exposure levels as NOAELs compared with larger but otherwise similarly designed studies.
- Different LOAELs and NOAELs represent different response rates, so direct qualitative and quantitative comparisons are not possible.

PODs identified from BMD models overcome some of the deficiencies associated with LOAELs and NOAELs. Benchmark models were used for two inhalation data sets, Hanrahan et al. (1984) and Krzyzanowski et al. (1990).

It should also be noted, however, that even for BMCLs/BMDLs there is often uncertainty, in particular for continuous responses, about what response level to select as the BMR, i.e., where to define the cut-off point between a level of change that is not adverse and one that is adverse. In addition, BMD models currently in use are purely mathematical models and are not intended to accurately reflect the biology of the effect being modeled.

Another source of uncertainty in the POD is the adjustment for continuous exposure. RfCs are meant to apply to continuous (24 hour/day) exposures. Exposure patterns in human and laboratory animal inhalation studies are typically not continuous and assumptions must be made in converting reported exposure levels to equivalent continuous exposures. Similarly, there are uncertainties about potential dose rate effects, in particular the effect of peak exposures in occupational studies.

5.1.4.2. *Extrapolation from Laboratory Animal Data to Humans*

Because the inhalation database for formaldehyde contains many human studies for a variety of health effects, it was not necessary to rely on animal data for the endpoints from which

to derive the RfC. Thus, unlike for most RfCs, this is not a source of uncertainty in the RfC for formaldehyde.

5.1.4.3. *Human Variation*

Heterogeneity among humans is another uncertainty associated with extending results observed in a limited human study population or laboratory animal experiment to a larger, more diverse human population.

For three of the studies used to derive the RfC, a value of 3 was used for the human variability UF (rather than the default value of 10) because the studies had an apparent over-representation of populations expected to have increased susceptibility (see Section 5.5.3.1):

- The residential study by Ritchie and Lehnen (1987) evaluated eye, nose, and throat irritation in a large number of subjects, including children and the elderly. As a result of the study's participation criteria, individuals with greater sensitivity were potentially over-represented.
- Thirty percent of the subjects in the residential study by Krzyzanowski et al. (1990) were children who are more sensitive to formaldehyde-associated decreases in PEFR than adults. The cRfC determination for this study focused on the results in the children, among whom asthmatics were over-represented (roughly three times) compared with the national average of 9.4% in 2008 (Bloom et al., 2009).
- Garrett et al. (1999 a,b) conducted a cross-sectional survey of allergy and asthma-like symptoms in children with or without a doctor's diagnosis of asthma. The study was designed to include a high proportion of asthmatic children, a sensitive population for the effects being studied.

EPA notes, however, that, while a human variability UF of 3 rather than 10 was used to account for certain special attributes of these studies/effects, there is still uncertainty about how much of the overall population heterogeneity is actually reflected even in these relatively diverse residential studies.

5.1.4.4. *Subchronic-to-Chronic Extrapolation*

RfCs are intended to apply to chronic lifetime exposures. If a study is subchronic (typically less than 10% of a lifetime), a UF for subchronic-to-chronic extrapolation is generally applied to the cRfC for that study. For the key human residential and occupational studies used to derive the RfC in this assessment, the average durations of exposure in the households or workplaces under study are unknown. In this assessment, these studies were considered chronic in nature and no subchronic-to-chronic UF was applied. However, there is uncertainty about

whether or not the responses observed fully reflected the potential effects of chronic exposure, especially in children, where, for example, impacts on the developing respiratory and immune systems could be predisposing the children to further adverse effects later in life.

5.1.5. Previous Inhalation Assessment

There is no previous EPA RfC assessment for formaldehyde with which to compare and contrast the RfC developed in this assessment.

5.2. QUANTITATIVE CANCER ASSESSMENT BASED ON THE NATIONAL CANCER INSTITUTE COHORT STUDY

For quantitative assessment of cancer risk, it is generally preferable to use good-quality epidemiologic data, when available, over laboratory animal data. The follow-up studies by Hauptmann et al. (2004) and Beane Freeman et al. (2009) of the large National Cancer Institute (NCI) retrospective cohort mortality study of U.S. workers involved in the production or use of formaldehyde, with quantitative exposure estimates for the individual workers, present an opportunity to perform quantitative cancer risk assessments of nasopharyngeal cancer (NPC) and lymphohematopoietic cancers (Hodgkin lymphoma and leukemia) based on human data. Although other upper respiratory tract cancers were also identified as being causally associated with formaldehyde exposure in the weight-of-evidence analysis in Section 4.5, NPC was the only upper respiratory tract cancer with exposure-response data adequate for the derivation of unit risk estimates in the Hauptmann et al. (2004) follow-up study of solid tumors. Similarly, the weight-of evidence analysis in Section 4.5 concluded that there were causal relationships between formaldehyde exposure and all lymphohematopoietic cancers as a group, leukemias as a group and myeloid leukemia (see Section 4.1.2.2.1.4). Overall the epidemiologic evidence was considered supportive of a causal association between formaldehyde exposure and both Hodgkin lymphoma and multiple myeloma (see Section 4.1.2.2.1.4 and Section 4.5). However, from the Beane Freeman et al. (2009) follow-up study of lymphohematopoietic malignancies, only all leukemias combined and Hodgkin lymphoma were judged to have exposure-response data adequate for the derivation of unit risk estimates (see Section 5.2.3.1 below).

5.2.1. Choice of Epidemiology Study

Several follow-up studies of formaldehyde exposure in industrial workers with some exposure-response information have recently become available. These studies are discussed in more detail in chapter 4 and the appendix (Human Health) and are reviewed only briefly here. Hauptmann et al. (2004) and Beane Freeman et al. (2009) presented follow-ups of the NCI study (originally described by Blair et al. [1986]) of workers at 10 U.S. plants producing or using formaldehyde. Marsh et al. (2007, 2002) focused on pharyngeal cancer and, in particular, NPC mortality in sequential follow-up analyses of the Marsh et al. (1996) cohort study, which examined 1 of the 10 plants studied by NCI. Pinkerton et al. (2004) presented a follow-up of the National Institute for Occupational Safety and Health (NIOSH) study of workers exposed to formaldehyde in three U.S. garment plants (originally described by Stayner et al. [1988]). Coggon et al. (2003) presented an extended follow-up of a study of workers in six British factories where formaldehyde was produced or used (originally described by Acheson et al. [1984] and previously followed up by Gardner et al. [1993]). In addition, Hauptmann et al. (2009) recently conducted a case-control study of lymphohematopoietic and brain cancers, with exposure-response analyses, nested in the cohorts of "professional" workers (funeral industry workers, in this case) studied by Hayes et al. (1990) and Walrath and Fraumeni (1983, 1984).

The analyses presented here are based on the NPC (Hauptmann et al., 2004) and lymphohematopoietic cancer (Beane Freeman et al., 2009) results from the NCI follow-up studies. The NCI cohort study is the largest of the three independent industrial worker studies and is the only one with sufficient individual exposure data for exposure-response modeling. In addition, the NCI study is the only one of the three studies that used internal comparisons rather than standardized mortality ratios (SMRs), thus minimizing the impact of the healthy worker effect, which can attenuate observed effect estimates. The NCI cohort consists of 25,619 workers (88% male) employed in any of the 10 plants prior to 1966. A follow-up through 1994 presented exposure-response analyses for nine NPC deaths as well as analyses of deaths from other solid cancers based on 865,708 person-years of follow-up (Hauptmann et al., 2004). The most recent follow-up based on 998,106 person-years of observation (through 2004) analyzed 319 deaths attributed to lymphohematopoietic malignancy from a total of 13,951 deaths (Beane Freeman et al., 2009). The results for solid cancers from this recent follow-up had not yet been published at the time of this draft assessment. A detailed exposure assessment was conducted for each worker in the NCI cohort, based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986). Exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure. Respirator use and exposures to formaldehyde-containing particulates and other chemicals were

also considered. For the NPCs, significant trends were observed for the cumulative and peak exposure metrics (Hauptmann et al., 2004). For the lymphohematopoietic cancers, significant trends were observed primarily for all lymphohematopoietic cancers and for Hodgkin lymphoma with the peak exposure metric (Beane Freeman et al., 2009).

The NIOSH follow-up study (Pinkerton et al., 2004) analyzed mortality data (2,206 deaths; 59 from lymphatic and hematopoietic cancers) from their cohort of 11,098 workers (82% female). Leukemia and aleukemia were elevated for workers with >10 years of exposure and for workers with ≥20 years since first exposure. However, since no historical exposure level data were available for this cohort, individual worker exposures could not be estimated and exposure-response modeling was not conducted. The British cohort updated by Coggon et al. (2003) consisted of 14,014 male workers, and the follow-up included 5,185 deaths (83 from lymphohematopoietic cancers). In this cohort, lung cancer mortality was statistically significantly increased, especially in workers in the high-exposure category; however, actual exposure estimates were not available for exposure-response modeling (worker exposures were categorized as nil/background, low, moderate, or high, depending on the job considered to have had the highest exposure). Lymphohematopoietic cancers were not elevated in the British cohort, although, as discussed above, the results were based on external comparisons against national mortality statistics. Neither the NIOSH nor the British study reported increased risks of NPC, although only 1 case (0.96) was expected in the NIOSH cohort (Pinkerton et al., 2003) and only 2.0 cases were expected in the British cohort (Coggon et al., 2003). 95% confidence intervals for the relative risk of NPC from these studies (0.07–3.55 and 0.00–3.00, respectively) were estimated by Bosetti et al. (2008) and are not inconsistent with the NPC findings of Hauptmann et al. (2004).

In the Hauptmann et al. (2009) nested case-control study, exposures were estimated for each case and control using multiple exposure metrics. Because of limitations in the exposure assessment, however, this study, while useful for hazard assessment, was not used by EPA to derive quantitative risk estimates. Of primary concern, the worker histories were obtained from surrogate responders (next of kin and coworkers). While this approach can produce good quality results for general metrics such as ever embalming or years of embalming, which yielded statistically significant associations (for ever embalming) and trends (for years in jobs with embalming) for lymphohematopoietic cancer of nonlymphoid origin and, in particular, myeloid leukemia, validity declines for more specific variables such as number and duration of embalmings per calendar time period and frequency of spills per calendar time period. These latter variables are needed in the exposure model used to estimate exposures for metrics such as cumulative exposure. Where information on a particular variable was obtained from multiple

respondents, Hauptmann et al. (2009) reported a substantial amount of discordance for variables such as number of any embalmings and number of autopsied embalmings. Furthermore, considerable amounts of data were missing. For example, Hauptmann et al. (2009) reported that all but 16 of 44 cases of lymphohematopoietic cancer of nonlymphoid origin had 30% or more of their work history missing. Moreover, although of lesser concern in and of itself, even where good retrospective data on the model variables may have been available, there was additional uncertainty in the estimates resulting from the exposure model. In a validation phase, using real measurements from independent embalmings, the final exposure model, after modifications to correct for initial overestimation, explained 74% of the variability.

In addition to limitations in the exposure assessment used in the Hauptmann et al. (2009) study, there were substantial uncertainties about the quantitative precision of the exposure-response relationship observed for myeloid leukemia, which was the one cancer type examined in this study for which there was consistent evidence of an association with formaldehyde exposure. Of the 34 myeloid leukemia cases in the Hauptmann et al. (2009) study, there was only one unexposed case for all of the exposure metrics. Thus, the relative risk estimates (odds ratios) derived in comparison to the referent group are unstable. To address this problem, Hauptmann et al. (2009) created an alternate referent group comprised of workers with <500 lifetime embalmings. As might be expected, since this alternate referent group is no longer an unexposed referent group, odds ratios for the various levels of the different exposure metrics declined considerably (e.g., for the cumulative exposure metric, odds ratios based on the unexposed referent group were 4−5 times higher than those based on the <500-embalmings referent group), although they remained increased relative to the referent group. Thus, although the results of the Hauptmann et al. (2009) study were supportive of the hazard assessment, the overall uncertainty in the quantitative exposure-response data, particularly in the exposure assessment, from the study was considered prohibitive for the development of quantitative cancer risk estimates.

5.2.2. Nasopharyngeal Cancer

5.2.2.1. *Exposure-Response Modeling of the National Cancer Institute Cohort*

A detailed exposure assessment was conducted for the NCI cohort, and quantitative exposure estimates were generated for each worker (Stewart et al., 1986). Formaldehyde exposure estimates, including 8-hour time-weighted average (TWA) exposures and level and frequency of peak exposures, were derived for each job, work area, and calendar year combination. A peak was defined as a short-duration exposure (typically <15 minutes) above the TWA. Cumulative exposures (in ppm × years) were estimated by multiplying the time a

worker spent in a specific job by the TWA exposure for that job and summing over all the jobs held by the worker. Duration was the total time spent in jobs with formaldehyde exposure, and average intensity was the ratio of cumulative exposure to duration. Formaldehyde exposures after 1980 were not taken into account in the follow-up study, but this was considered to have a minimal impact on the results (see Section 5.2.2.4).

The results of NCI's internal analyses for NPC, using the peak exposure, average intensity, cumulative exposure, and duration of exposure metrics, are presented in Table 5-7. The relative risks (rate ratios) (RRs) were estimated using log-linear Poisson regression models stratified by calendar year, age, sex, and race and adjusted for pay category (salary/wage/unknown). The NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). A 15-year lag interval was used in estimating exposures in order to account from a minimal latency period for the development of solid cancers, including NPCs.

As can be seen in Table 5-7, peak exposure is the exposure metric that provides the strongest exposure-response relationship with NPC. However, it is not clear how to extrapolate RR estimates based on these peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures, where the risk is usually considered to be from continuous lifetime exposures to low environmental levels. In addition, peak exposure is a more subjective measure than the other metrics, it is not based on actual measurements, and it is a categorical rather than continuous measure. Furthermore, the "true" exposure metric best describing the biologically relevant delivered dose of formaldehyde is unknown. The cumulative exposure metric provides a good fit to the data (p trend = 0.029 for all person-years), and, since this is generally the preferred metric for quantitative risk assessment for environmental exposure to carcinogens, cumulative exposure was chosen as the exposure metric for the risk estimate calculations for NPC in this assessment.

The nonexposed person-years were included in the primary cancer risk analyses presented here in order to be more inclusive of all the exposure-response data. Such data are typically included in exposure-response modeling. Furthermore, the data were stratified by pay category, which should alleviate some concerns about the nonexposed workers having different socioeconomic characteristics. Final results for the exposed person-years only are presented for comparison.

As described above, Hauptmann et al. (2004) investigated the relationship between formaldehyde exposure and NPC mortality using log-linear Poisson regression models. They also conducted log-linear trend tests using the general model $RR = e^{\beta X}$, where β represents the

regression coefficient for exposure and X is exposure as a continuous variable. The trend models were stratified by calendar year, age, sex, and race and adjusted for pay category. Dr. Hauptmann

Table 5-7. Relative risk estimates for mortality from nasopharyngeal malignancies (ICD-8 code 147) by level of formaldehyde exposure for different exposure metrics

Relative risk (number of deaths)				*p* trend[b]	*p* trend[c]
Peak exposure (ppm)					
0	**>0 to <2.0[a]**	**2.0 to <4.0**	**≥4.0**		
1.00[d] (2)	–(0)	–(0)	1.83 (7)	0.044	<0.001
Average intensity (ppm)					
0	**>0 to <0.5**	**0.5 to <1.0**	**≥1.0**		
1.00[d] (2)	–(0)	0.38 (1)	1.67 (6)	0.126	0.066
Cumulative exposure (ppm × years)					
0	**>0 to <1.5**	**1.5 to <5.5**	**≥5.5**		
2.40 (2)	1.00 (3)	1.19 (1)	4.14 (3)	0.029	0.025
Duration of exposure (years)					
0	**>0 to <5**	**5 to <15**	**≥15**		
1.77 (2)	1.00 (4)	0.83 (1)	4.18 (2)	0.206	0.147

[a]Reference category for all categories.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among all (nonexposed and exposed) person-years.
[c]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among exposed person-years only.
[d]Reference category due to no cases in the low-exposure category.

Source: Hauptmann et al. (2004).

provided EPA with the β estimates (and their standard errors) from the trend tests for NPC and the cumulative exposure metric for all person-years and for exposed person-years only (personal communication from Michael Hauptmann, NCI, to Jennifer Jinot, EPA, March 29, 2004). These estimates are presented in Table 5-8.

Table 5-8. Regression coefficients from NCI log-linear trend test models for NPC mortality from cumulative exposure to formaldehyde[a]

Person-years	β (per ppm × year)	Standard error (per ppm × year)
All	0.05183	0.01915
Exposed only	0.05318	0.01914

[a]Models stratified by calendar year, age, sex, and race and adjusted for pay category; cumulative exposures calculated using a 15-year lag interval.

Source: Personal communication from Michael Hauptmann to Jenifer Jinot (March 29, 2004).

5.2.2.2. *Prediction of Lifetime Extra Risk of Nasopharyngeal Cancer Mortality*

The regression coefficients presented in Table 5-8 were used to predict the extra risk of NPC mortality from environmental exposure to formaldehyde.

Extra risk = (Rx–Ro)/(1–Ro),

where Rx is the lifetime risk in the exposed population and Ro is the lifetime risk in an unexposed population (i.e., the background risk). Extra risk estimates were calculated using the β regression coefficients and a life-table program that accounts for competing causes of death.[9] U.S. age-specific 1999 all-cause mortality rates for all race and gender groups combined (National Center for Health Statistics [NCHS], 2002) were used to specify the all-cause background mortality rates in the life-table program. NCHS 1996–2000 age-specific background mortality rates for NPC were provided by Dr. Eisner of NCI's Surveillance, Epidemiology and End Results (SEER) program (personal communication from Milton Eisner, SEER, to Jennifer Jinot, EPA, December 19, 2003). Risks were computed up to age 85 because cause-specific mortality (and incidence) rates for ages above 85 years are less reliable. Conversions between occupational formaldehyde exposures and continuous environmental exposures were made to account for differences in the number of days exposed per year (240 versus 365) and in the amount of air inhaled per day (10 versus 20 m^3). An adjustment was also

[9]This program is an adaptation of the approach that was previously used in BEIR IV, "Health Risks of Radon and Other Internally Deposited Alpha Emitters." National Academy Press, Washington, DC, 1988, pp. 131–134. The same methodology was also used more recently in EPA's 1,3-butadiene health risk assessment (U.S. EPA, 2002). A spreadsheet illustrating the life table used for the extra risk calculation for the derivation of the LEC_{0005} for NPC incidence (see Section 5.2.2.3) is presented in Appendix C.

made for the 15-year lag period. The reported standard errors for the regression coefficients were used to compute the one-sided 95% upper confidence limits (UCLs) for the extra risks based on a normal approximation.

Point estimates and one-sided 95% UCLs for the extra risk of NPC mortality associated with varying levels of continuous exposure to formaldehyde are presented in Table 5-9. The model predicts extra risk estimates that are fairly linear for exposures below about 0.001 to 0.01 ppm but not for exposures above 0.01 ppm.

Table 5-9. Extra risk estimates for NPC mortality from various levels of continuous exposure to formaldehyde

Exposure concentration (ppm)	Extra risk	95% UCL on extra risk
0.0001	1.69×10^{-7}	2.71×10^{-7}
0.001	1.69×10^{-6}	2.73×10^{-6}
0.01	1.76×10^{-5}	2.90×10^{-5}
0.1	2.63×10^{-4}	5.75×10^{-4}
1	6.22×10^{-1}	9.00×10^{-1}
10	9.82×10^{-1}	9.85×10^{-1}

Consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the same data and methodology were also used to estimate the exposure level (effective concentration [EC_x]) and the associated (one-sided) 95% lower confidence limit (LEC_x) corresponding to an extra risk of 0.05% (x = 0.0005). Although EPA guidelines emphasize the use of exposure levels associated with a 10% extra risk level for the POD for low-dose extrapolation, that would not be appropriate in this instance. A 10% extra risk level is very high for responses generally observed in epidemiology studies; thus, a 1% extra risk level is typically used for epidemiologic data to avoid upward extrapolation. For NPC, however, even the 1% level of risk is associated with RR estimates that are substantially higher than those observed in the epidemiology study. Hence, even a 1% extra risk level would be an upward extrapolation. Based on the life-table program, the RR estimate for an extra risk of 1% for NPC mortality is 46. Even 0.1% yields an RR estimate on the high end of the observable range of the epidemiology study (RR = 5.5). A 0.05% extra risk level yields an RR estimate of 3.27, which better corresponds to the RRs in the range of the data. Thus, 0.05% extra risk was selected for determination of the POD, and, consistent with EPA's *Guidelines for Carcinogen Risk*

Assessment (U.S. EPA, 2005a), the LEC value corresponding to that risk level was used as the POD. While this may appear to be an inordinately low response level, it must be recognized that NPC has a very low background mortality rate (e.g., lifetime background risk is about 0.00022); therefore, a 1% extra risk (i.e., 0.01) would be a huge increase relative to the background risk. This is consistent with the fact that, even with a large cohort followed for a long time, only nine NPC deaths were observed in the NCI follow-up through 1994.[10]

Because formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA (see Section 4.5), a linear low-dose extrapolation was performed in accordance with EPA's carcinogen risk assessment guidelines (U.S. EPA, 2005a). The EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for NPC mortality are presented in Table 5-10.

Table 5-10. EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for NPC mortality from formaldehyde exposure based on the Hauptmann et al. (2004) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (ppm^{-1})
All	0.15	0.093	5.4×10^{-3}
Exposed only	0.15	0.091	5.5×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

5.2.2.3. *Prediction of Lifetime Extra Risk of Nasopharyngeal Cancer Incidence*

EPA cancer risk estimates are typically derived to represent a plausible upper bound on increased risk of cancer *incidence*, as from experimental animal incidence data. Cancer data from epidemiology studies are more often mortality data, as is the case in the NCI study. For cancers with low survival rates, mortality-based estimates are reasonable approximations of cancer incidence risk. However, for NPC, the survival rate is substantial (51% at 5 years in the 1990s in the United States, according to Lee and Ko [2005]), and incidence-based risks are preferred because EPA is concerned with cancer occurrence, not just cancer mortality.

Therefore, an additional calculation was done using the same regression coefficients provided by Dr. Hauptmann (see Table 5-8) but with age-specific NPC incidence rates for

[10] Ten NPCs were reported on death certificates and included in NCI's SMR analysis, but one of these cases was apparently misclassified on the death certificate, so only nine cases were used to estimate the RRs in the internal comparison analysis, as discussed by Hauptmann et al. (2004).

1996−2000 from SEER in place of the NPC mortality rates in the life-table program. SEER collects cancer incidence data from a variety of geographical areas in the United States. The incidence data used here are from SEER 12, a registry covering about 14% of the U.S. population, which was the most current SEER registry at the time this analysis was done. SEER 1996–2000 age-specific background incidence rates for NPC were provided by Dr. Eisner of NCI's SEER program (personal communication from Milton Eisner, SEER, to Jennifer Jinot, EPA, December 18, 2003). The incidence-based calculation relies on the reasonable assumptions that NPC incidence and mortality have the same exposure-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of NPC or that relapses provide a negligible contribution. The calculation also relies on the fact that NPC incidence rates are small compared with the all-cause mortality rates.

The resulting EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for NPC incidence are presented in Table 5-11. The unit risk estimate for cancer incidence is twofold higher than the corresponding mortality-based estimate, for all person-years. This sizeable discrepancy can be attributed to the high survival rates for NPC.

Table 5-11. EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for NPC incidence from formaldehyde exposure based on the Hauptmann et al. (2004) trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (ppm^{-1})
All	0.074	0.046	1.1×10^{-2}
Exposed only	0.072	0.045	1.1×10^{-2}

[a]Unit risk = $0.0005/LEC_{0005}$.

The preferred estimate for the inhalation cancer unit risk for NPC is the estimate of 1.1×10^{-2} per ppm derived using incidence rates for the cause-specific background rates, for all person-years. The results from the exposed person-years are essentially identical.

Because NPC is a rare cancer, with a relatively low number of cases occurring per year in the United States, a rough calculation was done to assure that the unit risk estimate derived for NPC incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 5 ppb for the U.S. population, the inhalation unit risk estimate for NPC equates to a lifetime extra risk estimate of 5.5×10^{-5}. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years

but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 220 incident cases of NPC attributable to formaldehyde exposure per year. Alternatively, assuming an average constant lifetime formaldehyde exposure level of 20 ppb, the calculation suggests a crude upper-bound estimate of 880 incident cases of NPC per year. Both upper bound estimates, using different assumed lifetime exposure levels, are well below the estimated 2,100 total incident NPC cases per year calculated from a published NPC incidence rate for the United States of 0.7/100,000 person-years (Lee and Ko, 2005).[11]

5.2.2.4. *Sources of Uncertainty*

The two major sources of uncertainty in quantitative cancer risk estimates are generally interspecies extrapolation and high-to-low dose extrapolation. The risk estimates derived from the Hauptmann et al. (2004) analyses of the NCI cohort are not subject to interspecies uncertainty since they are based on human data. However, substantial uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures. Although the actual exposure-response relationship at low exposure levels is unknown, the linear low-dose extrapolation that was used is warranted by the strong support for formaldehyde carcinogenicity having a mutagenic MOA (see Section 4.5). The linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response is generally considered to provide a plausible upper bound on the risk at lower exposure levels. Actual low-dose risks may be lower to an unknown extent.

Other sources of uncertainty emanate from the epidemiologic study and its analysis (Hauptmann et al., 2004), including the retrospective estimation of formaldehyde exposures in the cohort, the modeling of the epidemiologic exposure-response data, the appropriate exposure metric for exposure-response analysis, and potential confounding or modifying factors.

The same team of investigators (Stewart et al., 1986) conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. Formaldehyde exposures were estimated for specific jobs/tasks based on monitoring data, discussions with workers and plant managers, and assessment by industrial hygienists. Individual worker estimates were derived for a variety of exposure metrics based on work histories. This exposure assessment was a major undertaking, involving over 100 person-months. Hauptmann et al. (2004) suggested that

[11] With the application of age-dependent adjustment factors (see Section 5.4.4), the lifetime unit risk estimate for NPC would increase by a factor of 1.66, and the crude upper-bound estimates of the incident cases per year attributable to formaldehyde exposure would similarly increase by a factor of 1.66. The resulting adjusted estimates of 365 and 1460 for 5 ppb and 20 ppb exposure levels, respectively, are still well below the estimated total number of 2100 incident cases per year in the United States.

employment of such a detailed exposure assessment would tend to minimize exposure misclassification for average and cumulative exposure and duration of exposure but that peak exposure estimates could be more susceptible to misclassification because they were not based on actual measurements. In addition, the follow-up study did not take into account exposures after 1980. Hauptmann et al. (2003) stated that any underestimation of (total) exposure resulting from the 1980 cutoff "would be small because only 3.7% of all person-years were contributed by workers who were 65 years or younger and in exposed jobs in 1980" and because exposure levels were believed to have been much lower after 1980 than in earlier years.

As discussed in Chapter 4 and the appendix (Human Health), Marsh et al. (1996) also estimated individual worker exposures at 1 of the 10 plants (Wallingford, Connecticut) studied by the NCI team, and 5 of the 9 NPC deaths were from that plant. The Marsh et al. (1996) exposure estimates were about 10-fold lower than those derived by the NCI team for the workers at the Wallingford plant. Marsh et al. (2002) hypothesized that "the NCI used data from several facilities to estimate exposures in a single facility." However, the NCI investigators maintained that they estimated exposures for each plant separately. While the exact reasons for such a large discrepancy are unclear, some differences in the assessment procedures which could have resulted in substantial differences in the estimates are apparent. First, according to Marsh et al. (1996), 91.7% of the white male Wallingford plant workers were specified as being exposed to formaldehyde in the NCI study, while only 83.3% were considered to have been exposed in the Marsh et al. (1996) analysis (it should be noted that these two cohorts of the Wallingford plant are not identical). Second, the NCI investigators (Stewart et al., 1987, 1986) did their own exposure monitoring at all the plants, including the Wallingford facility, in order to standardize the data provided by the plants as well as to fill data gaps for certain jobs. There is no indication that Marsh et al. (1996) made any additional measurements themselves. Third, although the Marsh et al. (2002, 1996) papers are not entirely consistent on this point, those investigators apparently assumed that the job-specific exposures at the plant were essentially constant over the history of the plant, whereas the NCI team, based on interviews with plant personnel knowledgeable about equipment and process changes, assumed that past exposures were higher.

In any event, despite the discrepancies in the absolute exposure values, the relative exposures for both the Marsh et al. (2002, 1996) and NCI studies, as reflected in the exposure-response relationships, are less subject to misclassification and are considered to be reliable. The Wallingford plant is just 1 of the 10 plants in the NCI study (representing 4,389 of the 25,619 workers in the NCI cohort), but if the Marsh et al. (1996) exposure estimates, which are roughly 10-fold lower than the NCI estimates, are closer to the actual exposures for those workers, then the true potency of formaldehyde could be greater than that suggested by the unit

risk estimates calculated above based on the NCI data. Furthermore, if the NCI exposure values were significantly overestimated across all 10 plants, then the actual potency could be higher still.

With respect to the exposure-response model, the log-linear model used by Hauptmann et al. (2003) for their trend tests (i.e., $RR = e^{\beta X}$) is a commonly used model for epidemiologic data with exposure as a continuous variable. However, the actual exposure-response relationship is unknown. Moreover, even if the correct exposure-response model were known, there would be substantial uncertainty in estimating the model parameters because there are only nine NPC deaths to model. Furthermore, Beane Freeman et al. (2009) reported that in the follow-up through 2004 it was discovered that 1,006 deaths that occurred during the 1980 to 1994 follow-up period had not been included in the analyses of the 1994 follow-up study (Hauptmann et al., 2004, 2003), for reasons that have not been identified. Because NPC is such a rare cancer, it is not expected that many, if any, NPC deaths were among the 1,006 excluded deaths; however, it is unknown how inclusion of the 1,006 deaths would have altered the overall exposure-response relationship and, hence, the regression coefficient. Additionally, a 15-year lag was used for all the NCI solid cancer models. The actual minimum latency is unknown; however, the investigators reported that lag intervals between 2 and 20 years yielded similar results.

Another potentially significant source of uncertainty is associated with the exposure metrics. With the log-linear model used for modeling the occupational data, the peak exposure metric gave the strongest exposure-response relationship between formaldehyde exposure and increased risk of NPCs. However, it is unclear how to extrapolate RR estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposure (i.e., extra risk from lifetime continuous low-level environmental exposures). The cumulative exposure metric also yielded a statistically significant exposure-response relationship and was used for the primary cancer risk calculations in this assessment. The "true" exposure metric best describing the toxicologically relevant dose of formaldehyde for nasopharyngeal carcinogenesis is unknown. If a peak-exposure type of metric is the best representative of the toxicologically relevant dose, this suggests that there are dose-rate effects in the exposure-response relationship for formaldehyde and NPC. If this is the case, the unit risk estimates presented here, which are based on a linear low-dose extrapolation, may overestimate the true risks to an unknown extent.

Hauptmann et al. (2004) gave a lot of consideration to potential confounding and modifying factors in their analyses. The important factors of age, race, sex, calendar year, and pay category were taken into account in their Poisson regression and trend analyses.

Furthermore, they used the low-exposure person-years, rather than the unexposed person-years, as their referent group in an effort to minimize any potential confounding effects resulting from differences in socioeconomic or other characteristics between exposed and unexposed workers. When the slope estimate (i.e., regression coefficient) for the exposed person-years only was used in the analyses presented here, the unit risk estimate was essentially identical to that calculated from the slope estimate for all person-years (see Tables 5-10 and 5-11).

In addition, these investigators evaluated routine respirator use, exposure to formaldehyde-containing particulates, durations of exposure to 11 other chemicals/substances in the plants (antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust, and benzene), and duration of employment as a chemist or laboratory technician. Only 133 workers ever routinely used a respirator (Hauptmann et al., 2003). Hauptmann et al. (2004) reported that RR estimates for NPC changed when adjusted for duration of melamine exposure, although trend tests remained significant for cumulative formaldehyde exposure ($p = 0.006$). The investigators suggested that the association with melamine may be spurious, and the regression coefficients (i.e., β estimates) used in this assessment were not adjusted for melamine. RR estimates reportedly did not change substantially when adjusted for exposure to any of the other 10 chemicals/substances. None of the workers who died of NPC was identified as being exposed to wood dust. On the other hand, each of the seven formaldehyde-exposed workers who died of NPC was also exposed to particulates, and neither of the two workers who died of NPC but were not exposed to formaldehyde was exposed to particulates. However, for those workers exposed to particulates, NPC risk increased with increasing formaldehyde exposure, suggesting a formaldehyde-associated effect. Nonetheless, because of the correspondence between formaldehyde and particulate exposures within the workers who died of NPC, there is uncertainty as to whether or not particulates were acting as a modifying factor. Adjusting for duration of time spent working as a chemist or laboratory technician did not substantially alter the results (Hauptmann et al., 2004).

Adjusting for plant may result in overadjustment because plant is highly correlated with exposure. Moreover, Hauptmann et al. (2004) adjusted for important plant-related factors by adjusting for the 11 chemicals/substances. Nonetheless, these investigators conducted analyses adjusted for plant to address potential unmeasured confounders associated with plant, and they reported that the association with NPC remained. As noted above, five of the nine NPC deaths were from the Wallingford plant also studied by Marsh et al. (2006, 2002). Marsh et al. (2007) hypothesized that the excess NPCs in the Wallingford plant could be due to external employment

in metal-working industries, but we found no evidence to support this supposition (see Section 4.1.1.1).

Although smoking data were not available for the cohort, smoking is unlikely to explain the excesses in NPCs because there was no consistent increase for tobacco-related diseases, including lung cancer, across the same exposure metrics. No information was available on Epstein-Barr virus, a major risk factor for NPC, in the cohort.

Despite inevitable uncertainties, it is important not to lose sight of the strengths of the NCI study. In addition to the use of internal analyses and the extensive exposure assessment and consideration of potential confounding or modifying variables, the NCI study has a large cohort that has been followed for a long time. The cohort included 25,619 subjects, 75% of whom entered before 1960, contributing a total of 865,708 person-years (730,312 for the exposed workers) to the 1994 follow-up. Duration of follow-up in 1994 ranged up to 58 years, with a median of 35 years. Duration of exposure ranged up to 46 years, with a median of 2 years.

Additional uncertainties are not so much inherent in the exposure-response modeling or in the epidemiologic data themselves but rather stem from the process of obtaining more general EPA risk estimates from these specific results. EPA cancer risk estimates typically represent a plausible upper bound on increased risk of cancer incidence in the general population for all tissue sites potentially affected by an agent. For experimental animal studies, this is accomplished by using tumor incidence data and summing across all the tumor sites that demonstrate significantly increased incidences, generally using data from the most sensitive sex and species. However, in estimating comparable risks from the NCI epidemiologic data, certain limitations are encountered. First, the NCI study is a retrospective mortality study, and cancer incidence data are unavailable for the cohort. Second, these occupational epidemiology data represent a worker cohort that is generally healthier than the general population (e.g., SMRs < 1) (see Table 2 of Hauptmann et al. [2004]).

The first limitation was addressed quantitatively in the calculation of cancer incidence risk estimates from the mortality results, and, even though there are assumptions made in using incidence data this way, the incidence-based estimates are believed to be better estimates of cancer incidence risk than the mortality-based estimates. With respect to the second limitation, the healthy worker effect is often an issue in occupational epidemiology studies, and it is difficult to know to what extent there is a healthy worker effect with respect to the development of NPC in this study. As discussed above, Hauptmann et al. (2004) sought to minimize potential confounding effects resulting from differences in socioeconomic or other characteristics between exposed and unexposed workers by using the low-exposure person-years, rather than the unexposed person-years, as their referent group. Nonetheless, when the slope estimates for the

exposed person-years only were used in the analyses in this assessment, unit risk estimates essentially identical to those calculated from the slope estimates for all person-years were obtained (see Tables 5-10 and 5-11). In terms of representing the general population, the NCI cohort was somewhat diverse, but the workers were predominantly white males (81%) then white females (12%), black males (7%), and black females (<1%), and they were all adults.

Finally, NPC is just one of the upper respiratory tract cancers concluded to be causally associated with formaldehyde exposure (see Section 4.5). These upper respiratory tract cancers are rare cancers and are difficult to detect in cohort studies. Thus, although NPC was the only such cancer with an exposure-response relationship amenable to the derivation of a unit risk estimate, additional, unquantified risk may exist for the other upper respiratory tract cancers. If there was a strong exposure-response relationship between these cancers and formaldehyde exposure, a more apparent association in the Hauptmann et al. (2004) study might have been expected, as was seen for NPC, despite the rare nature of these cancers. Thus, the exposure-response relationship for these other upper respiratory tract cancers is likely modest, at best, and, because these are rare cancers, the contribution of the risk for these cancers to the total cancer risk from formaldehyde exposure is not expected to be large. Nonetheless, with such rare cancers, there is uncertainty regarding the extent to which the estimate based on NPC may underestimate the risk for all upper respiratory tract cancers.

In summary, the inhalation cancer unit risk estimate of 1.1×10^{-2} per ppm for NPC is based on human data from a high-quality epidemiologic study with individual exposure estimates for each worker. A major uncertainty is the appropriate model/exposure metric for extrapolation to environmental exposures.

5.2.3. Lymphohematopoietic Cancer

5.2.3.1. *Exposure-Response Modeling of the National Cancer Institute Cohort*

The results of NCI's internal analyses for lymphohematopoietic cancers using the peak exposure, average intensity, and cumulative exposure metrics from the follow-up through 2004 are reported by Beane Freeman et al. (2009). There was reportedly no evidence of associations with duration of exposure, and those results were not presented. For the peak exposure metric, statistically significant log-linear trends were observed for all lymphohematopoietic cancers, Hodgkin lymphoma, and leukemia (the latter only when the unexposed person-years were included). There was also evidence for potential associations with myeloid leukemia specifically, especially when risks were viewed over time, and with multiple myeloma. Using the average exposure metric, there was a significant trend for Hodgkin lymphoma. With the cumulative exposure metric, there were no statistically significant trends; however, the Hodgkin

lymphoma trend results had *p*-values not much greater than 0.05 (*p* trends = 0.06 and 0.08 with and without the unexposed person-years, respectively), as did the leukemia trend results (*p* trends = 0.08 and 0.12 with and without the unexposed person-years, respectively). As discussed above with NPC, it is not clear how to extrapolate RR estimates based on the peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures. The average exposure metric is also problematic because it suggests that duration of exposure is not important (e.g., exposure to a given exposure level for 1 year conveys the same amount of risk as exposure to the same level for 70 years). Cumulative exposure is generally the preferred metric for quantitative risk assessment for environmental exposure to carcinogens, and, because the Hodgkin lymphoma and leukemia trend results had *p*-values not much greater than 0.05 using the cumulative exposure metric and the elevations in risk with that metric were consistent with significant elevations observed with the peak exposure (for Hodgkin lymphoma and leukemia) and average exposure (for Hodgkin lymphoma) metrics (see Table 5-12), a determination was made to calculate unit risk estimates for Hodgkin lymphoma and leukemia based on cumulative exposure. There is also support for associations between formaldehyde exposure and both Hodgkin lymphoma and leukemia from other studies (see Section 4.5.2). No other lymphohematopoietic cancer responses provided adequate exposure-response data with the cumulative formaldehyde exposure metric in the NCI cohort from which to derive unit risk estimates.

As for the NPC results discussed in Section 5.2.2, the RR estimates in Table 5-12 were derived using log-linear Poisson regression models stratified by calendar year, age, sex, and race and adjusted for pay category (salary/wage/unknown). The NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). A 2-year lag interval was used to determine exposures in order to account for a minimal latency period for lymphohematopoietic cancers.

Dr. Beane Freeman provided EPA with the regression coefficient estimates for Hodgkin lymphoma and leukemia mortality from the log-linear trend test models for cumulative exposure (i.e., RR = $e^{\beta X}$, with exposure [X] as a continuous variable) used in the NCI analyses (personal communication from Laura Beane Freeman, NCI, to John Whalan, EPA, August 26, 2009). These estimates are presented in Table 5-13. As with the NPC calculations in Section 5.2.2, the nonexposed person-years were included in the primary unit risk estimate derivations in order to

Table 5-12. Relative risk estimates for mortality from Hodgkin lymphoma (ICD-8 code 201) and leukemia (ICD-8 codes 204–207) by level of formaldehyde exposure

for different exposure metrics

Cancer type	Relative risk (number of deaths)				*p* trend[b]	*p* trend[c]
Peak exposure (ppm)						
	0	**>0 to <2.0[a]**	**2.0 to <4.0**	**≥4.0**		
Hodgkin lymphoma	0.67 (2)	1.0 (6)	3.30 (8)	3.96 (11)	0.004	0.01
Leukemia	0.59 (7)	1.0 (41)	0.98 (27)	1.42 (48)	0.02	0.12
Average intensity (ppm)						
	0	**>0 to <0.5**	**0.5 to <1.0**	**≥1.0**		
Hodgkin lymphoma	0.53 (2)	1.0 (10)	3.62 (9)	2.48 (6)	0.03	0.05
Leukemia	0.54 (7)	1.0 (67)	1.13 (25)	1.10 (24)	0.50	>0.50
Cumulative exposure (ppm × years)						
	0	**>0 to <1.5**	**1.5 to <5.5**	**≥5.5**		
Hodgkin lymphoma	0.42 (2)	1.0 (14)	1.71 (7)	1.30 (4)	0.06	0.08
Leukemia	0.53 (7)	1.0 (63)	0.96 (24)	1.11 (29)	0.08	0.12

[a]Reference category for all categories.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among all (nonexposed and exposed) person-years.
[c]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among exposed person-years only.

Source: Beane Freeman et al. (2009).

Table 5-13. Regression coefficients for Hodgkin lymphoma and leukemia mortality from NCI trend test models[a]

Cancer type	Person-years	β (per ppm × year)	Standard error (per ppm × year)
Hodgkin lymphoma	All	0.02959	0.01307
	Exposed only	0.02879	0.01333
Leukemia	All	0.01246	0.006421
	Exposed only	0.01131	0.00661

[a]Models were stratified by calendar year, age, sex, and race and adjusted for pay category; exposures included a 2-year lag interval.

Source: Personal communication from Laura Beane Freeman to John Whalan (August 26, 2009).

be more inclusive of all the exposure-response data. Final results for the exposed person-years only are presented for comparison.

5.2.3.2. *Prediction of Lifetime Extra Risks for Hodgkin Lymphoma and Leukemia Mortality*

Extra risk estimates for Hodgkin lymphoma and leukemia mortality were calculated using the same general methodology described above for the NPC mortality estimates (see Section 5.2.2.2), with the following exceptions. U.S. age-specific 2006 all-cause mortality rates (NCHS, 2009) and NCHS age-specific 2002–2006 background mortality rates for Hodgkin lymphoma and leukemia (http://seer.cancer.gov/csr/1975_2006/) for all race and gender groups combined were used in the life-table programs. In addition, a 2-year lag period was used instead of a 15-year lag period.

The resulting point estimates and one-sided 95% UCLs for the extra risk of Hodgkin lymphoma mortality associated with varying levels of continuous exposure to formaldehyde are presented in Table 5-14. The results for leukemia are shown in Table 5-15. In both cases, the models predict extra risk estimates that are fairly linear for exposures below about 0.01–0.1 ppm but not for exposures above 0.1 ppm.

As discussed in Section 5.2.2.2 above, 1% extra risk levels are typically used as the basis for the POD for low-dose extrapolation from epidemiologic data. As for NPC, however, Hodgkin lymphoma has a very low background mortality rate (e.g., lifetime background risk is about 0.00038), and the 1% level of risk is associated with RR estimates that are substantially higher than those observed in the epidemiology study. Hence, a 1% extra risk level would be an

Table 5-14. Extra risk estimates for Hodgkin lymphoma mortality from various levels of continuous exposure to formaldehyde

Exposure concentration (ppm)	Extra risk	95% UCL on extra risk
0.0001	2.04×10^{-7}	3.53×10^{-7}
0.001	2.05×10^{-6}	3.55×10^{-6}
0.01	2.10×10^{-5}	3.71×10^{-5}
0.1	2.79×10^{-4}	6.17×10^{-4}
1	1.63×10^{-1}	8.36×10^{-1}
10	9.89×10^{-1}	9.90×10^{-1}

Table 5-15. Extra risk estimates for leukemia mortality from various levels of continuous exposure to formaldehyde

Exposure concentration (ppm)	Extra risk	95% UCL on extra risk
0.0001	1.64×10^{-6}	3.02×10^{-6}
0.001	1.64×10^{-5}	3.03×10^{-5}
0.01	1.66×10^{-4}	3.10×10^{-4}
0.1	1.87×10^{-3}	3.90×10^{-3}
1	8.07×10^{-2}	5.19×10^{-1}
10	9.80×10^{-1}	9.89×10^{-1}

upward extrapolation. Based on the life-table program, the RR estimate associated with an extra risk of 1% for Hodgkin lymphoma mortality is 27. Even 0.1% yields an RR estimate at the higher end of what was observed in the epidemiology study (RR = 3.6) (note that our primary analyses include the nonexposed workers, and thus the 0-exposure group becomes the referent group and the RR estimates presented for Hodgkin lymphoma and cumulative exposure in Table 5-12 would be adjusted upward [about 2.4-fold] relative to the 0-exposure group). A 0.05% extra risk level yields an RR estimate of 2.3, which better corresponds to the RRs at the lower end of the observable range. Thus, 0.05% extra risk was selected for determination of the POD for Hodgkin lymphoma, and, consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the LEC value corresponding to that risk level was used as the POD.

RR estimate (2.5) that would be above the highest categorical result reported, even after adjusting the RR estimates upward relative to the 0-exposure group (see above paragraph). A 0.5% extra risk level yields an RR estimate of 1.8, which better corresponds to the RRs in the range of the data. Thus, the LEC value corresponding to 0.5% extra risk was selected for the POD for leukemia.

Because formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA (see Section 4.5), a linear low-dose extrapolation was performed, also in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). The EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for Hodgkin lymphoma mortality are presented in Table 5-16, and the EC_{005}, LEC_{005}, and inhalation unit risk estimates for leukemia mortality are presented in Table 5-17.

Table 5-16. EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for Hodgkin lymphoma mortality from formaldehyde exposure based on Beane Freeman et al. (2009) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (ppm^{-1})
All	0.151	0.0875	5.7×10^{-3}
Exposed only	0.155	0.0881	5.7×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

Table 5-17. EC_{005}, LEC_{005}, and inhalation unit risk estimates for leukemia mortality from formaldehyde exposure based on Beane Freeman et al. (2009) log-linear trend analyses for cumulative exposure

Person-years	EC_{005} (ppm)	LEC_{005} (ppm)	Unit risk[a] (ppm^{-1})
All	0.224	0.121	4.1×10^{-2}
Exposed only	0.246	0.126	4.0×10^{-2}

[a]Unit risk = $0.005/LEC_{005}$.

5.2.3.3. *Prediction of Lifetime Extra Risks for Hodgkin Lymphoma and Leukemia Incidence*

As for NPC, both Hodgkin lymphoma and leukemia have substantial survival rates (84.7% at 5 years for Hodgkin lymphoma [http://seer.cancer.gov/statfacts/html/hodg.html] and 53.1% at 5 years for leukemia [http://seer.cancer.gov/statfacts/html/leuks.html], based on 1999−2005 SEER data); thus, it is preferable to derive incidence estimates. Unit risk estimates for Hodgkin lymphoma and for leukemia incidence were calculated as described above for the NPC incidence estimates (see Section 5.2.2.3). Age-specific background incidence rates for 2002−2006 for Hodgkin lymphoma and for leukemia from SEER17, a registry covering about 26% of the U.S. population, were obtained from the SEER Web site (http://seer.cancer.gov/csr/1975_2006/). The incidence-based calculation relies on the assumptions that Hodgkin lymphoma (and leukemia) incidence and mortality have the same exposure-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of Hodgkin lymphoma (and leukemia) or that relapses provide a negligible contribution. The first assumption is more uncertain for leukemia because it is a grouping of subtypes with different survival rates (see Section 5.2.3.4 for further discussion). The calculation also relies on the fact that Hodgkin lymphoma (and leukemia) incidence rates are small compared with the all-cause mortality rates. The resulting EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for Hodgkin lymphoma incidence are presented in Table 5-18, and the EC_{005}, LEC_{005}, and inhalation unit risk estimates for leukemia incidence are presented in Table 5-19. The unit risk estimate for Hodgkin lymphoma incidence is about threefold higher than the corresponding mortality-based estimate, for all person-years. This sizeable discrepancy can be attributed to the high survival rates for Hodgkin lymphoma. For leukemia, the incidence unit risk estimate is about 40% higher than the mortality-based estimate. This difference is lower than the twofold

Table 5-18. EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for Hodgkin lymphoma incidence from formaldehyde exposure, based on Beane Freeman et al. (2009) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (ppm^{-1})
All	0.0515	0.0298	1.7×10^{-2}
Exposed only	0.0529	0.0301	1.7×10^{-2}

[a]Unit risk = $0.0005/LEC_{0005}$.

Table 5-19. EC_{005}, LEC_{005}, and inhalation unit risk estimates for leukemia incidence from formaldehyde exposure based on Beane Freeman et al. (2009) log-linear trend analyses for cumulative exposure

Person-years	EC_{005} (ppm)	LEC_{005} (ppm)	Unit risk[a] (ppm^{-1})
All	0.162	0.0875	5.7×10^{-2}
Exposed only	0.178	0.0909	5.5×10^{-2}

[a]Unit risk = $0.005/LEC_{005}$.

difference seen with NPC estimates, despite comparable survival rates, probably because of different age distributions of the mortality and incidence rates.

The preferred estimate for the inhalation cancer unit risk for Hodgkin lymphoma is the estimate of 1.7×10^{-2} per ppm derived using incidence rates for the cause-specific background rates, for all person-years. Similarly, the preferred estimate for leukemia is the estimate of 5.7×10^{-2} per ppm derived using incidence rates, for all person-years. In both cases, the results from the exposed person-years only are essentially identical.

Because Hodgkin lymphoma is a rare cancer, with a relatively low number of cases occurring per year in the United States (according to SEER statistics, an estimated 8,510 people were diagnosed with Hodgkin lymphoma in the United States in 2009 [http://seer.cancer.gov/statfacts/html/hodg.html]), a rough calculation was done to assure that the unit risk estimate derived for Hodgkin lymphoma incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 5 ppb for the U.S. population, the inhalation unit risk estimate for Hodgkin lymphoma equates to a lifetime extra risk estimate of 8.5×10^{-5}. Assuming an average lifetime

of 75 years (this is not EPA's default average lifetime of 70 years but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 340 incident cases of Hodgkin lymphoma attributable to formaldehyde exposure per year. Alternatively, assuming an average constant lifetime formaldehyde exposure level of 20 ppb, the calculation suggests a crude upper-bound estimate of 1,360 incident cases of Hodgkin lymphoma per year. Both upper bound estimates, using different assumed lifetime exposure levels, are well below the estimated 8,510 total incident Hodgkin lymphoma cases diagnosed per year in the United States.[12]

5.2.3.4. *Sources of Uncertainty*

By and large, the sources of uncertainty discussed above (see Section 5.2.2.4) for the NPC risk estimates, such as high-to-low dose extrapolation, retrospective exposure estimation, exposure metric/model uncertainties, and application of data from a "healthy" worker cohort to the more diverse general population also apply to the Hodgkin lymphoma and leukemia risk estimates. The Hodgkin lymphoma risk estimates are based on 27 deaths, which is more than were available for the NPC risk estimates, but 27 is still a small number for exposure-response modeling. The leukemia risk estimates are based on 123 deaths, so there is less uncertainty with the parameter estimation from the exposure-response modeling for that cancer type, although uncertainties still exist about the general model form. A 2-year lag interval was used for lymphohematopoietic cancers versus the 15-year lag for NPC. Beane Freeman et al. (2009) evaluated lag intervals between 2 and 25 years and reported that lag intervals of about 18 years provided the best fit to the lymphohematopoietic cancer data but did not change the risk estimates; thus, they retained the 2-year lag interval that was used in the previous follow-up (Hauptmann et al., 2003). The most appropriate lag intervals for Hodgkin lymphoma and leukemia are unknown, but alternate lags are unlikely to have a large impact on the results.

[12] With the application of age-dependent adjustment factors (see Section 5.4.4), the lifetime unit risk estimate for Hodgkin lymphoma would increase by a factor of 1.66, and the crude upper-bound estimates of the incident cases per year attributable to formaldehyde exposure would similarly increase by a factor of 1.66. The resulting adjusted estimates of 564 and 2,260 for 5 ppb and 20 ppb exposure levels, respectively, are still well below the estimated total number of 8,500 incident cases per year in the United States.. Similar calculations for leukemia yield even lower relative upper-bound estimates of cases attributable to formaldehyde exposure, in comparison to estimated total incident cases, because, although the unit risk estimate for leukemia is about 3.3 times the unit risk estimate for Hodgkin lymphoma, the total estimated number of incident leukemia cases in the United States. is 5.3 times the estimate for Hodgkin lymphoma (an estimated 44,790 cases diagnosed in the U.S. for 2009, according to SEER [http://seer.cancer.gov/statfacts/html/leuks.html]). For leukemia, crude upper-bound ADAF-adjusted estimates of the incident cases per year attributable to formaldehyde exposure levels of 5 ppb and 20 ppb are 1900 and 7,580, respectively, which are well below the estimated total number of 44,790 incident cases per year in the United States.

The same potential confounding or modifying factors that were investigated for NPC and the other solid cancers, as discussed in Section 5.2.2.4 above, were evaluated for the lymphohematopoietic cancers. Beane Freeman et al. (2009) reported that controlling for duration of exposure to the 11 other substances that they considered (see Section 5.2.2.4) or for working as a chemist or laboratory technician "did not meaningfully change results"; results were not shown. The investigators also reported that excluding the 586 individuals with exposure to benzene, a known leukemogen, did not change the RR estimates for myeloid or lymphoid leukemia in the highest peak exposure category. Furthermore, Beane Freeman et al. (2009) found no evidence of heterogeneity of RR estimates for lymphohematopoietic cancers by race, sex, or pay category, and adjusting for plant reportedly did not substantively change results.

A further uncertainty is which lymphohematopoietic cancer types are linked to formaldehyde exposure. As discussed in Section 4.5.2, lymphohematopoietic cancers are a diverse group of cancers with different etiologies, and the epidemiologic database suggests associations with multiple different subtypes of these cancers. Section 4.5 concludes that formaldehyde is causally associated with all lymphohematopoietic cancers as a group and with leukemias as a group (with the strongest evidence for myeloid leukemia). However, at present, exactly which subtypes are etiologically linked to formaldehyde exposure is unknown. Cancer risk estimates were derived for Hodgkin lymphoma and leukemia because, in addition to support for an association between these lymphohematopoietic cancer subtypes and formaldehyde exposure with other exposure metrics and from other studies, these had the strongest associations with cumulative exposure in the Beane Freeman et al. (2009) update of the large, high-quality NCI study. However, it is unknown whether these two subtypes best represent the total lymphohematopoietic cancer risk.

In addition, leukemia itself is a grouping of diverse (e.g., acute lymphocytic, chronic lymphocytic, acute myeloid, chronic myeloid) subtypes, and using this grouping injects additional uncertainty into the derivation of cancer incidence estimates. One of the assumptions that the incidence-based calculation relies on is that the cancer incidence and mortality have the same exposure-response relationship for formaldehyde exposure. This assumption may be problematic for the leukemia incidence estimates if not all of the leukemia subtypes represented in the grouping are associated with formaldehyde exposure to the same extent. This is because different leukemia subtypes have different survival rates, so if a subtype with a relatively high survival rate is included in the background incidence rates while not actually being associated with formaldehyde exposure or being associated to a lesser extent than other subtypes, then the incidence risk will be overestimated. The mortality risk calculations are not similarly affected

by including subtypes that may not actually be associated with formaldehyde exposure because background mortality for the subtypes is already taken into account in the regression coefficient. Figure 5-10 shows the mortality versus incidence rates for all leukemia and the two main subtypes, myeloid leukemia and lymphoid leukemia. This figure does not show the acute versus chronic myeloid and leukemia subtypes or the monocytic or other leukemia subtypes; however, it serves to illustrate the impact of using rates for groupings that contain subtypes with different survival rates. For example, if lymphoid leukemia is the predominant subtype associated with formaldehyde exposure, then using the leukemia grouping for the incidence rates may underestimate the cancer incidence risk because the incidence rates for leukemia (relative to the mortality rates) are diluted with inclusion of the incidence rates for myeloid leukemia, which has a smaller incidence-to-mortality ratio (i.e., poorer survival). On the other hand, if myeloid leukemia is the predominant subtype associated with formaldehyde exposure, then using the leukemia grouping for the incidence rates may overestimate cancer incidence risk. If incidence risks are being overestimated, the effect should be minimal because the incidence risk estimates for leukemia calculated in Section 5.2.3.3 are not that much greater (about 40%) than the mortality-only estimates.

Finally, as for the NPC risk estimates, when the slope estimates for the exposed person-years only were used for the Hodgkin lymphoma and leukemia risk calculations, unit risk estimates similar to those calculated from the slope estimates for all person-years were obtained (see Tables 5-16 to 5-19); thus, the impacts of including the unexposed person-years are minimal.

As discussed in Section 5.2.2.4, despite inevitable uncertainties, it is important not to lose sight of the strengths of the NCI study. In addition to the use of internal analyses and extensive exposure assessment and consideration of potential confounding or modifying variables, the NCI study has a large cohort that has been followed for a long time. With the additional follow-up through 2004, reflected in the lymphohematopoietic cancer results of Beane Freeman et al. (2009), the median duration of follow-up was 42 years, and the 25,619 cohort members had accrued 998,106 person-years of follow-up. Over half of the cohort was deceased, and there was a substantial number of lymphohematopoietic deaths (319 total; 286 in the exposed workers).

In summary, the inhalation cancer incidence unit risk estimates of 1.7×10^{-2} per ppm for Hodgkin lymphoma and 5.7×10^{-2} per ppm for leukemia are based on human data from a high-quality epidemiologic study with individual exposure estimates for each worker. The major source of uncertainty in both risk estimates is the extrapolation to environmental exposures.

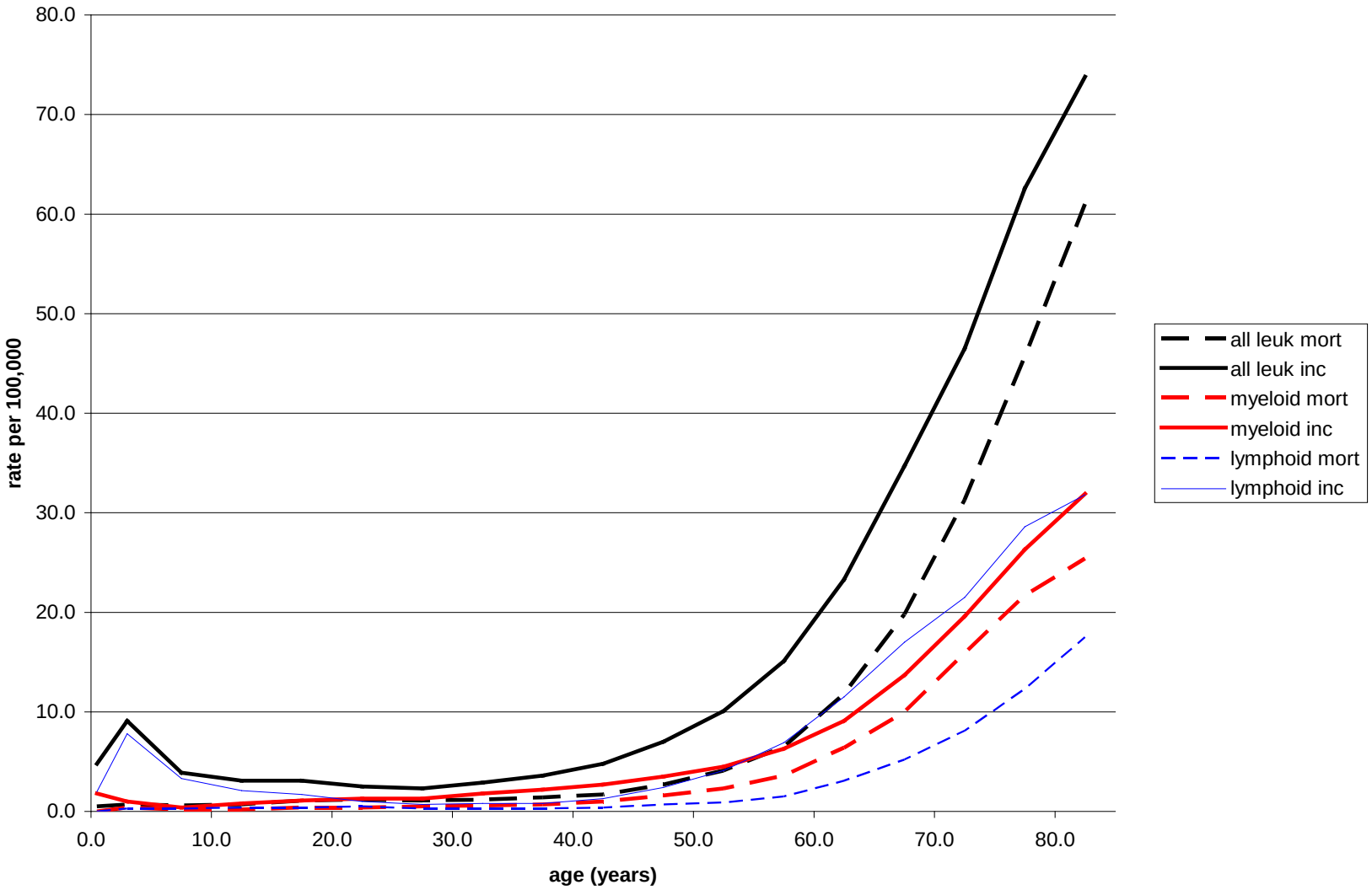


Figure 5-10. Age-specific mortality and incidence rates for myeloid, lymphoid, and all leukemia.

5.2.4. Conclusions on Cancer Unit Risk Estimates Based on Human Data

In this assessment, a (plausible upper bound) lifetime extra cancer unit risk of 5.4×10^{-3} per ppm of continuous formaldehyde exposure was estimated using a life-table program and linear low-dose extrapolation of the excess NPC mortality and log-linear modeling results (for cumulative exposure) reported in a high-quality occupational epidemiologic study (based on nine NPC deaths). Applying the same regression coefficient and life-table program to background NPC incidence rates yielded a lifetime extra cancer unit risk estimate of 1.1×10^{-2} per ppm (8.8×10^{-6} per μg/m^3).

Using similar methods and data for Hodgkin lymphoma (27 deaths) and leukemia (123 deaths) mortality based on the cumulative exposure metric, from a further follow-up of the same cohort study, (plausible upper bound) lifetime extra cancer risk estimates of 1.7×10^{-2} per ppm (1.4×10^{-5} per μg/m^3) and 5.7×10^{-2} per ppm (4.6×10^{-5} per μg/m^3) for Hodgkin lymphoma incidence and leukemia incidence, respectively, were derived.

To estimate the total cancer risk from formaldehyde exposure, risk estimates for these three cancer types (NPC, Hodgkin lymphoma, and leukemia) were combined, although, as discussed above, these three cancer types may not fully reflect the total cancer risk for all cancers thought to be causally associated with formaldehyde exposure. For an approximate estimate of the combined (upper bound) risk, risk estimates were combined assuming a normal distribution. For comparability, risk estimates for formaldehyde were combined at a common level of 0.1 ppm. This level was selected because it is close to the PODs (LEC_{005}s) used above for leukemia mortality (0.121 ppm) and leukemia incidence (0.0875 ppm), and leukemia is the predominant cancer type in terms of extra risk. Note that unit risk estimates for the different cancer types calculated at 0.1 ppm will differ slightly from those reported above (see Sections 5.2.2 and 5.2.3) because they are calculated at a level other than the PODs used in the above calculations. To derive the combined risk, maximum likelihood estimates (MLEs) of risk and their 95% upper bounds (UCLs) were calculated for each cancer type using the same methods and life-table programs employed in sections 5.2.2 and 5.2.3. The standard errors (SEs) were then estimated from the risk estimates using the equation: UCL = MLE + 1.645 × SE. The variances can then be calculated from the SEs according to the equation: Variance = SE^2. The sum of the variances then provides an estimate of the variance for the sum of the MLEs, and the 95% upper bound on the sum of the MLEs can be estimated by applying the above equations in reverse. Tables 5-20 and 5-21 provide a summary of the results of these calculations for the combined cancer mortality and incidence risks, respectively.

Table 5-20. Calculation of combined cancer mortality unit risk estimate at 0.1 ppm

Cancer type	MLE of risk	95% upper bound on risk	SE	Variance
NPC	2.63×10^{-4}	5.75×10^{-4}	1.90×10^{-4}	3.60×10^{-8}
Hodgkin lymphoma	2.79×10^{-4}	6.17×10^{-4}	2.05×10^{-4}	4.22×10^{-8}
Leukemia	1.87×10^{-3}	3.90×10^{-3}	1.23×10^{-3}	1.52×10^{-6}
Sum	2.41×10^{-3}	5.09×10^{-3}		1.60×10^{-6}
Combined risk		4.49×10^{-3}	1.27×10^{-3}	
Combined unit risk[a] (per ppm)		4.49×10^{-2}		

[a]Unit risk = 95% upper bound on combined risk/0.1 ppm.

Table 5-21. Calculation of combined cancer incidence unit risk estimate at 0.1 ppm

Cancer type	MLE of risk	95% upper bound on risk	SE	Variance
NPC	7.56×10^{-4}	1.62×10^{-3}	5.25×10^{-4}	2.76×10^{-7}
Hodgkin lymphoma	1.10×10^{-3}	2.35×10^{-3}	7.60×10^{-4}	5.77×10^{-7}
Leukemia	2.84×10^{-3}	5.89×10^{-3}	1.85×10^{-3}	3.44×10^{-6}
Sum	4.70×10^{-3}	9.86×10^{-3}		4.29×10^{-6}
Combined risk		8.10×10^{-3}	2.07×10^{-3}	
Combined unit risk[a] (per ppm)		8.10×10^{-2}		

[a]Unit risk = 95% upper bound on combined risk/0.1 ppm.

As can be seen from the results in Table 5-20, the upper bound risk estimates for cancer mortality for the individual cancer types at 0.1 ppm are within 10% of the values that would be obtained from the unit risk estimates derived in sections 5.2.2 and 5.2.3 (see Tables 5-10, 5-16, and 5-17). Furthermore, the combined unit risk estimate for mortality for the three cancer types (4.5×10^{-2} per ppm) is appropriately bounded by the mortality unit risk estimate for leukemia (4.1×10^{-2} per ppm), which has the highest individual mortality unit risk estimate, and by the sum (5.2×10^{-2} per ppm) of the individual unit risk estimates presented in sections 5.2.2 and

5.2.3. Similarly, the combined risk calculated at 0.1 ppm is necessarily bounded by the sum of the MLEs and the sum of the 95% upper bounds for the individual risks calculated at 0.1 ppm. Thus, the value of 4.5×10^{-2} per ppm (3.7×10^{-5} per µg/m^3) calculated at 0.1 ppm for the combined unit risk is a reasonable estimate for the total cancer mortality unit risk (based on the three cancer types considered).

As can be seen from the results in Table 5-21, the upper bound risk estimates for cancer incidence for the individual cancer types at 0.1 ppm are within 33% of the values that would be obtained from the unit risk estimates derived in sections 5.2.2 and 5.2.3 (see Tables 5-11, 5-18, and 5-19). Furthermore, the combined (incidence) unit risk estimate for the three cancer types (8.1×10^{-2} per ppm) is appropriately bounded by the unit risk estimate for leukemia (5.7×10^{-2} per ppm), which has the highest individual unit risk estimate, and by the sum (8.6×10^{-2} per ppm) of the individual unit risk estimates presented in sections 5.2.2 and 5.2.3. Similarly, the combined risk calculated at 0.1 ppm is necessarily bounded by the sum of the MLEs and the sum of the 95% upper bounds for the individual risks calculated at 0.1 ppm. Thus, the value of 8.1×10^{-2} per ppm (6.6×10^{-5} per µg/m^3) calculated at 0.1 ppm for the combined unit risk is a reasonable estimate for the total cancer unit risk (based on the three cancer types considered).

As documented in Section 4.5, formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA. Therefore, since there are no chemical-specific data to evaluate susceptibility of different life stages, increased early-life susceptibility should be assumed, and, if there is early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). See Section 5.4.4 below for more details on the application of the ADAFs.

5.3. DOSE-RESPONSE MODELING OF RISK OF SQUAMOUS CELL CARCINOMA IN THE RESPIRATORY TRACT USING ANIMAL DATA

In the previous section, dose-response analyses based on human data for lymphohematopoietic cancer and NPC were presented. The dose-response analyses of cancer risk presented in this section are based on nasal tumor data from laboratory bioassays using F344 rats. Because the analyses involved are extensive, most of the details are provided in the appendices.

An increased incidence of nasal squamous cell carcinoma (SCC) was seen in two long-term bioassays using F344 rats (Monticello et al., 1996; Kerns et al., 1983). Although other

studies in laboratory animals exist, these two studies, when combined, provide the most robust data for analyses. These inhalation data on nasal SCC tumor incidence were used to estimate human respiratory cancer risk in the nose and were also extrapolated to the entire respiratory tract; in other words, a site concordance between rat and human is not assumed. This is reasonable because the respiratory and transitional epithelial cell types considered to be at risk of SCC in the upper respiratory tract are also prevalent in the lower human respiratory tract, and there is greater penetration of formaldehyde flux posteriorly in the nose and in the rest of the human respiratory tract relative to that of the rat. These considerations are strengthened by the findings of DNA-protein cross-links (DPXs) in the proximal portions of the rhesus monkey lower respiratory tract (Casanova et al., 1991). In addition, some epidemiologic studies (Gardner et al., 1993; Blair et al., 1990, 1986) reported an increase in lung cancer associated with formaldehyde exposure, while others (Collins et al., 1997; Stayner et al., 1988) reported no such increases.

EPA's cancer guidelines (U.S. EPA, 2005a) suggest using a BBDR model for extrapolation when data permit. A BBDR model for formaldehyde was developed by scientists at the CIIT Centers for Health Research (see Appendix D) (Conolly et al., 2004, 2003, 2000; Kimbell et al., 2001a, b; Overton et al., 2001; CIIT, 1999), which interfaced several models to combine the extensive mechanistic information available in studies involving the F344 rat and rhesus monkey and time-to-tumor incidence data in long-term bioassays, as shown by the schematic in Figure 5-11. This mechanistic information included formaldehyde and DPX dosimetry in the F344 rat, rhesus monkey, and human airways and cell proliferation data in the F344 rat nasal lining. This document presents extensive evaluation of the underlying models and data and of the alternative parametrizations of the models that were also explored for the purpose of the current assessment (see Appendix E, Appendix F). A summary of conclusions is presented in Section 5.3.3. In particular, the following conclusions by EPA were critical in determining how the models could be used to inform the quantitative dose-response assessment:

- When used to model the dose-response in the range of the available data, the BBDR models were judged to have the advantage of being more accurate and biologically based (than purely statistical descriptions such as the multistage-weibull model) and allowing utilization of various data in an integrated manner.
- Variations to modeling the F344 rat tumor incidence data in Conolly et al. (2003) were examined. Given the data, each of these models, including the modeling in Conolly et al. (2003), was judged to be just as biologically plausible as the other. Each of the models described the rat tumor incidence equally well, was based on different characterizations

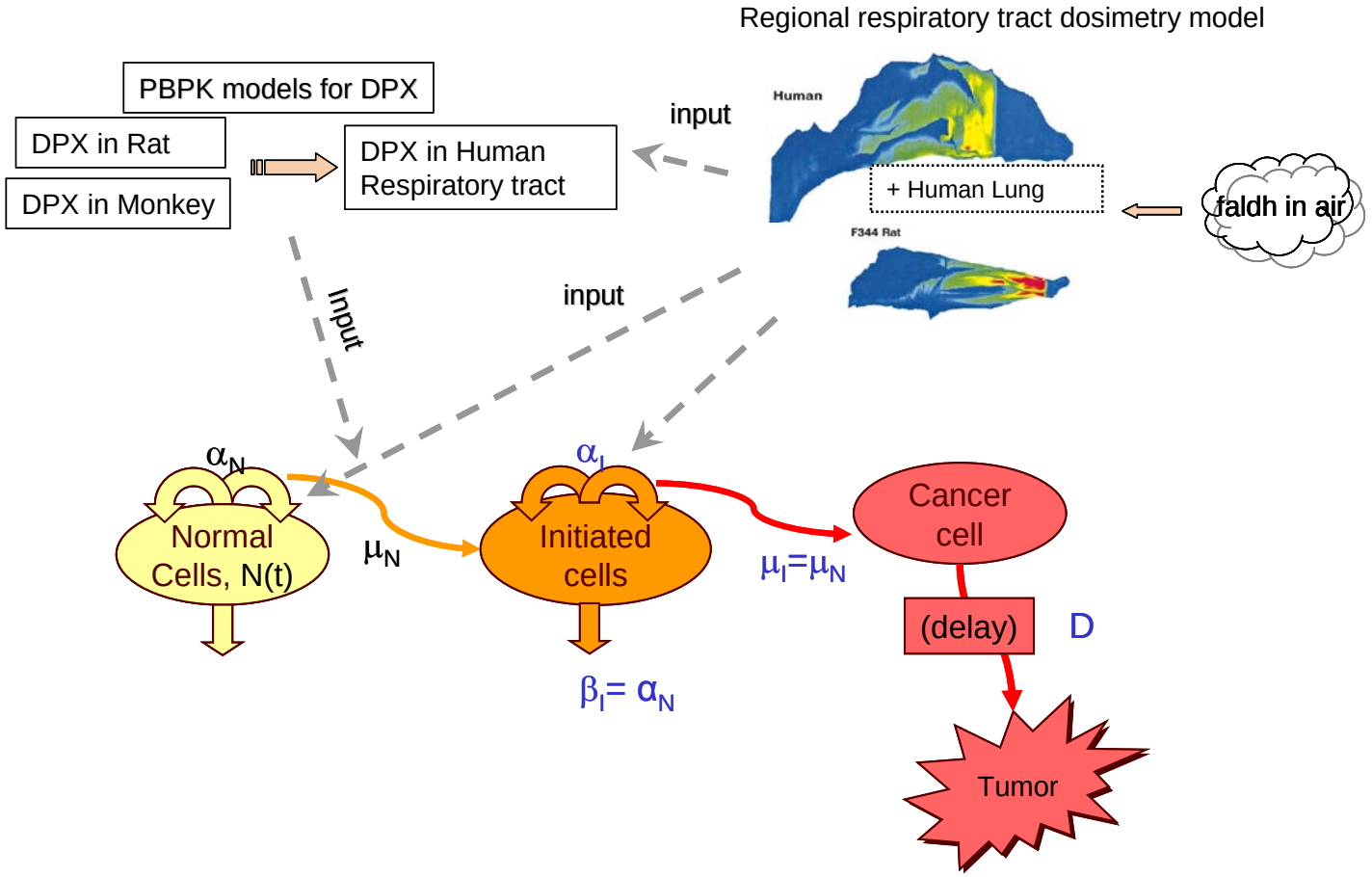


Figure 5-11. Schematic of integration of pharmacokinetic and pharmacodynamic components in the CIIT model.

Note: β = death rate; μ = mutation rate per cell division; α_N, N(t), μ_N are informed (partially or fully) by empirical data; other parameters are estimated by fitting to tumor incidence data.

of the same empirical cell kinetic data, and was based on the same empirical data on DPX measurements. However, the added human risk over baseline levels estimated by these models (including the original model) were extremely different, and ranged from negative to large positive values at environmental exposure concentrations.

- When used for the purpose of extrapolating risk, the BBDR models did not appear to reasonably constrain either risk estimates extrapolated to human exposures or risk estimates for the F344 rat when they were extrapolated below the range of observable data.
- Human respiratory cancer risk calculated in Conolly et al. (2004) was numerically unstable. Therefore, clonal growth modeling was not found to be a useful approach for human extrapolation of rodent risk estimates.
- Thus, the biologically based derivation of human risk estimates in Conolly et al. (2004) cannot be characterized as a plausible upper bound in the face of model uncertainties (a key conclusion of those authors).

For all these reasons, the BBDR modeling of the rat data

- was employed in this assessment to derive multiple PODs (for SCC in the respiratory tract) in the range of the observed data, using model-derived internal dose estimates,
- but was not used to extrapolate far below the observed data.

The inhalation unit risk estimates of SCC in the human respiratory tract were derived by using multiple methods to model the F344 tumor incidence data as follows:

1. conventional multistage Weibull time-to-tumor modeling
2. variations of the model for rat tumor incidence implemented in Conolly et al. (2003) that were considered in the process of the evaluation.

PODs were calculated as exposure concentrations corresponding to the 95% statistical upper bound extra risks of 0.005, 0.01, and 0.05 (0.005 used only with BBDR modeling). The inhalation unit risk for SCC in the human respiratory tract (upper and lower) derived from the above animal bioassay data was then calculated by linear extrapolation to the origin from the POD. Linear extrapolation is supported in part by the proven genotoxicity of the chemical and the observation of cytogenetic effects in human occupational exposures (see chapter 4). In particular, the formation of DPXs on formaldehyde interaction with DNA has been observed at doses well below those considered cytotoxic (see Section 5.3.1.2). In results obtained in some implementations of the biologically based models, formaldehyde-induced mutagenicity (modeled

as proportional to DPX concentration) was found to be a critical determinant of its tumorigenicity, both at the low dose pertaining to human exposure concentrations as well as in the dose range in which formaldehyde is considered to be cytotoxic.

The human equivalent concentration was calculated by assuming that continuous lifetime exposure to a given steady-state flux of formaldehyde (expressed in pmol/mm^2-hour) leads to equivalent risk of nasal cancer across species. Risk per respiratory or transitional epithelial cell with replicative potential was computed as a function of formaldehyde flux in the nasal region and extrapolated to the rest of the respiratory tract.

5.3.1. Long-Term Bioassays in Laboratory Animals

This section briefly describes the various animal data and dosimetry information utilized in the above (but not in all) models, based on which estimates for the inhalation unit risk are derived later in this chapter.

5.3.1.1. *Nasal Tumor Incidence Data*

Various bioassays have reported the effects of formaldehyde on rats, mice, and rhesus monkeys and have been discussed at length earlier in this document. Two of these bioassays (Monticello et al., 1996; Kerns et al., 1983), when combined, allow for the most robust characterization of the long-term dose response in a laboratory species; therefore, the focus here is on these bioassays, combined. These long-term bioassays found an increased incidence of nasal SCCs in rats exposed to formaldehyde by the inhalation route. In these combined data, rats were exposed to 0, 0.7, 2.0, 6.01, 9.93, and 14.96 ppm (0, 0.86, 2.5, 7.4, 12.2, and 18.4 mg/m^3) exposure concentrations of formaldehyde. SCCs were observed only at 6.01 ppm and higher exposure concentrations. Table 5-22 provides a summary of the tumors from these bioassays, and the time-to-tumor characteristics are as shown by the data in Figure 5-12 (in Section 5.3.3). Other tumor bioassays were also conducted by various researchers and have been detailed in chapter 4.

Table 5-22. Summary of tumor incidence in long-term bioassays on F344 rats

Formaldehyde exposure, ppm	Number of animals	Number with SCC	Percent with SCC
0.0	341	0	0
0.7	107	0	0
2	353	0	0
6.01	343	3	0.87
9.93	103	22	21.4
14.96	386	162	42.0

Sources: Combined data from Monticello et al. (1996) and Kerns et al. (1983).

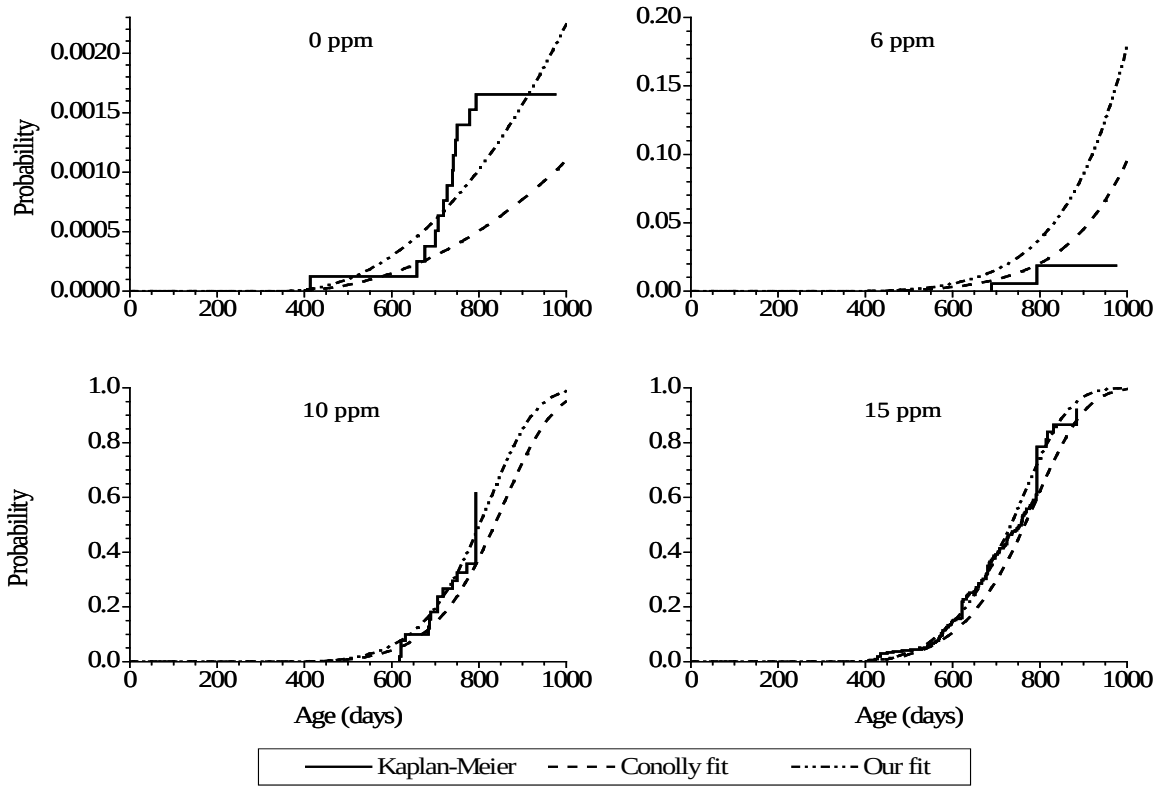


Figure 5-12. Fit to the rat tumor incidence data using the model and assumptions in Conolly et al. (2003).

Note: Fitting was performed on data of Kerns et al. (1983) and Monticello et al. (1996) combined with ALL NTP historical controls under the assumption that all SCCs are fatal. Figure compares the fit obtained by Conolly et al. (2003) with the reproduction of these results under identical conditions, inputs, and assumptions by Subramaniam et al. (2007). There were minor residual differences among the implementations; see the appendix in Subramaniam et al. (2007) for explanation.

Source: Subramaniam et al. (2007). Reprint permission required.

5.3.1.2. *Mechanistic Data*

The Kerns et al. (1983) and Monticello et al. (1996) tumor studies were accompanied or followed by additional studies that provided extensive mechanistic information on both pharmacokinetics and pharmacodynamics. These studies have been summarized elsewhere in this document and in other reviews (CIIT, 1999; Monticello and Morgan, 1997; Morgan, 1997; Heck et al., 1990). In addition to the tumor incidence data, the following data and mechanistic information (some of which were model derived) are used in the quantitative models utilized in

this chapter. Additional data for the rhesus monkey are also available that inform the hazard assessment but which have not been explicitly used in deriving the inhalation unit risk. Rhesus monkey data have been discussed in chapter 4 and chapter 3 (DPX and formaldehyde dosimetry).

- DPX: Formaldehyde interacts with DNA to form DPXs. These cross-links are considered to induce mutagenic as well as clastogenic effects. Casanova et al. (1994, 1989) carried out two studies of DPX measurements in F344 rats. In the first study, rats were exposed to concentrations of 0.3, 0.7, 2, 6, and 10 ppm for 6 hours and DPX measurements were made over the whole respiratory mucosa of the rat, while, in the second study, the exposure was to 0.7, 2, 6, or 15 ppm formaldehyde for 3 hours and measurements were made at "high" and "low" tumor sites. DPX formation was observed at all exposure concentrations in both studies (0.3 ppm–15 ppm); the DPX levels were statistically significantly elevated at concentrations ≥2 ppm, with the trend also indicating elevated DPXs at 0.7 ppm. These data were used in the development of a PBPK model for predicting DPX levels in the nasal lining (see chapters 3 and 4).
- Cell labeling index data: Male F344 rats were exposed to formaldehyde gas over a range of concentrations (0, 0.7, 2, 6, 10, or 15 ppm) in two phases of a labeling study. The first phase (Monticello et al., 1991) employed injection labeling with a 2-hour pulse labeling time, and animals were exposed to formaldehyde for periods of 1, 4, and 9 days and 6 weeks. The second phase (Monticello et al., 1996) used osmotic minipumps for labeling with a 120-hour release time to quantify labeling in animals exposed for 13, 26, 52, and 78 weeks. These data have been analyzed at length in Appendix E.
- Airflow models: Physical and computer models of airflow in anatomically realistic representations of the F344 rat and human upper respiratory tract have been constructed (Kimbell et al., 1993, 1997a; Kepler et al., 1998; Subramaniam et al., 1998; see Chapter 3).
- Formaldehyde dosimetry: Regional uptake of formaldehyde has been calculated for the upper respiratory tract of the rat and human by using the above computer representations and for the lower respiratory tract of the human by using an idealized representation of the human lower respiratory tract (Kimbell et al., 2001a; Overton et al., 2001; also see chapter 3 and further discussion of uncertainties in Appendix F).

5.3.2. The CIIT Biologically Based Dose-Response Modeling

The studies mentioned above in 5.3.1.1 and 5.3.1.2 were generated at the CIIT Centers for Health Research and led to the development of a biologically motivated dose-response model for formaldehyde-induced cancer as represented in a series of papers and in a health assessment report (CIIT model) (Conolly et al., 2004, 2003, 2000; Conolly, 2002; Kimbell et al., 2001a, b; Overton et al., 2001; CIIT, 1999). EPA's cancer guidelines (U.S. EPA, 2005a) suggest using a BBDR model for extrapolation when data permit since it facilitates the incorporation of MOA in

risk assessment. The CIIT modeling and available data were evaluated in a series of peer-reviewed papers (Klein et al., 2010; Crump et al., 2008; Subramaniam et al., 2008, 2007) and debated further in the literature (Conolly et al., 2009; Crump et al., 2009). Alternatives to the parametrization and model structure in the CIIT biological modeling (but based on that original model) are further explored and evaluated in this assessment (Appendix E). Appendix F carries out a sensitivity analysis of the human risk estimates in Conolly et al. (2004) based on key uncertainties evaluated in Appendix E. These BBDR models are used in this assessment to calculate PODs from the dose-response curve for the F344 rat nasal tumor risk; extrapolation to human is then carried out by using EPA's baseline ("default") approach (U.S. EPA, 1994) but using model-derived internal dose metrics for rat and human. See Section 5.3.3 for rationale supporting these decisions.

First, the key features of the BBDR modeling in Conolly et al. (2003, 2004) are briefly described, and the following notation is used throughout this section: N cell = normal cell; I cell = initiated cell; LI = labeling index and is equal to the number of labeled cells/(number labeled + unlabeled cells); ULLI = unit length LI equal to the number of labeled cells/length of basement membrane; α_N = division rate of normal cells ($hour^{-1}$); μ_N = rate at which an initiated cell is formed by mutation of a normal cell (per cell division of normal cells).

In Conolly et al. (2003), tumor incidence data in the Kerns et al. (1983) and Monticello et al. (1996) long-term bioassays were modeled by using an approximation of the two-stage clonal growth model (Moolgavkar et al., 1988) and allowing formaldehyde to have a direct mutagenic action. Conolly et al. (2003) combined these data with historical control data on 7,684 animals obtained from National Toxicology Program (NTP) bioassays. These models are based on the Moolgavkar, Venzon, and Knudson (MVK) stochastic two-stage model of cancer (Moolgavkar et al., 1988; Moolgavkar and Knudson, 1981; Moolgavkar and Venzon, 1979), which accounts for growth of a pool of normal cells, mutation of normal cells to initiated cells, clonal expansion and death of initiated cells, and mutation of initiated cells to fully malignant cells.

The MVK model for formaldehyde accounted for two MOAs as follows that may be relevant to formaldehyde carcinogenicity:

1. An indirect MOA in which the regenerative cell proliferation in response to formaldehyde cytotoxicity increases the probability of errors in DNA replication. This MOA was modeled by using labeling data on normal cells in nasal mucosa of rats exposed to formaldehyde.
2. A possible direct mutagenic MOA, based on information indicating that formaldehyde is mutagenic (Speit and Merk, 2002; Heck et al., 1990; Grafström et al., 1985), was modeled by using rat data on formaldehyde production of DPXs (Monticello et al., 1996,

1991). In Conolly et al. (2003), the intracellular dose that induces mutations is considered proportional to the local DPX dose.

The human model for formaldehyde carcinogenicity (Conolly et al., 2004) is conceptually very similar to the rat model. The model uses, as input, results from a dosimetry model for an anatomically realistic representation of the human upper airways and an idealized representation of the lower airways. However, the model does not incorporate any data on human responses to formaldehyde exposure.

A novel contribution of the CIIT model, described by the schematic in Figure 5-11, is that cell replication rates and DPX concentrations are driven by local dose, which is formaldehyde flux to each region of nasal tissue expressed as pmol/mm^2-hour. This dosimetry is predicted by computational fluid dynamics (CFD) modeling using anatomically accurate representations of the nasal passages of a single F344 rat or Caucasian male human (see chapter 3). Such a feature is important in incorporating site-specific toxicity in the case of a highly reactive gas like formaldehyde for which uptake patterns are spatially localized and significantly different across species (see chapter 3). In the CIIT model, each of these parameters is characterized by local flux (see Figure 5-11). The inputs to the two-stage cancer modeling consisted of results from other model predictions as well as empirical data as follows:

- Regional uptake of formaldehyde in the respiratory tract was predicted by using CFD modeling in the F344 rat and human (Kimbell et al., 1997a, 2001a, b; Overton et al., 2001; Subramaniam et al., 1998).
- Replication rates for normal cells were inferred from LI data on rats exposed to formaldehyde (Monticello et al., 1996, 1991, 1990).
- Concentrations of DPXs linked to the regional flux of formaldehyde were predicted by a PBPK model (Conolly et al., 2000) calibrated to fit the DPX data in F344 rat and rhesus monkey (Casanova et al., 1994, 1991) and subsequently scaled up to humans. The DPX concentration levels were incorporated into the two-stage clonal expansion model by defining mutation rate of normal and initiated cells as the same linear function of DPX. That is,

$$\mu_N = \mu_I = \mu_{Nbasal} + KMU \times DPX \qquad (5\text{-}1)$$

where μ_N is the rate at which an initiated cell is formed by mutation of a normal cell (per cell division of normal cells), and likewise μ_I is the rate at which a malignant cell is formed by mutation of an initiated cell (per cell division of initiated cells). The unknown

constants μ_{Nbasal} (the baseline rate) and KMU were estimated by fitting model predictions to the tumor bioassay data.

The rat model in Conolly et al. (2003) involved six unknown statistical parameters that were estimated by fitting the model to the rat formaldehyde bioassay data shown in Table 5-22 (Monticello et al., 1996; Kerns et al., 1983) plus data from several thousand control animals from all the rat bioassays conducted by the NTP. These NTP bioassays were conducted from 1976 through 1999 and included 7,684 animals with an incidence of 13 SCCs (i.e., 0.17% incidence). The resulting model predicts the probability of a nasal SCC in the F344 rat as a function of age and exposure to formaldehyde. The fit to the tumor incidence data is shown in Figure 5-12 (in Section 5.3.3.). (For later reference in Appendix E, this figure compares the fit to the data obtained by the modeling in Conolly et al. [2003] with that obtained by the reimplementation of this model in Subramaniam et al. [2007].)

Subsequent to the BBDR model for modeling rat nasal cancer, Conolly et al. (2004) developed a corresponding model for humans for the purpose of extrapolating the risk to humans estimated by the rat model. Also, rather than considering only nasal tumors, the model is used to predict the risk of SCC in the entire human respiratory tract. The human model for formaldehyde carcinogenicity in Conolly et al. (2004) is conceptually very similar to the rat model in Conolly et al. (2003) and follows the schematic in Figure 5-11. The following points need to be noted:

- The model does not incorporate any data on human responses to formaldehyde exposure.
- The model is based on an anatomically realistic representation of the human nasal passages (in a single individual) and an idealized representation of the lower respiratory tract. Local formaldehyde flux to respiratory tissue is estimated by a CFD model for humans (Kimbell et al., 2001a; Overton et al., 2001; Subramaniam et al., 1998).
- Rates of cell division and cell death are, with a minor modification, assumed to be the same in humans as in rats.
- The concentration of formaldehyde-induced DPXs in humans is estimated by scaling up from values obtained from experiments in the F344 rat and rhesus monkey (Conolly et al., 2000, and also discussed further in Section 3.6.6 of this document). The human value for KMU in Equation1 is obtained by assuming that the ratio KMU/μ_{basal} is invariant across species. The other statistical parameters for the human model are either: (a) estimated by fitting the model to the human background incidence of tumors, (b) assumed to have the same value as that obtained in the rat model, or, (c) in one case, fixed at a value suggested by the epidemiologic literature.

Some further clarification pertaining to the structure and calibration of the models in Conolly et al. (2004, 2003) that are key to understanding model assumptions is provided in Appendix D.

5.3.2.1. *Major Results of the CIIT Modeling Effort*

Based on the biologically based modeling of the rat SCC data, CIIT (1999) and Conolly et al. (2004, 2003) presented the following major conclusions. The evaluation of the strength of these conclusions is summarized in Section 5.3.3., and as addressed in that section, this current assessment is not in agreement with these conclusions.

- The putative, directly mutagenic action of formaldehyde "does not play a significant role in the tumor response in the rat (and also in the human), [and such a conclusion] should be robust for any potentially mutagenic effect of formaldehyde with a time course similar to that of DPX."
- Respiratory cancer risks associated with inhaled formaldehyde are de minimis (10^{-6} or less) at relevant human exposure levels. This was based on using an upper bound on the model estimate for the directly mutagenic action of formaldehyde.
- Therefore, exposure standards protective of effects of formaldehyde-induced cytotoxicity should be sufficient to protect from its potential carcinogenic effects.
- The human risk estimates in Conolly et al. (2004) were judged by the authors to be conservative in the face of model uncertainties because the model: (a) included a hockey-stick model for normal cell replication rates when the cell replication dose-response curve as averaged by the authors had a J shape, (b) used overall respiratory tract cancer incidence data in humans, and (c) evaluated the model at the statistical upper bound of the proportionality parameter relating DPXs to the probability of mutation.
- The dose-response assessment in Conolly et al. (2004) did not explicitly evaluate the risk of lymphohematopoietic cancers. However, Conolly et al. (2004) argued that formaldehyde was unlikely to cause the cancers reported in Hauptmann et al. (2003). Their reasoning was based on the steepness of the dose-response curve predicted in Conolly et al. (2004) for respiratory cancer at exposures of 1 ppm and above, and the conclusions in Heck and Casanova (2004).

5.3.3. This Assessment's Conclusions from Evaluation of Dose-Response Models of DPX, Cell-Replication and Genomics Data, and of BBDR Models for Risk Estimation

The CIIT modeling of the rat tumor incidence and mechanistic information detailed in Section 5.3.1 and alternative models that were developed based on the conceptual framework in the CIIT modeling were extensively evaluated for this assessment. These results are presented in Appendices D, E (BBDR modeling of the rat data), and F (sensitivity analysis of BBDR model

results for human risk). In particular, Table E-1 in Appendix E and Table F-1 in Appendix F tabulate all the uncertainties and assumptions that were examined along with results of that evaluation. The quantitative and qualitative characterization of the cell replication data from Monticello et al. (1996, 1991) are presented in Appendix E. The most significant conclusions resulting from these various analyses, focusing on the ones that have maximal impact on the dose-response assessment, are presented below.

Description of Time-to-Tumor Data

The overall approach and use of data in Conolly et al. (2004, 2003) have substantial advantages to offer in describing the dose response observed in animal bioassays. The authors' model provides a good statistical description of the time-to-tumor data. The fit to the data was found to be superior to that obtained by using multistage-Weibull time-to-tumor modeling of the tumor incidence data (comparison based on visual inspection [see Figure 5-12 in this section and Figures 5-17, 5-18, 5-19 in Section 5.3.4]).

Integration of Various Relevant Data

The model framework integrates various pharmacokinetic and pharmacodynamic components (regional formaldehyde flux, DPX, cell-replication, and tumor incidence data) within a single conceptual framework and thus facilitates description of the tumor dose response that utilizes the extensive mechanistic information available for formaldehyde.

Regional Dosimetry

Regional (site-specific) dosimetry in the upper respiratory tract is considered important for understanding the tumorigenicity of a reactive chemical like formaldehyde. The regional dosimetry models discussed in chapter 3 compute local formaldehyde flux to the tissue and are based on anatomically realistic constructions of the nasal airways in each species. The other relevant mechanistic data, DPX and cell replication, are expressed as a function of this local formaldehyde flux.

Confidence in Dosimetry

Model predictions of formaldehyde flux to the respiratory lining have not been verified experimentally, and such verification would present formidable experimental challenges. Overall, the formaldehyde dosimetry modeling utilized in the CIIT modeling presents a reasonable level of confidence, as detailed in chapter 3, Section 3.6, by virtue of agreement among multiple model predictions (models that predict airflow profiles as well as a PBPK model

for DPX, which uses the calculated formaldehyde flux as input) and various kinds of available data. These data comprise airflow profiles in physical casts of the nasal cavity of an F344 rat (Kimbell et al., 1997a, 2001a), a human (Subramaniam et al., 1998), and a rhesus monkey (Kepler et al., 1998); DPX data (see discussion of Cohen-Hubal et al. [1997] in chapter 3); and qualitative concordance between uptake patterns and cell proliferation (Morgan et al., 1997; Monticello et al., 1996). The CFD models of formaldehyde flux represent only an individual of each species. However, considerable interindividual differences are to be expected in the regional dosimetry, particularly in the human (Garcia et al., 2009: Subramaniam et al., 2008). This is discussed briefly in Chapter 3 (see Section 3.6) and further in Appendices B and F.

Control Tumor Data

In developing their model, Conolly et al. (2004, 2003) included control rats from all NTP cancer bioassays—a total of 7,684 rats. As elaborated in Appendix E, lumping **all** NTP historical control animals along with the control animals in the Kerns et al. (1983) and Monticello et al. (1996) inhalation bioassays does not appear to be supportable and substantially alters dose-response predictions (Crump et al., 2009, 2008; Subramaniam et al., 2008, 2007). There are legitimate questions regarding comparability of results in rats from different stocks, studied at different times, in different laboratories, and by different routes of exposure and evaluated by using somewhat different pathological procedures (Haseman, 1995; Rao et al., 1987). If historical controls are used from only those inhalation studies that present a low potential for genetic and time-related variations in tumor incidence and survival of animals or if only concurrent controls are used, the model for extrapolation of risk to humans (the human BBDR model) becomes numerically unstable. In such a model, it is not possible to bound human risk by using the extrapolation approach applied in the CIIT model. When the included NTP control data were restricted to those from NTP **inhalation** studies, the upper bound human risk estimate obtained by Conolly et al. (2004) (i.e., with everything else in their modeling retained unchanged) was increased by 50-fold (Crump et al., 2008).

Cell Replication Dose Response

As discussed in chapter 4, characterization of the uncertainties and variability in the cell replication dose response is crucial to understanding formaldehyde carcinogenicity. Analyses of the data in Monticello et al. (1991, 1996) to derive dose response curves for cell replication are presented in Appendix E and are partly published in Subramaniam et al. (2008). The raw individual animal data from this bioassay were made available to EPA. The analyses demonstrate the following:

- Sustained exposure to formaldehyde affects cell division rates (compared to baseline levels) over a continuum of formaldehyde flux to the nasal lining that includes flux levels below those thought to be cytotoxic.
- Given the qualitative and quantitative uncertainties in the data and in their interpretation, a variety of cell replication dose-response models are plausible as reasonable characterization of the data. Cell replication response differs substantially among nasal sites and over time during the course of the bioassay. In consideration of these differences, the dose response for cell replication included shapes that were monotonic increasing as well as nonmonotonic at low dose (also see Meng et al. 2010 and a discussion of their data in Appendix F). For example, rather different statistical descriptions of the data result depending on whether
    i. different sites and exposure times were modeled separately;
    ii. all exposure times were pooled to model the response at each site;
    iii. the labeling index was time-weighted and averaged over all sites;
    iv. flux and labeling index were weighted by the number of cells at a given site;
    v. the short exposure durations in Monticello et al. (1991) were examined separately. In addition, transient increases in cell turnover at subcytotoxic doses are seen in other experiments in rats exposed to formaldehyde (see chapter 4).
- At higher, cytolethal formaldehyde flux levels, regenerative hyperplasia-induced cell proliferation clearly takes over.

Genotoxicity

Chapter 4 provides multiple lines of evidence to characterize formaldehyde as a genotoxicant. Of particular note is the observation of cytogenetic effects at human occupational exposures and the formation of DPXs upon formaldehyde interaction with DNA at doses well below those considered cytotoxic. As noted earlier, DPX formation was detected in rats at exposures ranging from 0.3 ppm to 15 ppm. These DPX levels are seen to be statistically significantly increased over baseline levels at 2 ppm and above. The DPX measured at 0.7 ppm shows a trend that is consistent with an increase at this dose (see chapter 3), and it is critical to consider "trend" when analyzing low-dose data.

Inferences on MOA from Modeling the Data

The highly curvilinear nature of dose responses associated with DPX formation, LI data, and tumor response, as well as mechanistic interpretation of these observed data, have provided grounds for arguments in the literature that formaldehyde tumorigenicity (at exposures ≥6 ppm) should be uncoupled from its potential carcinogenicity in the low-dose region. Furthermore, some researchers have argued that any potential low-dose risk is due to formaldehyde's mutagenicity, that this mutagenic potential is too weak to be of significance, and that the observed risk is entirely due to cell proliferation induced by regenerative hyperplasia in response to cell injury at cytotoxic doses (i.e., without a relevant role for the direct mutagenic action of formaldehyde). Conolly et al. (2004, 2003) represented a quantitative expression of this point of view. However, alternative parametrizations of the model used in Conolly et al. (2004, 2003) have shown that the mutagenic component can be important to explaining the observed tumor incidence and that the risk at low dose due this mutagenicity can be significant (Subramaniam et al., 2007; Appendix E).

As mentioned in 5.3.3.6, analysis of the considerable uncertainty-variability in the cell labeling data indicates that, upon exposure to formaldehyde, cell replication is significantly altered over a continuum that includes low and high concentration levels. At high dose, the effect on cell replication is regenerative. At lower doses, the data indicate that both monotonic and nonmonotonic dose-response curves for cell replication are plausible. Various plausible dose-response curves for cell replication were incorporated into the alternate BBDR models evaluated in this assesment (see Appendix E) and were seen to strongly influence the low-dose response curves for risk. The following exercise was particularly instructive in illuminating the uncertainty in the shape of the dose-response curve at low dose. The BBDR models were exercised with normal cell replication rates considered to be less than (nonmonotonic) or equal to (threshold) baseline rates over a segment of the low-dose range. Such a scenario did not necessarily lead to lower than baseline or threshold in formaldehyde respiratory cancer risk in the rat in that low-dose range[13]. This is partly because there are no data to inform how formaldehyde-induced mutation might alter cell replication and apoptotic rates (in particular if the mutation is to be construed as an initiating event in the carcinogenesis).

Accordingly, the dose-response assessment in this document does not treat formaldehyde as a threshold carcinogen.

[13] all the models reproduced the chronic time-to-tumor data well

Kinetics of Initiated Cells

Modeling results are hypersensitive to the division and death rate of initiated cells that cannot be further inferred by the available empirical cell labeling data (Conolly et al., 2009; Crump et al., 2009, 2008). Several plausible alternate model structures for describing initiated cell kinetics, none of which degrade the agreement of the model with the underlying data used to construct the model originally, led to low-dose risk estimates in the rodent that varied by many orders of magnitude, including negative values (see Figures E-5A,B and E-6A,B in Appendix E).

Extremely small perturbations in the division rate (and, likewise, of death rates) of initiated cells in the model lead to human risk estimates ranging anywhere from negative values to +0.01 at 0.01 ppm (see Crump et al. 2008 and Appendix F, Figure F-5). These perturbations were small compared with the normal variation in the division rates of normal cells.

The sensitivity analyses on the basis of which these conclusions were reached have been criticized as resulting in implausible risk estimates (given the epidemiologic data) as a consequence of implementing model variations that are not biologically reasonable (Conolly et al. 2009). This criticism was rebutted by Crump et al. (2009) on biological and epidemiological grounds. These debates are discussed fully in Appendix F.

In addition, there are major qualitative uncertainties in extrapolating normal cell replication rates from the rat to human (see Table F-1 in Appendix F, and Subramaniam et al. [2008]). Subramaniam et al. (2008) examined the inferences that arise from the assumptions in the CIIT model on initiated cell replication and death rates and concluded that several inferences were not supportable on the basis of available biological information (see Appendix E, Section E.3.3.1 for a summary).

Risk Extrapolation

The modeling approach in the human formaldehyde model of Conolly et al. (2004) and the variations examined showed extreme sensitivity, including numerical instability, to uncertain model assumptions. This model, and the alternative BBDR models examined, were therefore determined not to be informative for extrapolation from animal to human at any exposure concentration. In the face of model uncertainties, the biologically based derivation of human risk estimates of 10^{-6} or less at exposures of 0.1 ppm and below in Conolly et al. (2004) or CIIT (1999) cannot be characterized as a plausible upper bound.

The use of clonal growth modeling for extrapolation of risk from high to low exposures in the rodent followed by a conventional (default) approach to extrapolate the low-dose animal risk to the low-dose human risk was next evaluated. However, as explained earlier, the models do not adequately constrain risk in the rodent. For example, various model representations as

shown in Figure E-6A,B in Appendix E were used to evaluate added MLE risk at the 10^{-5} level (see Figure F-5A,B in Appendix E) in the F344 rat. Human exposures were then calculated that would result in equivalent lifetime risk by using formaldehyde flux estimated in each species as the dosimeter and conventional extrapolation methods (U.S. EPA, 1994b). A 25-fold difference was found between the different models in the equivalent exposure concentration so derived. Model uncertainty was substantially higher than the statistical uncertainty arising out of a given model specification. Therefore, this avenue was also found not to be informative. Consequently, the CIIT model or its variations were not used in this assessment as a biologically-based or biologically-motivated means of extrapolating outside the observed dose-response in the F344 rat.

Thus, in view of all the above considerations and in accordance with EPA's cancer guidelines (U.S. EPA, 2005a), the derivation of unit risk for human respiratory cancer from animal bioassay data in this document is based on a linear extrapolation to the origin from a POD on the dose-response curve. Low-dose linearity was exhibited by the risk estimates from most of the models that were examined in the sensitivity analysis (see discussion surrounding Figure E-5A,B in Appendix E).

BBDR Modeling for Deriving an "Integrated" POD

The CIIT BBDR modeling approach provides a good fit to the time-to-tumor data and therefore allows for an appropriate determination of a POD while at the same time incorporating a large amount of mechanistic information in an integrated manner and allowing the use of model-derived internal dose estimates. Thus, use of this model provides an alternative to developing separate PODs based on several of the underlying components of the data, such as DPX, flux, and labeling data. Accordingly, the model is used in this assessment to derive a POD from a dose response, based on the nasal cancers in rats. Uncertainties in the derivation of the POD were represented by using the variations of the CIIT model examined in this chapter. These POD calculations as well as others are detailed below.

Genomics Data

The genomics data of Thomas et al. (2007) and Andersen et al. (2008) provide additional insight into formaldehyde's biological effects in the URT and the steep dose-response curve for tumorigenesis. However, as summarized in a review by Chiu et al. (2010), there are various limitations in the interpretation of these genomics data and their relevance for the pathways contributing to the disease process in humans. In particular, the data from these studies, as analyzed, do not inform the critical MOA questions pertaining to formaldehyde carcinogenicity. These insights have been elaborated in Section 4.4.5, and the difficulties in the use and interpretation of the quantitative modeling of these data, as presented in these studies, are detailed at length in Appendix G.

5.3.4. Benchmark Dose Approaches to Rat Nasal Tumor Data

This section describes various BMD analyses to determine PODs for low-dose extrapolation of SCC risk in the human respiratory tract (upper and lower).

5.3.4.1. *Benchmark Dose Derived from BBDR Rat Model and Flux as Dosimeter*

5.3.4.1.1. ***Response for benchmark dose.***

Typically, the BMD is calculated at the 5 or 10% response level. However, it appears appropriate to consider the benchmark response (BMR) at lower levels in exceptional cases that are supported by empirical data. In the case of data combined from the Kerns et al. (1983) and Monticello et al. (1996) bioassays, the lowest observed tumor response of SCC was below the 1% level (at 0.85%) (see Table 5-22). Additionally, the BBDR modeling incorporates precursor response in the form of LI data. Therefore, it was determined that it would also be appropriate to evaluate the POD at the 0.5% level while still staying in the neighborhood of the experimentally observed response.

The various data presented earlier in this chapter point to highly curvilinear dose responses for formaldehyde-induced tumor incidence as well as DPX and cell replication. This is also borne out by dose-response information based on gene array data (Thomas et al. 2007; Andersen et al. 2008). Cytotoxicity-driven regenerative replication and epithelial degeneration play a critical role in the steeply rising nature of the tumor dose-response. These observations raise the concern that cancer potency derived by straight-line extrapolation from the low end of observed tumor data (roughly at the 1% response) has the potential to be a significant overestimate for a reasonable upper bound. The pertinent question then is: what is a low-dose linear dose-response modeling of the data that is statistically consistent with the uncertainties in the observed time-to-tumor data. To address this question, the risk estimate based on the linear

extrapolation from a POD (based on the statistical upper confidence bound on risk) to the origin is compared with that predicted at the low-dose end by the Multistage-Weibull model fitted to the observed time-to-tumor data. The unit risk based on this model is obtained by calculating q1*, the 95% statistical upper bound on the coefficient associated with the linear term in the multistage model polynomial. This model fits the data reasonably well, reflects the highly curvilinear shape of the dose-response because of its mathematical flexibility, and allows for the possibility of low-dose linearity. Thus, for comparison the following estimates of unit risk are also presented (in addition to the unit risks calculated at the 1%, 5% and 10% response levels):

1. Unit risk that is based on q1*, which is derived from fitting the multistage Weibull model to the observed data.
2. Unit risk based on low-dose linear extrapolation from a POD at the 0.5% level.

5.3.4.1.2. ***Dose metric.***

The dose metric used for the extrapolation was the average wall mass flux of formaldehyde (expressed in pmol/mm^2-hour to the entire surface of the airway lining but excluding tissue lined by nonmucus-coated squamous tissue, which was considered to not absorb formaldehyde). The use of flux as a dosimeter is similar to the calculation of a regional gas dose ratio (RGDR) as proportional to minute volume divided by the surface area in the given species and is thus in line with EPA's guidance for calculating a dosimetric adjustment factor (DAF) for category 1 gases, whose effects are presumed to be at the POE (U.S. EPA, 1994b) (i.e., ratio of average flux over the same respiratory region in each species = ratio of the quantity [minute volume/surface area of the region] between the two species). This lends support to an interspecies extrapolation based on the equivalence of formaldehyde flux as a determinant of risk.

The spatial distribution of formaldehyde over the nasal lining was characterized by partitioning the nasal surface by formaldehyde flux to the tissue, resulting in 20 "flux bins" (see Figure 5-13). Each bin is comprised of elements (not necessarily contiguous) of the nasal surface that receive a particular interval of formaldehyde flux per ppm of exposure concentration (Kimbell et al., 2001b). The spatial coordinates of elements comprising a particular flux bin are fixed for all exposure concentrations, with formaldehyde flux in a bin scaling linearly with exposure concentration (ppm). The number of cells at risk varies across the bins, as shown in Figure 5-14.

5.3.4.1.3. ***Extrapolation to humans.*** For linear extrapolation from the 0.5 and 1% levels, two alternative versions of the biologically based model in Conolly et al. (2003) for the F344 rat were used. In both cases, only the historical control data from NTP inhalation studies (as opposed to all NTP studies) were added to the concurrent controls and weekly averaged DPX concentrations as calculated by Subramaniam et al. (2007) (who implemented a variant of the PBPK model in Conolly et al. 2000) were used. Both models provided good fits to the tumor incidence data, similar to the fit shown in Figure 5-12. Neither model could be considered better than the other on the basis of model description of tumor incidence data. The values of the parameters in these models and their fit to the data are provided in Tables E-4 and E-5 of Appendix E.

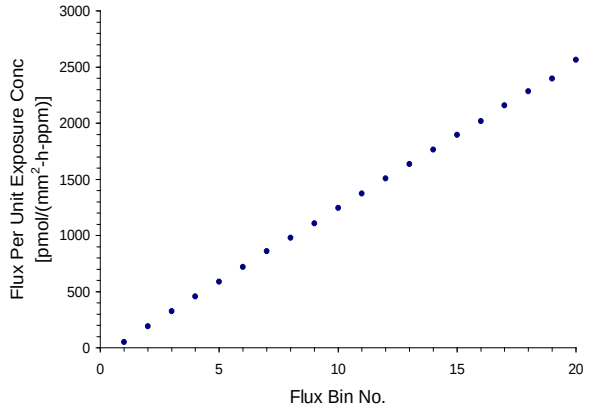


Figure 5-13. Spatial distribution of formaldehyde over the nasal lining, as characterized by partitioning the nasal surface by formaldehyde flux to the tissue per ppm of exposure concentration, resulting in 20 flux bins.

Source: Subramaniam et al. (2008).

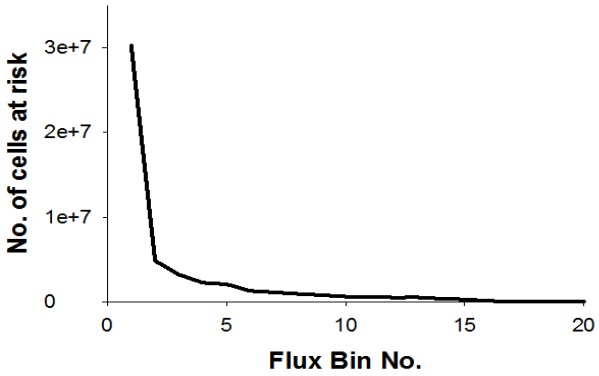


Figure 5-14. Distribution of cells at risk across flux bins in the F344 rat nasal lining.

Source: Subramaniam et al. (2008).

In Model 1 the normal cell replication dose response was described by the same hockey-stick-shaped curve used in Conolly et al. (2003). The form of the dose-response curves for initiated cell kinetics (division and death) was also the same as that considered by Conolly et al. (2003). This model is the same as Model E in Table III of Subramaniam et al. (2007) and values of the parameters and model fit to the data can be obtained from their Table.

Model 2 was an alternative to the Conolly et al. (2003) model, and is denoted as Model 15 in the sensitivity analysis described in Appendix E (see Figures E-6A and Table E-4 for parameter values). The dose response for replication of normal cells was monotone increasing and did not exhibit a threshold in dose. This was obtained by fitting the 13-week cell replication data in Monticello et al. (1996). The raw replicate animal data from this study was provided to EPA by the Hamner Institutes for Health Research. The cell replication dose response for initiated cells was a sigmoidal-shaped curve, increasing monotonically with flux from a background value up to an asymptotic value. The baseline cell-replication for initiated cells was constrained to be equal to or greater than the baseline rate of division of normal cells. Initiated cell death rate was considered proportional to initiated cell birth rate. The biological rationale for these choices is given in Appendix E.

Models 1 and 2 predicted monotonic dose-response curves.

The sequence of steps in arriving at a unit risk for SCC in human nasal airways from a given BBDR modeling of the F344 rat nasal tumor incidence data is outlined below. Extrapolation to the lower respiratory tract is described later.

1. Calculate the MLE risk and 95% upper confidence bound on risk at various exposure concentrations (d_{RAT} in ppm) by exercising the two BBDR models. Here, the POD is defined as d_{RAT} for which the 95% upper bound added risk is either 0.005 or 0.01. These values approximate the 95% lower bounds on the BMD corresponding to the added risks (i.e., the $BMDL_{RAT}$).
2. Using CFD modeling simulations in Kimbell et al. (2001b), calculate the average flux over the entire rat nose at resting breathing rates corresponding to d_{RAT}. Here, the subscript "i" is over flux bins and N is the number of cells at risk in a given bin.

$$AvgFlux(d_{RAT}) = d_{RAT} \times \left[\frac{\sum_i \left(\frac{flux}{ppm}\right)_i \cdot N_i}{\sum_i N_i} \right]_{RAT} \quad (5\text{-}3)$$

3. The experiment exposure was for periods of 5 days/week, 6 hours/day. Therefore, calculate the average daily exposure, obtained by making a 5/7 × 6/24 duration adjustment; that is, 5/7 × 6/24 × AvgFlux(d_{RAT}).
4. Now assume that lifetime exposure to similar levels of average formaldehyde flux to cells at risk leads to similar lifetime risk (MLE or upper bound, respectively) of tumor incidence across animal species. Also, in calculating human equivalent

concentrations, EPA has traditionally assumed chronic animal laboratory exposure scenarios to be equivalent to human lifetime exposures (U.S. EPA, 1994b).

5. Since a CFD model for a human upper respiratory tract is available (Subramaniam et al., 1998), it is possible to determine the average wall mass flux in this particular human nose for any specific breathing scenario. Likewise, a computational "single-path" model to determine average mass flux at any specific lung depth was available (Overton et al. 2001); however, risk in the lower respiratory tract will be addressed later. From the human CFD simulations in Kimbell et al. (2001a, b), the human airborne exposure concentration level that would yield an average wall mass flux in the human nose equal to [(5/7) × (6/24) × AvgFlux(d_{RAT})] is then calculated. In other words, given a risk-specific dose in the rat, the equivalent human exposure concentration is given by

$$d_{HUMAN} = (5/7) \times (6/24) \times AvgFlux(d_{RAT}) \times \left[\frac{\sum_i N_i}{\sum_i (\frac{flux}{ppm})_i \times N_i} \right]_{HUMAN} \quad (5\text{-}4)$$

6. To use this equivalent human exposure concentration, make the following assumption: when humans are exposed to the above concentration of formaldehyde (d_{HUMAN}) throughout the course of a lifetime, the added risks are anticipated to be similar to those experienced by the animal in the chronic bioassay.

7. Let *f* denote the ratio of the average flux per ppm of exposure concentration in the two species:

$$f = \frac{\left[\frac{\sum_i (\frac{flux}{ppm})_i \times N_i}{\sum_i N_i} \right]_{RAT}}{\left[\frac{\sum_i (\frac{flux}{ppm})_i \times N_i}{\sum_i N_i} \right]_{HUMAN}} \quad (5\text{-}5)$$

Now, the olfactory epithelium comprises a substantial fraction of nasal tissue in the rat. Because the olfactory region in the rat projects directly in the path of main airstreams (Kimbell et al., 1997a), a sizable flux of formaldehyde is delivered to this region in the rat. Tumors were not observed in the olfactory tissue of the rat. Therefore, since effects observed in the rat are being extrapolated to the human, cells from olfactory tissue are excluded in calculating average flux in the rat in the Equation 4. For the human, both volumetric flow (2.5%, Subramaniam et al. [1998])

and surface area (~5%, Kelly et al. [2000]) for the olfactory region are relatively small, so inclusion of this region is not likely to make a difference of much significance in the calculation of average flux in the human. Since data on formaldehyde flux delivered to the human olfactory region were not readily available, the olfactory region was not excluded for the human. The average human flux calculated here uses a working level classification for the activity profile where an individual spent equal amounts of time in a day at resting and light and moderate activity levels, corresponding to minute volumes of 7.5, 9, and 25 L/minute, respectively. This resulted in the following ratio[14]:

$$f = 444_{[rat]}/956.4_{[human]} = 0.46 \quad (5\text{-}6)$$

8. The airborne exposure concentrations d_{HUMAN} corresponding to a given MLE and upper bound lifetime added risk levels are the human BMD_{HUMAN} and $BMDL_{HUMAN}$, respectively. These are shown in Figure 5-15. (The rather sudden increase by ~0.0015 in the upper confidence bound on risk for model 1 for exposure exceeding ~0.41 ppm could not be explained. This jump was verified by repeated calculations that used different initial simulation conditions and convergence criteria.)

Extrapolation to the human lower respiratory tract

Next, the human lower respiratory tract is also considered to be potentially at risk. Therefore, the above calculations of BMD and BMDL need to be augmented to include the lower respiratory tract for humans. This calculation was facilitated by dosimetry calculations of formaldehyde wall mass flux to various depths in the lung by using a single path model. Refer to Overton et al. (2001) for details on their dosimetry modeling. The calculations for including the lower respiratory tract in determining an overall BMD and BMDL involved the following steps:

a. As given by Equation 5-3, calculate d_{HUMAN} for various MLE risk levels. This gives a dose-response relationship for lifetime risk of SCC in the human nose due to continuous exposure to airborne formaldehyde.

b. Express this dose-response relationship in terms of average flux over the entire human nasal lining.

c. Next, express this dose-response relationship, calculated here for the entire nose, as risk per nasal cell versus average flux.

[14] This is to be contrasted with a corresponding value of 0.71 in Schlosser et al. (2003) who used only resting inspiratory rates.

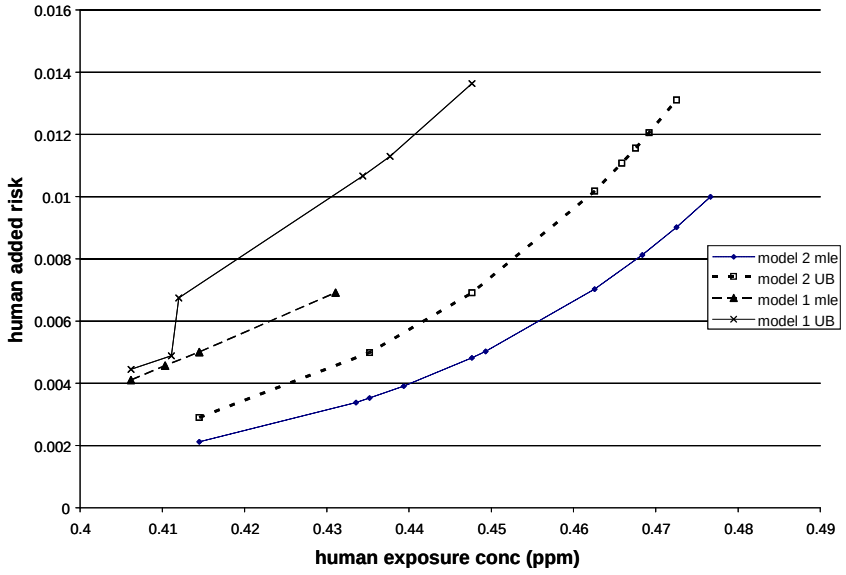


Figure 5-15. MLE and upper bound (UB) added risk of SCC in the human nose for two BBDR models.

Note: Airborne exposure concentrations d_{HUMAN} corresponding to a given MLE and upper bound lifetime added risk levels are the human BMD_{HUMAN} and $BMDL_{HUMAN}$, respectively.

d. Now, if the respiratory and transitional cell types in the human lung and nose are equally susceptible to formaldehyde-induced cancer risk (as is also assumed in Conolly et al. [2004]), then it appears reasonable to assume that MLE risk per cell at a given value of formaldehyde flux is the same in the lung as in the nose.

e. The number of cells and the average flux in a given flux bin in the lung are known (Overton et al., 2001). Thus, at a given air concentration, the MLE risk due to cells in the various flux bins of the lung is obtained.

f. One important feature of Overton et al. (2001) was that their flux bins mapped physically with lung depth. Therefore, in addition to extrapolating risk to the entire human lung, it was also relatively easy to extend the risk calculation in e. above as a function of airway generation in the lung (corresponding to different lung depths).

g. The MLE value risk to the lower respiratory tract (as determined above in steps a.−e.) was a small fraction of risk to the upper respiratory tract. This is because of high formaldehyde reactivity and solubility at the POE. Therefore, it sufficed to assume that the relative increase in upper bound risk for the combined upper respiratory tract + lower respiratory tract compared to that for only the upper respiratory tract would be the same as the corresponding relative increase in the

value of the MLE risk. The upper bound risk to the entire respiratory tract and consequently the BMDL value corresponding to a given response were thus determined.

These calculations indicated that including the risk of SCC in the lower respiratory tract resulted in at most a 3% increase in the added risk at the lower end of the human exposure range in Figure 5-15 (i.e., at 0.42 ppm) and about a 1.5% increase at the higher end of the range in that plot. Therefore, including the lower respiratory tract did not appreciably alter the human BMDs and BMDLs at the 0.5 and 1% response levels. This occurs because of the steepness in the dose-response curve in this exposure range and much lower risk in the lung at any exposure concentration.

Unit risks of SCC in the human respiratory tract extrapolated in this manner are reported in Table 5-23.

Table 5-23. BMD modeling of unit risk of SCC in the human respiratory tract

Extra risk level	Benchmark levels (ppm)		Unit risk[a] (per ppm)
	BMD	BMDL	
0.005	0.415–0.450	0.410–0.435	1.2×10^{-2}
0.010		0.430–0.460	2.2×10^{-2}

[a]Obtained from the mean of the two BMDLs.

Note: Findings are based on nasal tumors in rats and formaldehyde flux to tissue as dosimeter, using dose-response curves for the F344 rat predicted by clonal growth modeling. Two chronic bioassays (Monticello et al., 1996; Kerns et al., 1983) were combined, and control animals from the historical NTP inhalation bioassays were added to the control animals in these bioassays.

5.3.4.2. *Comparison with Other Benchmark Dose Modeling Efforts*

The CIIT assessment (Schlosser et al., 2003; CIIT, 1999) also presented, as their less preferred option, a benchmark approach on the data set obtained by combining the two chronic bioassays with similar protocols (Monticello et al., 1996; Kerns et al., 1983) along with data from 94 animals that had not been previously examined. These authors used two measures of response: tumor incidence and cell proliferation. In each case, they used two dosimeters: DPX and formaldehyde flux to the nasal lining.

The extrapolation to human was carried out by using a hybrid CFD and pharmacokinetic model. The CFD model (Kimbell et al., 2001a, b; Kepler et al., 1998; Subramaniam et al., 1998)

enabled calculation of site-specific flux in the nose of the rat, monkey, and human species for inhaled formaldehyde concentrations, and the PBPK model (Conolly et al., 2000) linked this flux to predicted DPX levels. The models were constructed for anatomically realistic representations of a single individual in each species. The CFD and PBPK modeling and uncertainties in these estimates have been reviewed in the Modeling the Toxicokinetics of Formaldehyde and DPX section of chapter 3.

5.3.4.2.1. ***Benchmark dose using administered concentration.***

Schlosser et al. (2003) fit multistage, Weibull, polynomial, and log-probit quantal models to the tumor data and exercised the models (except the log-probit) with and without requiring that the fits pass through the origin. The log-probit fit passed through the origin (see Figure 5-16). A fifth degree polynomial was used in the multistage model. The best fit was obtained with the polynomial and Weibull models for the tumor incidence data with a nonzero intercept (threshold) on the dose axis. Fits passing through the origin did not pass the statistical goodness-of-fit criteria ($p > 0.01$) for models other than the log-probit. The dose response near the lowest dose was steep, with the LED_{10}s and LED_{01}s for the administered concentrations nearly the same for each model, at least to one significant figure, and ranged from 3.8 to 6.4 ppm.

5.3.4.2.2. ***Benchmark dose derived with internal dose (flux and DPX) as dose metrics in Schlosser et al. (2003).***

Schlosser et al. (2003) used CFD simulations (Kimbell et al., 2001a, b) of mass flux of formaldehyde delivered across the nasal lining. The dose metric used by Schlosser et al. (2003) for the extrapolation was the average flux of formaldehyde, expressed in pmol/cm^2-minute, to the entire surface of the airway lining. This excluded tissue lined by nonmucus-coated squamous tissue, which was considered not to absorb formaldehyde.

In the CFD model, flux in any region is linearly related to the airborne exposure concentration (i.e., flux = $f \times C_{air}$ [ppm], where f is a constant of proportionality and C_{air} is the exposure concentration). The ratio of f (rat)/f (human) was determined as given by Equation 5-4. This ratio was equal to 0.71 and differed from the value of 0.46 used in this document (as presented in Equation 4-5) because Schlosser et al. (2003) used resting inspiratory rates.

In the next level of dosimetric complexity, Schlosser et al. (2003) used DPX as the relevant dosimeter based on values predicted by PBPK models developed by Conolly et al.

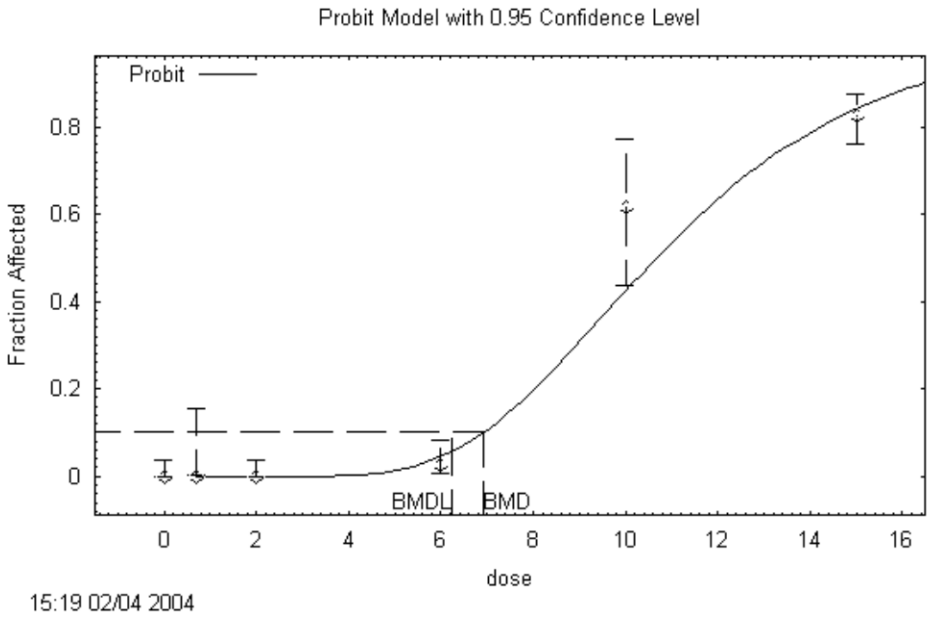


Figure 5-16. Replot of log-probit fit of the combined Kerns et al. (1983) and Monticello et al. (1996) data on tumor incidence showing BMC_{10} and $BMCL_{10}$.
Source: Adapted from Schlosser et al. (2003).

(2000). This expressed the local dose as pmol of formaldehyde equivalents covalently bound to DNA per unit volume of nasal tissue. Human CFD and PBPK models were exercised to determine the airborne concentration of formaldehyde that yields average DPX levels equal to those in the rat at the BMC. This airborne concentration was then the HEC. The human benchmark extrapolations in Schlosser et al. (2003) using flux and DPX are shown in Table 5-24, located at the end of Section 5.4.

The assumption in using DPX data was that lifetime exposure to the same DPX concentration for a given duration each day leads to equivalent risk across species. Table 5-24 shows their human benchmark calculations for a continuous environmental exposure. These were exposures that resulted in the same steady-state DPX concentrations as the weekly TWA DPX values in rats at the rat benchmark exposure concentrations.

5.3.4.2.3. ***Cell proliferation in CIIT benchmark modeling.***

Schlosser et al. (2003) also used cell proliferation as representing the adverse response. The BMDs and BMDLs calculated with these data did not differ appreciably from their other benchmark estimates. The use of cell proliferation as an end point is considered to have the

advantage that it represents an early step contributing to carcinogenesis. In this document, a BMD or BMDL is not calculated based solely on cell replication as a response. Instead, cell replication rates are used as input to the clonal growth model and a benchmark dose based on a fit to the tumor response using that model is considered a better choice since it integrates cell replication along with other relevant data, such as the number of cells at risk and DPXs.

5.3.4.3. *Kaplan-Meier Adjustment*

In the simplest consideration of the impact of competing risks on the nasal tumor incidence, tumor incidences were adjusted for early deaths according to Kaplan-Meier (KM) survival estimates (KS Crump Group, 2001). This procedure allows for the possibility that some tumors may otherwise have developed in the animals that died early due to other causes. All the animals in the study were considered except those that were kept past termination of exposure. A comparison of the adjusted incidence data is presented below in Table 5-25. While the adjustments have been provided in Table 5-25, it needs to be noted that the data allow for a full time-to-tumor analysis as presented below.

5.3.4.4. *EPA Time-to-Tumor Statistical Modeling*

Instead of using the KM adjustment, EPA has used the multistage Weibull time-to-tumor model (Portier et al., 1986; Krewski et al., 1983) in other assessments (e.g., ethylene oxide, 1,3-butadiene, chloroprene). This is a dose-response model that includes the exact time of observation of the tumors and therefore gives appropriate weight to the amount of time each animal was on study without a tumor and acknowledges earlier tumor incidence with increasing dose level. The data used in this analysis were obtained from the appendix in Conolly et al. (2003) with one crucial modification. These data combined the nasal squamous carcinoma data of Kerns et al. (1983) and Monticello et al. (1996) along with results from an additional 94 animals not previously examined in the Monticello et al. (1996) study. Animals in some exposure groups were held up to 6 months following the 24-month exposure period; these animals were deleted from the analysis for the following reason: there were no tumors among these animals, and inclusion of them would have required estimating an equivalent TWA exposure over the entire study period for these animals (40 in 2 ppm group, 39 in 6 ppm group, 3 in 15 ppm group), whereas the other animals would be represented by their actual exposure concentrations.

Table 5-24. Human benchmark extrapolations of nasal tumors in rats by using formaldehyde flux and DPX

Model	Source	Rat benchmark levels (ppm)				Extrapolated human benchmark levels (ppm)					Unit risk[a] $(ppm)^{-1}$		
			1%	5%	10%	Dose metric[b]		1%	5%	10%	1%	5%	10%
Weibull[c,d] (with threshold)	Schlosser et al. (2003)	ED	5.91	6.12	6.40	Flux[e]	ED	0.75	0.78	0.82			
		LED	5.58	5.94	6.22		LED	0.71	0.76	0.79	1.4×10^{-2}	6.6×10^{-2}	1.3×10^{-1}
						DPX[f]	ED	0.76	0.79	0.84			
							LED	0.71	0.76	0.81	1.4×10^{-2}	6.6×10^{-2}	1.2×10^{-1}
Multistage Weibull (time-to-tumor)[c,d,g]	EPA (this assessment)	ED	4.28	5.93	6.84	Flux[h]	ED	0.35	0.49	0.57			
		LED	3.57	5.52	6.41		LED	0.30	0.46	0.53	3.4×10^{-2}	1.1×10^{-1}	1.9×10^{-1}
											$q1^* = 2.2 \times 10^{-2}$		
BBDR models (see Table 5-23)	EPA (this assessment)	See Table 5-23 and associated text									at 1%: 2.2×10^{-2}		
											at 0.5%: 1.2×10^{-2}		

Note 1: Combined tumor incidence data from Kerns et al. (1983) and Monticello et al. (1996) were used for response.

[a]Slope of straight line extrapolation from the POD of the dose-response curve at the 1, 5, and 10% extra risk level.
[b]Flux: CFD modeling. DPX: CFD + PBPK modeling.
[c]*p* Value for Weibull model fit = 0.90. For the time-to-tumor modeling, goodness-of-fit *p* value was not provided by software package; therefore, fit was judged by comparing fitted curve to KM survival estimates (see Figure 5-19).
[d]For Weibull model, Schlosser et al. (2003) obtained best fit with a positive intercept on dose axis. For multistage Weibull model, curves pass through origin.
[e]Human benchmark levels extrapolated using flux were multiplied by $f_{HCHO\text{-}Rat}/f_{HCHO\text{-}Human}$ (= 0.71) for interspecies extrapolation and multiplied by (6/24) × (5/7) to adjust for continuous exposure.
[f]Human benchmark levels using DPX were continuous environmental exposures that would result in steady-state DPX levels in humans equal to the weekly TWA DPX levels in rats at the rat BMCs for 6 hours/day and 5 days/week.
[g]$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)^* t^z]$. q_0, q_1, q_2, q_3, q_4 were all taken to be zero. $q_5 = 2.9 \times 10^{-22}$, z = 8.1.
[h]Human benchmark levels extrapolated using flux were multiplied by $f_{HCHO\text{-}Rat}/f_{HCHO\text{-}Human} = 0.46$ for interspecies extrapolation and multiplied by (6/24) × (5/7) to adjust for continuous exposure (see Section 5.3.6.2).

Table 5-25. Formaldehyde-induced rat tumor incidences

Exposure level (ppm)	KM adjusted incidence	Observed tumor/ number at risk[a]
0.0	0.0	0/242
0.7	0.0	0/70
2.0	0.0	0/254
6.0	0.02	3/120[a]
10.0	0.61	22/36[a]
15.0	0.83	57/190[a]

[a]KM adjusted. Numbers not indicated by footnote were not amenable to KM adjustment because there were no tumors; these numbers at risk reflect all animals surviving 1 year on study.

Source: Monticello et al. (1996); Kerns et al. (1983).

Due to earlier tumor occurrence with increasing exposure level and increased mortality with increasing exposure level, methods that can reflect the influence of competing risks and intercurrent mortality on site-specific tumor incidence rates are preferred. EPA has generally used the multistage Weibull model because it incorporates the time at which death with tumor occurred, giving appropriate weight to the amount of time each animal was on study without a tumor; the model has the following form: $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) \times (t - t_0)^z]$, where *p(d)* represents the lifetime risk (probability) of cancer at dose *d* (i.e., human equivalent exposure in this case); parameters $q_i \geq 0$, for i = 0, 1, ..., k; *t* is the time at which the tumor was observed; and *z* is a parameter estimated in fitting the model, which characterizes the change in response with age. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death.

A further consideration is the distinction between tumor types as being either fatal or incidental in order to adjust for competing risks. Incidental tumors are those tumors thought not to have caused the death of an animal (such as those observed during interim or terminal sacrifices), while fatal tumors are thought to have resulted in animal death. For these data, nasal tumors observed with early deaths were considered to be fatal.

The dose-response analyses (see Figures 5-17, 5-18, 5-19) were conducted by using the computer software program TOX_RISK, version 5.3 (ICF, Fairfax, VA), which is based on Weibull models drawn from Krewski et al. (1983). Parameters were estimated by using the

method of maximum likelihood. Specific multistage Weibull models were selected for the individual tumor types for each sex, based on the values of the log likelihoods according to the strategy used by EPA (2002b). If twice the difference in log-likelihoods was less than a χ^2 with degrees of freedom equal to the difference in the number of stages included in the models being compared, the models were considered comparable, and the most parsimonious model (i.e., the lowest-stage model) was selected contingent on visual fits of the data as follows. For incidental tumors, plots of model fits compared with Hoel-Walburg estimates of cumulative incidence were also examined for goodness of fit in the lower exposure region of the observed data (Gart et al., 1986) (see Figure 5-18). For fatal tumors, plots of model fits were compared with KM estimates of cumulative incidence. If a model with one more stage fitted the low-dose data better than the most parsimonious model, then the model with one higher stage was selected.

Due to the sharp increase in responses between 6 and 10 ppm, no adequate fit was achieved. Data for the highest dose were dropped in an effort to focus the fitting process for this empirical model on the low-dose region. The model that then provided the best overall fit included five stages but with coefficients for the lower stages estimated to be zero (see Figures 5-17, 5-18, 5-19). The parameter t_0 was estimated to be zero, consistent with rapidly fatal tumors. On the other hand, an alternate run treating all tumors as incidental to the death of the affected animals yielded BMCLs and BMCs within 10% of these estimates (see Figure 5-18); thus, tumor context is not a sensitive consideration for these data.

For the same reasons as discussed in Section 5.3.3 (the concluding discussion of the BBDR modeling), a linear low-dose extrapolation approach was used to estimate human carcinogenic risk associated with formaldehyde exposure. PODs for estimating low-dose risk were identified at doses at the lower end of the observed data, corresponding to 1% extra risk, defined as the extra risk over the background tumor rate $[P(d) - P(0)]/[1 - P(0)]$. PODs corresponding to 10% extra risk are also provided to facilitate comparison with other chemicals. Rat benchmark levels obtained by analysis of the tumor data are shown in Table 5-24. PODs were converted to continuous human-equivalent exposure levels by multiplying by (5 days/7 days) × (6 hours/24 hours), or 0.178, and by multiplying by the ratio of fluxes developed in Section 5.3.6.1.3. The lifetime continuous inhalation unit risk for humans is defined as the slope of the line from the lower 95% bound on the exposure at the POD, calculated by dividing the BMR level (1%) by the corresponding $BMCL_{01}$. This 95% UCL represents a plausible upper bound on the true risk.

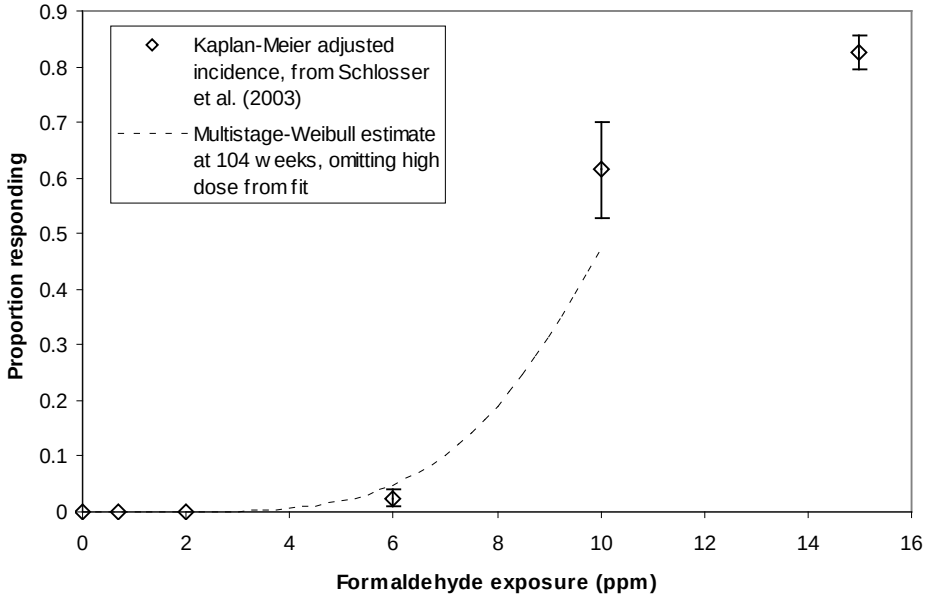


Figure 5-17. EPA Multistage Weibull modeling: nasal tumor dose response.

Note: Time-to-tumor modeling of Kerns et al. (1983) and Monticello et al. (1996) data compared with incidences adjusted by using KM estimates evaluated at 104 weeks.

Source: Adapted from Schlosser et al. (2003).

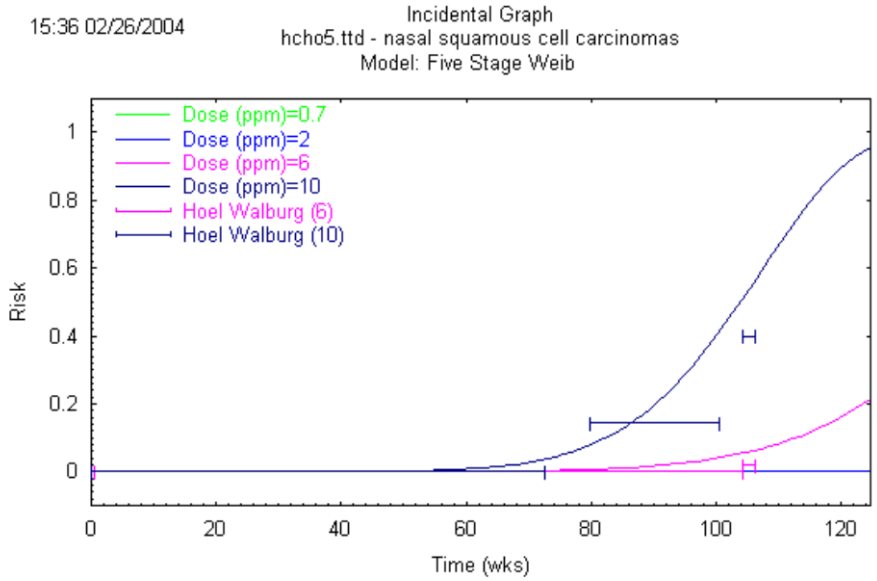


Figure 5-18. Multistage Weibull model fit.
Note: Data of Kerns et al. (1983) and Monticello et al. (1996) compared with Hoel-Walburg estimates of tumor incidences occurring at interim and terminal sacrifices.

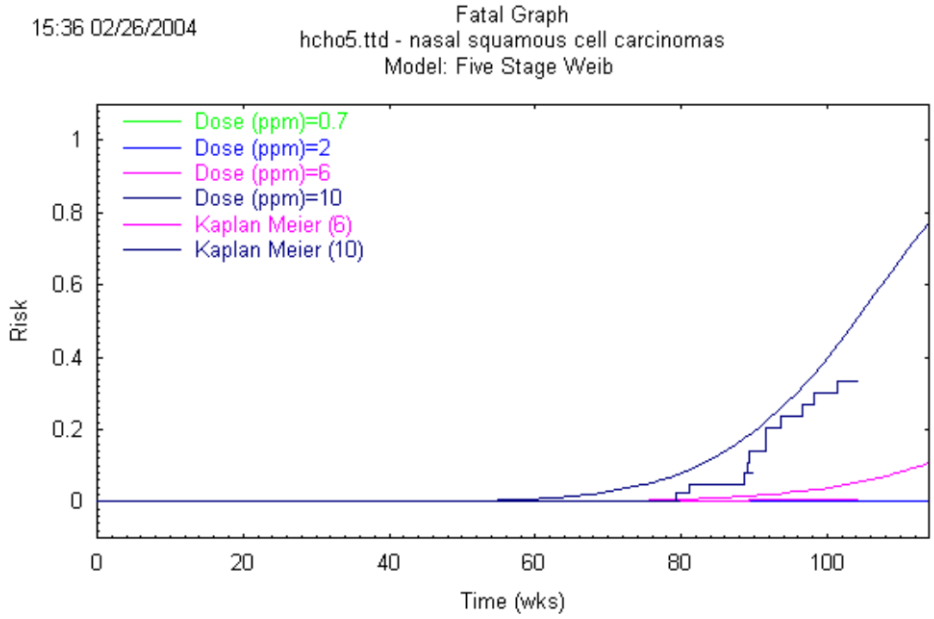


Figure 5-19. Multistage Weibull model fit of tumor incidence data compared with KM estimates of spontaneous tumor incidence.
Source: Developed from data reported in Kerns et al. (1983) and Monticello et al. (1996).

The extrapolation to humans in terms of using formaldehyde flux to tissue as the dose metric is shown in Table 5-24, where unit risk in terms of q1*, the statistical upper bound on the coefficient, q1, of the term linear in dose in the multistage model, is also presented. q1* is presented even though this is no longer done, as per current EPA practice (see Section 5.3.6 for discussion).

These results are to be compared with the preferred benchmark estimates obtained in Table 5-23 by using the results of biologically based models. In summary, the unit risks obtained by various methods, including the results in Schlosser et al. (2003), fall within a rather tight range. In particular, q1* was obtained to within a factor of two of other values even though q1 itself was zero. The general result may be noted here, that even in cases where q1 is zero, the upper bound q1* is linear with dose (Subramaniam et al., 2006; Guess et al., 1977). The large difference between q1 and q1* aptly reflects the large uncertainty in the low-dose response.

5.4. CONCLUSIONS FROM THE QUANTITATIVE ASSESSMENT OF CANCER RISK FROM FORMALDEHYDE EXPOSURE BY INHALATION

5.4.1. Inhalation Unit Risk Estimates Based on Human Data

As described in Section 5.2, a (plausible upper bound) lifetime extra cancer unit risk of 1.1×10^{-2} per ppm (8.8×10^{-6} per µg/m^3) of continuous formaldehyde exposure was estimated for NPC incidence using the log-linear modeling results (for NPC mortality from cumulative exposure) from a high-quality occupational epidemiologic study in a life-table analysis to obtain a POD and then applying linear low-dose extrapolation from the POD. Using similar methods and data from the same study for Hodgkin lymphoma and leukemia mortality from cumulative formaldehyde exposure, (plausible upper bound) lifetime extra cancer risk estimates of 1.7×10^{-2} per ppm (1.4×10^{-5} per µg/m^3) for Hodgkin lymphoma incidence and 5.7×10^{-2} per ppm (4.6×10^{-5} per µg/m^3) for leukemia incidence were derived. Sources of uncertainty in these estimates are discussed in sections 5.2.2.4 and 5.2.3.4. For the incidence risk for these three cancer types combined, a total (upper bound) cancer unit risk estimate of 8.1×10^{-2} per ppm (6.6×10^{-5} per µg/m^3) was obtained (see Section 5.2.4).

5.4.2. Inhalation Unit Risk Estimates Based on Rodent Data

As described in Section 5.3, the unit risk derived for SCC in the upper and lower respiratory tract (combined) based on linear extrapolation from PODs from several plausible models, including purely statistical modeling (nose only, quantal and time-to-tumor modeling) and biologically based modeling (entire respiratory tract), resulted in a narrow range of

1.2×10^{-2} to 2.2×10^{-2} per ppm. Risk to the lower respiratory tract was numerically insignificant compared to the nasal cancer risk.

5.4.3. Summary of Inhalation Unit Risk Estimates

The epidemiologic and rodent inhalation data indicate multiple sites of concern. Unit risk estimates calculated separately from these data are presented in Table 5-26.

As can be seen in the summary table (see Table 5-26), the unit risk estimate based on human data for NPC is in the range of the estimates calculated for respiratory tract cancer from the rodent nasal cancer data. The unit risk estimate for Hodgkin lymphoma is also in the same range, while the unit risk estimate for leukemia and the total cancer unit risk estimate are up to fourfold higher.

As noted in EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), when high-quality human data are available, they are generally preferred over laboratory animal data for quantitative risk assessment. Thus, the preferred (plausible upper bound) unit risk estimate in this assessment is the value of 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu g/m^3$) based on human data for NPC, Hodgkin lymphoma, and leukemia.

As documented in Section 4.5, formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA. Therefore, since there are no adequate chemical-specific data to evaluate the susceptibilities of different life stages by the inhalation route of exposure, increased early-life susceptibility should be assumed, and, if there is early-life exposure, the ADAFs should be applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). See Section 5.4.4 below for more details on the application of the ADAFs.

The inhalation unit risk estimates presented above, which are calculated based on a linear extrapolation from the POD (95% lower confidence bound on the EC), are expected to provide upper bounds on the risk of cancer incidence. However, for certain applications, such as benefit-cost analyses, estimates of "central tendency" for the risk below the POD are desired. Extra risk estimates per ppm based on linear extrapolation from the EC (e.g., $0.005/EC_{005}$) for the cancer responses based on the human data are reported in Table 5-27. Note that these extrapolated risk estimates are not central tendency estimates in any statistical sense because once risk is linearly extrapolated below the EC, it is no longer a function of the original (Cox regression) model which generated the ECs and the LECs. These estimates are dependent on the suitability of the EC estimates as well as on the applicability of the linear low-dose extrapolation. The assumption of low-dose linearity is supported by the mutagenicity of formaldehyde (see Section

4.5.3). [If

Table 5-26. Summary of inhalation unit risk estimates

Cancer type[a]	Dose metric	Unit risk estimate (ppm^{-1})
Based on epidemiologic data		
Nasopharyngeal	Cumulative exposure	0.011
Hodgkin lymphoma	Cumulative exposure	0.017
Leukemia	Cumulative exposure	0.057
Total cancer risk[b]	Cumulative exposure	0.081
Based on experimental animal data		
SCC of the respiratory tract	Local dose (flux) of formaldehyde in $pmol/mm^2$-hour	0.011–0.022

[a]The unit risk estimates are all for cancer incidence.
[b]The total cancer unit risk estimate is an estimate of the upper bound on the sum of risk estimates calculated for the 3 individual cancer types (nasopharyngeal cancer, Hodgkin lymphoma, and leukemia); it is not the sum of the individual (upper bound) unit risk estimates (see Section 5.2.4).

these estimates were to be used for benefit-cost analyses or some other purpose, ADAFs should be applied, as appropriate, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), as discussed above and in Section 5.4.4.]

5.4.4. Application of Age-Dependent Adjustment Factors (ADAFs)

When there is sufficient weight of evidence to conclude that a mutagenic MOA is operative in a chemical's carcinogenicity and there are inadequate chemical-specific data to assess age-specific susceptibility, as is the case for formaldehyde (by inhalation exposure; see Section 5.4.3), EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b) recommends the application of default ADAFs to adjust for potential increased susceptibility from early-life exposure (see U.S. EPA [2005b] for detailed information on the general application of these adjustment factors). In brief, EPA (2005b) establishes ADAFs for three specific age groups: 10 (for <2 years), 3 (for 2 to <16 years), and 1 (for 16 years and above). For risk assessments based on specific exposure assessments, the 10-fold and threefold adjustments to the unit risk estimates are to be

Table 5-27. Extra risk estimates per ppm based on ECs[a]

Cancer type	BMR[b]	Outcome	EC (ppm)[c]	BMR/EC_{BMR} (per ppm)[c]
nasopharyngeal cancer	0.0005	mortality	0.15	3.3×10^{-3}
		incidence	0.074	6.8×10^{-3}
Hodgkin lymphoma	0.0005	mortality	0.15	3.3×10^{-3}
		incidence	0.051	9.8×10^{-3}
leukemia	0.005	mortality	0.22	2.3×10^{-2}
		incidence	0.16	3.1×10^{-2}
Total cancer[d]		mortality		2.4×10^{-2} [d]
		incidence		4.7×10^{-2} [d]

[a]Based on all person-years. Values based on exposed person-years only would be virtually identical.
[b]BMR = benchmark response, i.e., extra cancer risk level used to calculate the ECs and LECs.
[c]To convert ppm to μg/m^3, multiply by 1,230; to convert ppm^{-1} to (μg/m^3)$^{-1}$, divide by 1,230.
[d]The extra risk estimates per ppm for total cancer are not derived from ECs but rather from the calculations of combined cancer risk at 0.1 ppm presented in Section 5.2.4 (see Table 5-20 for mortality and Table 5-21 for incidence). The sums of the MLEs of risk from Tables 5-20 and 5-21, multiplied by 10 to convert from per 0.1 ppm to per ppm, correspond to the extra risk estimates per ppm calculated from the ECs (in that they are based on MLEs and not bounds) but they are not equivalent to the sum of the EC-based values because those are calculated at different ECs and the MLEs of risk are all calculated at a common exposure level of 0.1 ppm.

combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years age) exposure. The ADAFs and their age groups may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines.

For inhalation exposures, assuming ppm equivalence across age groups (i.e., equivalent risk from equivalent exposure levels, independent of body size) and using the preferred unit risk estimate of 6.6×10^{-5} per μg/m^3 from Section 5.4.3, the calculation is fairly straightforward. For example, the ADAF-adjusted total cancer unit risk estimate for a constant lifetime exposure level is calculated as shown in Table 5-28.

This 70-year risk estimate of 1.1×10^{-4} for a constant exposure of 1 μg/m^3 calculated in Table 5-28 is equivalent to a lifetime unit risk of 1.1×10^{-4} per μg/m^3 (0.13/ppm), adjusted for early-life susceptibility, assuming a 70-year lifetime and constant exposure across age groups. As mentioned above, for risk assessments based on specific exposure assessments, application of

Table 5-28. Total cancer risk from exposure to a constant formaldehyde

exposure level of 1 μg/m^3 from ages 0–70 years

Age group	ADAF	Unit risk (per μg/m^3)	Exposure concentration (μg/m^3)	Duration adjustment	Partial risk
0 to < 2 years	10	6.6×10^{-5}	1	2 years/70 years	1.9×10^{-5}
2 to < 16 years	3	6.6×10^{-5}	1	14 years/70 years	4.0×10^{-5}
≥ 16 years	1	6.6×10^{-5}	1	54 years/70 years	5.1×10^{-5}
				Total risk =	1.1×10^{-4}

(Note that the partial risk for each age group is the product of the values in columns 2–5 [e.g., $10 \times (6.6 \times 10^{-5}) \times 1 \times 2/70 = 1.9 \times 10^{-5}$], and the total risk is the sum of the partial risks.)

the ADAFs is to be combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years age) exposure. Further example calculations can be found in EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b).

In addition to the uncertainties discussed above for the inhalation unit risk estimate, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The ADAFs are general default factors, and it is uncertain to what extent they reflect increased early-life susceptibility for exposure to formaldehyde, if, in fact, early-life susceptibility is increased as assumed. To some extent, the unit risk estimates for Hodgkin lymphoma and leukemia already reflect some partial increased risk from early-life exposure because the life-table programs include background rates for childhood cancers. However, the impact of this partial increased risk is negligible compared to the effect of the ADAFs on the final risk estimate. For example, eliminating the background rates up to age 16 from the life-table programs decreases the lifetime extra risks at the PODs by about 0.5% for leukemia and about 1.2% for Hodgkin lymphoma. The ADAFs, on the other hand, increased the lifetime unit risk estimate by about 66%.

5.4.5. Conclusions: Cancer Inhalation Unit Risk Estimates

As presented in Section 5.4.3, the preferred (plausible upper bound) cancer unit risk estimate for formaldehyde exposure in this assessment is the total cancer risk estimate of **8.1×10^{-2} per ppm (6.6×10^{-5} per μg/m^3) based on (adult) human data for NPC, Hodgkin lymphoma, and leukemia**.

In addition, as described in Section 5.4.4, because the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA and there are inadequate chemical-specific data to assess age-specific susceptibility, increased early-life susceptibility should be assumed and, if there is early-life exposure, ADAFs should be applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). Consequently, applying the ADAFs to the preferred unit risk estimate to obtain a **full lifetime unit risk estimate** yields

$$0.081/\text{ppm} \times [(10 \times 2 \text{ years}/70 \text{ years}) + (3 \times 14/70) + (1 \times 54/70)]$$
$$= \mathbf{0.13/ppm = 1.1 \times 10^{-4}/(\mu g/m^3)}$$

Using the above full lifetime unit risk estimate of 0.13 per ppm, the lifetime chronic exposure level of formaldehyde corresponding to an increased cancer risk of 10^{-6} can be estimated as follows: $(10^{-6})/(0.13/\text{ppm}) = 7.7 \times 10^{-6}$ ppm = 0.008 ppb = 0.009 μg/m^3. Similarly, the lifetime chronic exposure level of formaldehyde corresponding to an increased cancer risk of 10^{-4} is 0.8 ppb, or 0.9 μg/m^3. (Note that for less-than-lifetime exposures scenarios [or for exposures that vary with age], the adult-based combined estimate of 0.081 per ppm should be used, but if there is early-life exposure, the ADAFs should be applied in accordance with EPA's *Supplemental Guidance* [see Section 5.4.4]).

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE-RESPONSE

6.1. SUMMARY OF HUMAN HAZARD POTENTIAL

6.1.1. Exposure

Formaldehyde (CH_2O) occurs as a gas at room temperature. It is highly reactive and dissolves readily in water. Formaldehyde is present in a wide variety of products including plywood adhesives, abrasive materials, insulation, insecticides and embalming fluids (IPCS, 2002a; Agency for Toxic Substances and Disease Registry [ATSDR], 1999). The major sources of anthropogenic emissions of formaldehyde are motor vehicle exhaust, power plants, manufacturing plants that produce or use formaldehydes or substances that contain formaldehyde (i.e., glues), petroleum refineries, coking operations, incineration, wood burning, and tobacco smoke (INEG, 2003). Reported outdoor air concentrations of formaldehyde in urban and suburban areas are near 3 $\mu g/m^3$ (~ 3 ppb) (U.S. EPA, 2008) and indoor residential levels are approximately 10 times higher (Health Canada and Environment Canada, 2001).

Limited United States data indicate that the upper end of the formaldehyde concentration range in drinking water is approximately 10 µg/L IPCS, 2002a). Formaldehyde is a natural component of a variety of foodstuffs (IARC, 1995; IPCS, 1989). In addition, foods may also be contaminated with formaldehyde as a result of fumigation (e.g., grain, seeds), cooking (as a combustion product), and release from formaldehyde resin-based tableware (IARC, 1995). Limited data measuring formaldehyde in food indicates that the concentration range is <0.03−14 mg/kg Health Canada and Environment Canada, 2001). Daily intake of formaldehyde has been estimated to be between 1.5 and 14 mg/day for an average adult (IPCS, 1989; Fishbein, 1992).

6.1.2. Absorption, Distribution, Metabolism, and Excretion

In water, less than 0.1% of formaldehyde exists unhydrated, with the majority reported to be in the hydrated form, methylene glycol ($CH_2(OH)_2$) (Priha et al., 1996). Formaldehyde is a reactive molecule that can react with both low molecular weight cellular components (e.g., GSH) as well as high molecular weight components. It is also a well-known cross-linking agent.

Further, formaldehyde is a product of normal cellular metabolic processes. Endogenous formaldehyde is a constituent of the one-carbon pool. It is thought that most endogenous formaldehyde exists in a form that is reversibly bound to nucleophiles (Heck et al., 1990; 1982) and that the formaldehyde hemithioacetal adduct formed with glutathione could account for 50−80% of the total formaldehyde normally present in cells (Heck et al., 1982).

Inhaled formaldehyde is efficiently absorbed ("scrubbed") in the upper respiratory tract. The fraction that is absorbed was determined to be approximately 97% in rats (Morgan et al., 1986), and 85% and 90% respectively in computer simulations of one rhesus monkey and human at rest (Kepler et al., 1998; Kimbell et al., 2001b). As the inspiratory rate increased, this fraction decreased to about 70% during light exercise and to 58% during heavy exercise conditions in the human (Kimbell et al. 2001). During heavy exercise, the absorption of formaldehyde in the first six to eight generations of the tracheobronchial airways is estimated to be comparable to that in the nasal region (Overton et al., 2001).

Airway geometry is an important determinant of inhaled-formaldehyde dosimetry in the respiratory tract. There are large differences across species in the anatomy of the upper respiratory tract and in airflow patterns. Using computer simulation, the regional uptake patterns of formaldehyde in the upper respiratory tract are observed to be spatially nonhomogeneous and to exhibit strong species differences. Airflow patterns are also significantly different as breathing patterns and activity profiles change, depending on whether breathing is oral or nasal.

The overall information on the disposition of inhaled formaldehyde comes from many studies using different experimental methods including: [^{14}C] radiolabeling, gas chromatography-mass spectroscopy (GC-MS), dual isotope labeling (^{3}H, ^{14}C) and high-performance liquid chromatography (HPLC) studies. In a study of rats following exposure to radiolabeled formaldehyde, the radioactivity was very high in the nasal mucosa but was also extensively distributed to various tissues including the bone marrow (Heck et al., 1983). The elevated ^{14}C in various tissues was thought unlikely to be due to free formaldehyde but instead to arise from either rapid metabolic incorporation or formation of covalent adducts or incorporation via carboxylation reactions of the $^{14}CO_2$ formed during metabolism (Heck et al., 1983; Casanova-Schmitz et al., 1984). Studies using the GC-MS method indicate that exposure to formaldehyde over a wide range of exposure concentrations and durations does not result in elevated levels in blood, above those of endogenous formaldehyde levels in rats, rhesus monkeys and humans (Heck et al., 1985; Casanova et al., 1998). These GC-MS measurements are consistent with the conclusions that formaldehyde does not appreciably reach the blood, is rapidly metabolized, interacts with macromolecules when it escapes metabolism, or is otherwise undetected.

In further studies on the disposition of inhaled formaldehyde, Casanova-Schmitz et al. (1984) and Casanova-Schmitz and Heck (1983) used dual-isotope labeling of inhaled formaldehyde as an approach to distinguish between formaldehyde adduct formation and metabolic incorporation. These were followed by more sensitive experiments using HPLC measurements in rats and rhesus monkeys exposed to radiolabeled formaldehyde (Casanova et

al. 1989, 1991). Results from this sets of experiments found that labeling in the nasal mucosa was due to both covalent binding and metabolic incorporation and labeling of bone marrow macromolecules was found to be entirely due to metabolic incorporation. Overall, Heck, Casanova-Schmitz, and their coworkers interpreted the results of these experiments to indicate that inhaled formaldehyde does not reach distant sites (beyond the portal of entry) at detectable levels.

Formaldehyde is primarily metabolized by glutathione-dependent formaldehyde dehydrogenase. In humans this enzyme is referred to using the protein code of ADH3. The major factor in the disposition of formaldehyde is metabolic clearance by oxidation to formate, which is either further metabolized to CO_2 and water, incorporated into the one-carbon pool, and/or eliminated in the urine as a sodium salt.

In radiolabeling studies, Heck et al. (1983) determined that the relative contributions of various excretion pathways in F344 rats following inhalation exposure to formaldehyde were independent of exposure concentration. Nearly 40% of inhaled [^{14}C] -formaldehyde appeared to be eliminated via expiration, presumably as CO_2, while about 17% and 5% was eliminated in the urine and feces, respectively. Nearly 40% of inhaled [^{14}C] -formaldehyde remained in the carcass, presumably due to metabolic incorporation. For exposure via the oral route, absorption of [^{14}C] -formaldehyde (7 mg/kg) in rats resulted in 40% exhaled (as $^{14}CO_2$), 10% excreted in urine, 1% excreted in feces, and much of the remaining 49% retained within the carcass, presumably due to metabolic incorporation (IARC, 1995; Buss et al., 1964).

Several human and animal studies have reported formaldehyde in exhaled breath (see Section 3.6.2). However, limitations of analytical techniques employed for breath analysis can only tentatively identify formaldehyde (Španěl and Smith, 2008, Wehinger et al., 2007). A recent study has illustrated that the use of proton transfer reaction in SIFT-MS may result in false positive results for formaldehyde as the characteristic analytical product ion for formaldehyde is also produced from methanol and ethanol (Španěl and Smith, 2008). Therefore, ethanol and methanol in exhaled breath will contribute to the analytical product tentatively identified as formaldehyde in the existing literature. Additionally, some studies do not have appropriate control samples to define formaldehyde levels for inhaled air prior to breath analysis. Therefore, the two major limitations of available studies of formaldehyde levels in human breath include the potential for false positives for formaldehyde from the primary analytical technique for breath analysis and the need for concurrent room air controls.

Although several studies of healthy subjects report levels of formaldehyde between the detection limit and 12 ppb (Wang et al., 2008; Cap et al., 2008 and Kushch et al., 2008), there was no adjustment for an artifact in the analytical method that makes it impossible to distinguish

between formaldehyde and reaction products for 1% of exhaled methanol and ethanol which are detected at the same mass to charge ratio as formaldehyde in these analytical techniques (Spanel and Smith, 2008). To date, there is no published study of formaldehyde in exhaled breath which makes this adjustment for reporting formaldehyde levels. Therefore, reports of formaldehyde in exhaled breath should be carefully interpreted as the mass reported as formaldehyde—is only tentatively identified as formaldehyde. A review of the data where methanol and ethanol levels are also provided, indicate that levels of formaldehyde (tentatively identified as m/z = 31) may reflect a significant contribution from reaction products of methanol and ethanol (see Section 3.6.2). In summary, there are insufficient data at this time to confidently establish a concentration of formaldehyde in exhaled breath that can be attributed to endogenous sources. This assessment identifies a critical research need for further studies on the measurement of exhaled formaldehyde.

6.1.3. Noncancer Health Effects in Humans and Laboratory Animals

A wide variety of human clinical and observational epidemiology and animal studies provide evidence for health effects in response to formaldehyde exposure. Some of these health effects are commonly noted at the portal of entry, as expected for exposure to a reactive gas. In addition, effects on the nervous and reproductive systems, developmental effects, and immunomodulation have been reported. The overall weight of evidence (WOE) of human and animal studies for the hazard potential of formaldehyde is discussed below, along with information on plausible modes of action (MOAs).

6.1.3.1. *Sensory Irritation*

Formaldehyde, a chemical irritant, binds to protein receptors of the trigeminal nerve, triggering a burning and painful sensation in humans. This process is distinct from taste and smell (Nielsen 1991; Cometto-Muniz and Cain, 1992). The trigeminal nerve, which has three branches (ophthalmic, maxillary and mandibular), not only acts as an afferent nerve relaying these sensations to the central nervous system, but also has efferent nerve activity (Stedman's Medical Dictionary: Meggs, 1993). Stimulation of the trigeminal nerve may result in reflex responses including lacrimation, coughing, and sneezing. Both the reflex responses as well as sensations such as burning, pain, and itching of the eyes, nose, and throat are considered adverse.

Formaldehyde-induced eye, nose, and throat irritation has been well documented in a wide range of epidemiologic studies. Common effects of chemically-induced sensory irritation include lacrimation, burning of the eyes and nose, rhinitis, burning of the throat, and cough

(Feron et al., 2001). Studies examining these endpoints were either controlled chamber studies with a defined population (e.g., healthy volunteers or sensitive individuals), worker/student studies, or general population studies (e.g., residential). Chamber studies, by design, are acute studies, although some researchers have investigated the outcomes after repeated exposures. Occupational, student, and residential exposures are generally of longer duration, although there is variability in exposure level and duration among subjects. The endpoints for assessing irritation include self-reporting of symptoms (e.g., pain, burning, itching) and objective measures of irritation (e.g., eye-blink counts, lacrimation).

Eye irritation is the most sensitive of reported effects in human studies. Two different short-term chamber studies provide similar 10% BMDLs for eye irritation of 560 ppb and 240 ppb for 3 and 5 hour exposures, respectively (Kulle, 1993; Andersen and Molhave, 1983, modeled by Arts et al., 2006b). Various occupational studies have noted increased eye irritation for average exposures ranging from 180 ppb to 690 ppb (Horvath et al., 1988, Alexandersson and Hedenstiera, 1998; Holmström and Wilhelmsson, 1988). The results of residential studies, where in-home formaldehyde levels are used to document exposure, indicate eye irritation may increase with increasing exposure from 70 to 200 ppb for these chronic exposure scenarios (Ritchie and Lehnen, 1987, Hanrahan et al., 1984; Liu et al., 1991.)

When a rodent is exposed to an irritant, the inhaled dose and pattern of deposition can be profoundly affected by reflex bradypnea, a protective reflex observed in rodents but not in humans. Reflex bradypnea is manifest as markedly decreased activity or prostration, reduced metabolism, hypothermia (as much as 5ºC), significantly reduced respiratory rate and minute volume, and altered blood and brain chemistry. Reflex bradypnea can occur when the trigeminal nerve is exposed to a sufficient concentration of an irritant, such as formaldehyde. Because of their small size, rodents are able to rapidly lower their metabolism and body temperature and therefore their oxygen demand. The consequence is that their inhaled dose of an irritating chemical is dramatically lowered. Reflex bradypnea is quantified as the RD_{50}, which is the concentration of a chemical that results in a 50% decrease in respiratory rate (see Tables 4-7 and 4-8). After the irritant exposure is removed, it can take up to two hours for rodents to fully recover from the effects of reflex bradypnea. Even though humans do not exhibit reflex bradypnea, involvement of trigeminal nerve stimulation, which is the mechanism for reflex bradypnea in rodents, may be relevant to MOAs for formaldehyde in other species, such as primates and humans. For example, trigeminal nerve stimulation has been associated with sensory irritation in humans, highlighting the relevance of this effect.

6.1.3.2. *Respiratory Tract Pathology*

Formaldehyde-induced respiratory tract pathology includes inflammation, rhinitis, goblet cell hyperplasia, metaplastic changes, squamous cell hyperplasia, and impaired mucociliary transport. Formaldehyde binding to the trigeminal nerve triggers the release of neurogenic mediators of inflammation resulting in tissue edema, lacrimation, mucus production, and leukocyte infiltration. Therefore, observed pathological changes may be directly related to neurogenic inflammation from activation of the trigeminal nerve or result, at least in part, from formaldehyde-induced cell damage to the mucosal tissue. A series of exposures has also been positively associated with reduced mucociliary clearance, and the induction of histopathologic lesions in the nose in both human and animal studies assessing formaldehyde-induced changes in the nasal mucosa suggest that these changes may be, at least in part, a protective or adaptive response and that increased mucus flow and metaplastic changes would progress in relation to the concentration and duration of exposure protecting the underlying tissue (Swenberg et al., 1983).

In rodent studies, formaldehyde-induced histopathological lesions ranging from inflammation to ulceration, necrosis, and metaplasia have been frequently reported in nasal turbinates, maxilloturbinates, and in goblet and microvilli cells (e.g., Bhalla et al., 1991; Monteiro-Riviere and Popp, 1986; Cassee and Feron, 1994; Ionescu et al., 1978; Schreibner et al.,1979; Monticello et al., 1989). These effects were observed after a variety of exposure scenarios (e.g., 10 ppm for 4 hrs (Bhalla et al., 1991), 0.5 or 2 ppm for 6 hrs/day for 1 or 4 days and 6 or 15 ppm for 6 hrs/day for 1 or 2 days (Monteiro-Riviere and Popp, 1986), 3.6 ppm intermittently for 3 days (Cassee and Feron, 1994), 3% aerosols of formaldehyde for 3 hrs/day for 50 days (Ionescu et al., 1978)). The progressive pathology of the nasal passages from formaldehyde inhalation exposure is dependent on increasing concentration and duration of exposure, as well as from proximal to distal regions of the nasal cavity. For example, some lesions may be transient (e.g., low-exposure cell proliferation), while others may have a maximum response and be irreversible (e.g., allergic rhinitis). The nasal epithelium responds with both adaptive and adverse epithelial changes. As respiratory epithelium transitions to squamous metaplasia, the effective tissue dose of formaldehyde increases posterior to these lesions. As epithelial barriers degrade (e.g., squamous metaplasia, keratinization), formaldehyde penetrates more deeply into the nasal passages. Therefore, the relationship between concentration and duration of exposure and health outcomes has been difficult to define and, in fact, may be different for various health effects. Formaldehyde-related histopathological lesions of the nasal mucosa have been observed at concentrations as low as 2 ppm for chronic exposure

and after a duration as short as 6 hrs at higher concentrations (e.g., 6 ppm) (**see** Table 4-32, Table 4-38).

Similar pathology has been reported for workers exposed to formaldehyde, including loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia and dysplasia, and these pathology scores were significantly elevated in workers over controls (Holmström and Wilhelmsson, 1988; Edling et al., 1988; and Boysen et al., 1990). Holmström and Wilhelmsson (1988) reported associations between the mean daily exposure of 240 ppb (8hr TWA) and these changes. Edling et al. (1988) reported that workers experienced a range of exposures (80−900 ppb), with peak exposures of 4,000 ppb. Boysen et al. (1990) provided a range of estimated exposures from 500 ppb to more than 2,000 ppb for workers with elevated mean pathology scores. One controlled chamber study indicated formaldehyde-induced inflammatory changes which persisted for 18 hours in adults exposed at 400 ppb for only 2 hours (Pazdrak et al., 1993).

Short-term formaldehyde exposure also impairs the function of the mucociliary apparatus which is a critical defensive barrier for the upper respiratory tract. Numerous laboratory animal studies have reported impaired mucociliary clearance activity associated with formaldehyde exposures as low as 500 ppb (see Table 4-10). Low-concentration or short-term exposures first lead to an increased rate of ciliary beat, followed by impaired mucus flow, with slowed rate of ciliary beat and eventual mucostasis (lack of mucus flow) and ciliastasis (lack of ciliary beat) occurring at higher doses or longer exposure times. These effects have been shown to be both concentration- and duration-dependent and to occur within 15 minutes after the initial exposure. Morgan et al. (1983c) suggested that the initial stimulation of ciliary activity may be a defensive response to the irritant gas, at which time some penetration of formaldehyde to the underlying epithelial cells may occur. Later effects of mucostasis and ciliastasis may occur as a result of formaldehyde-induced glycoprotein cross-links, creating a rigid mucus that effectively stops mucus flow.

Formaldehyde-induced cell proliferation has been demonstrated in nasal epithelium in animal studies after a range of exposure conditions (e.g., Swenberg et al., 1986; Cassee and Feron, 1994; Reuzel et al., 1990; Woutersen et al., 1987) (see Table 4-43). Formaldehyde-induced histopathology and mitogenesis may occur as a direct effect of exposure (Tyihak et al., 2001) or as a secondary effect resulting from adaptive responses and/or compensatory tissue repair that can occur after formaldehyde exposure (Swenberg, 1983). In a study of Rhesus monkeys Monticello et al. (1996) noted that increased cell proliferation was seen in locations with minimal histological changes in the respiratory tract indicating that cell proliferation may be a more sensitive predictor of more severe health effects due to formaldehyde exposure.

Cellular proliferative responses may initiate lesion formation. A number of studies illustrate that the duration of repeated exposures may be an important determinant of cell proliferation rates (Wilmer et al., 1987; Swenberg et al., 1986). Reduced mucociliary clearance and the induction of histopathologic lesions in the nose effects have been noted in human formaldehyde studies.

Histopathological lesions and biochemical changes have been reported in the lung following formaldehyde inhalation exposure in experimental animal studies (Kamata et al., 1996a; Ionescu et al., 1978) following high exposure levels (128.4 or 294.5 ppm formaldehyde).

6.1.3.3. *Effects on Pulmonary Function*

The potential of formaldehyde exposure to cause pulmonary functional deficits in humans has been examined on several time scales. The epidemiologic literature includes studies of acute exposures among naïvely exposed anatomy graduate students (Kriebel et al., 1993; 2001), anatomy graduate students with several weeks of episodic exposure (Kriebel et al., 1993), and post-shift versus pre-shift worker pulmonary function among those with regular occupational exposure (Malaka and Kodama, 1990; Herbert et al., 1994; Alexandersson et al., 1982; Alexandersson and Hedenstierna, 1989). Depending on whether the exposures are naïve or not, the epidemiologic studies that assessed the pulmonary effects after acute exposures to formaldehyde are assessing different biological responses, namely, the acute effect alone or the acute effect(s) in people who may have already been sensitized to different and unknown degrees.

The observed effects in the previously unexposed anatomy students provide additional information on acute exposures in two naïve populations (Kriebel et al., 1993; 2001), as well as insight into the possible intermediate stages of sensitization (Kriebel et al., 1993). Kriebel and colleagues (1993) examined the prelaboratory and postlaboratory peak expiratory flow (PEF) in students attending anatomy classes once a week. They found the strongest pulmonary response when examining the average cross-laboratory decrement in peak expiratory flow in the first 2 weeks of the study when formaldehyde concentrations collected in the breathing zones had a geometric average concentration of 0.73 ppm. Overall, the students exhibited a 2% decrement in PEF, while the students with any history of asthma showed a 7.3% decrement in PEF. These findings of acute decreases in PEF following students' initial formaldehyde exposure were corroborated by the Kriebel et al. (2001) study, using a similar study design applied to a separate class of anatomy students. Similar findings have been reported for low-level residential formaldehyde exposure including decreased peak expiratory flow rates (PEFRs) (Krzyzanowski et al., 1990). Workers chronically exposed to formaldehyde have exhibited signs of reduced

lung function consistent with bronchial constriction, inflammation, or chronic obstructive lung disease. Lung function deficits have been reported both in preshift versus postshift measurements *and* as a result of chronic exposures (Malaka and Kodama, 1990; Herbert et al., 1994; Pourmahabadian et al., 2006, Alexandersson et al., 1982; Alexandersson and Hedenatiena 1989). Decreases in spirometric values, including vital capacity (VC), forced expiratory volume (FEV), forced vital capacity (FVC) and FEV/FVC have been reported in humans. Chronic studies also reported increased respiratory symptoms such as cough, increased phlegm, asthma, chest tightness and chest colds in exposed workers (Malaka et al., 1990; Herbert et al., 1994; Pourmahabadian et al., 2006, Alexandersson et al., 1982; Alexandersson and Hedenatiena 1989). Similar findings have been reported following low-level residential formaldehyde exposure including decreased PEFRs (Krzyzanowski et al., 1990).

Worker exposures associated with cross-shift differences in spirometric values are consistent with formaldehyde-induced sensory irritation. Concordance has also been reported between subjective irritant response and measured changes in pulmonary function further supporting the possibility that cross-shift and short-term evidence of bronchial constriction may be a reflexive response to sensory irritation.

A well-conducted residential epidemiology study by Krzyzanowski et al. (1990) was considered to be the strongest among the candidate studies on the adverse pulmonary function effects of formaldehyde for the purposes of deriving an RfC.

6.1.3.4. *Asthmatic Responses and Increased Atopic Symptoms*

The health effects of respiratory function, asthma and increased atopic response, have been shown to be clinically related. For example, asthma affects pulmonary function and may be triggered by an allergic response. These and other data suggest that there may be mechanistic links between these two health effects. Formaldehyde-induced sensitization (see Section 4.2.1.5) may enhance the asthmatic response or may enhance an individual's response to an allergen (see Section 4.4). In both cases, sensitization results in phenotypic switching—or an individual exhibiting clinical symptoms of a predisposition to asthma or atopy. Because of the connection between the two endpoints, they are considered together herein.

Several cross-sectional studies have described a positive association between formaldehyde concentration and asthma prevalence. A study on risk factors for the initial physician diagnosis of asthma has shown concentration-dependent associations between formaldehyde exposure and asthma (Rumchev et al., 2002). In a categorical analysis, Rumchev et al. (2002) observed statistically significant effects above in-home formaldehyde concentrations of 60 $\mu g/m^3$, with increased but nonsignificant effects at 50−59 $\mu g/m^3$ that were

consistent with a concentration-response relationship. No effect was apparent at concentrations in the next lower interval between 30−49 μg/m^3. Garrett et al. (1999 a,b) reported a borderline statistically significant association between bedroom formaldehyde concentrations and an increased risk of atopy. The authors computed a respiratory symptom score for each child based on the frequency of each of eight respiratory symptoms and this score was substantially and statistically significantly higher among the asthmatic children compared to nonasthmatic children. Health effects were reported at formaldehyde concentrations greater than 50 μg/m^3 but the lowest formaldehyde concentration interval at which health effects were observed was 20−50 μg/m^3. The findings of Garrett et al. (1999 a,b) are supported by the results of a chamber study reported by Casset et al. (2006) of 19 sensitized adult asthmatics exposed to formaldehyde at a concentration of 100 μg/m^3 for 30 minutes. Casset and colleagues observed an increased bronchial responsiveness to mite allergen exposure (p = 0.05) and noted the provocative dose (PD20 for FEV1) for mite allergen was 34.3 ng after formaldehyde exposure and 45.4 ng after air exposure. However, in study by Ezratty et al. (2007) exposure to 500 μg/m^3 formaldehyde did not affect an allergen-induced increase in responsiveness to methacholine (p = 0.42) and there was no formaldehyde-associated effect on the airway inflammatory response.

These observed health effects in humans are similar to the outcome of studies in laboratory animals that show that formaldehyde can exacerbate existing immunogenic hypersensitivity to known allergens (Sadakane et al., 2002; Tarkowski and Gorski, 1995; Riedel et al., 1996). While potentiation varied based on sensitization protocols and formaldehyde exposure regimens, the results support the finding that formaldehyde exposure can aggravate a Type-I hypersensitivity response and may do so via a neurogenically initiated response. Formaldehyde itself does not function as an allergen recognized by the immune system (Lee et al., 1984) and does not appear to trigger formation of formaldehyde-specific IgE. Although formaldehyde exposure has been reported to alter cytokine levels and immunoglobulins in some experimental systems (Fujimaki et al., 2004a; Ohtsuka et al., 2003), these effects do not support an immunogenically mediated type-I hypersensitivity. In studies in which either egg protein (ovalbumin, OVA)-sensitized or dust mite (DerF)-sensitized animals were exposed to formaldehyde, OVA-specific and DerF-specific antibody production was increased over sensitization alone, suggesting that formaldehyde may potentiate sensitization responses (Riedel et al., 1996; Sadakane et al., 2002). Formaldehyde-induced sensitivity responses may be neurogenic in origin based on findings that neurogenic factors such as nerve growth factor (NGF) and substance P were associated with formaldehyde exposure in sensitization protocols (Fujimaki et al., 2004b).

6.1.3.5.*Effects on the Immune System*

Formaldehyde-induced systemic immunomodulation in laboratory animals has been documented in the literature (Leach et al., 1983; Dean et al. 1984; Adams et al., 1987). A number of studies have evaluated the ability of formaldehyde to induce systemic immunotoxic effects in humans (Ohtani et al., 2004a, b; Erdei et al., 2003; Thrasher et al., 1990, 1987; Pross et al., 1987). Some studies have reported altered innate immune responses associated with formaldehyde exposure (Erdei et al., 2003), while others have noted adaptive immune response suppression associated with formaldehyde exposure (Thrasher et al., 1990, 1987) and changes associated with alterations to a predominant T-lymphocyte helper 2 (Th2) pattern (Ohtani et al., 2004a, b). In contrast, Pross et al. (1987) did not observe formaldehyde-associated changes in systemic immune function.

Diverse studies have investigated the possibility that formaldehyde exposure leads to increased respiratory tract infections (Lyapina et al., 2004; Krzyzanowski et al., 1990; Holness and Nethercott, 1989). Lyapina et al. (2004) reported increased respiratory tract infections and decreased neutrophil respiratory burst activity (NRBA) in formaldehyde-exposed workers (at 722 ppb TWA). Incidences of doctor-diagnosed chronic bronchitis were more prevalent in children under age 15 living in homes with higher formaldehyde (>60 ppb) readings in the kitchen ($p < 0.001$) (Krzyzanowski et al., 1990). Holness and Nethercott (1989) also report increased chronic bronchitis in formaldehyde-exposed funeral workers (380 ppb average exposure).

6.1.3.6.*Neurological Effects*

Formaldehyde exposure via inhalation has been shown to adversely impact nervous system function in laboratory animals and humans, although human data for formaldehyde-induced neurological effects are limited. Studies in formaldehyde-exposed histology technicians provide evidence of neurological impairment, including lack of concentration, impaired memory, disturbed sleep, impaired balance, variations in mood and irritability. These effects were significantly correlated with increasing duration of exposure to formaldehyde, but the findings are not conclusive due to confounding by concomitant exposures to other neurotoxic solvents (Kilburn et al., 1985, 1987). In a prospective study, Weisskopf et al. (2009) found a strong association between duration of formaldehyde exposure and death from amyotrophic lateral sclerosis (ALS), but information regarding exposure levels was not available. Short-term studies with controlled exposure to humans (chamber studies) also provide limited support for changes in cognitive function immediately following a single, controlled formaldehyde exposure (Bach et al., 1990; Lang et al. 2008).

Available animal data provide substantial evidence of behavioral changes in animals following single or short-term repeated inhalation exposures to relatively low levels of formaldehyde. Among the animal studies, none of the available studies examined effects on nervous system function following chronic formaldehyde inhalation, however.

Reported perturbations in nervous system function following formaldehyde exposure in animal studies include reductions in motor activity, lack of habituation, impairment in acquisition of a new learning task, deficits in retention of a previously learned task, increases in corticosterone levels, sensitization to cocaine-induced locomotor activity, and enhanced fear conditioning using an olfactory conditioned stimulus (CS) (see Table 4-57). Behavioral effects have been seen in multiple laboratories and in studies conducted by different investigators using a variety of testing paradigms. Many of these effects were observed at acute exposure levels at or below 1.0 ppm, and some persisted days to weeks after termination of exposure.

More limited data indicate possible effects on the development of the nervous system, including changes in brain structure and in the behavior of offspring (see Table 4-57). Similarly, there is very little information regarding the mechanism by which effects on the nervous system might be produced. The data regarding behavioral sensitization provide some support for a stress-related mechanism for those specific findings, but the applicability of this mechanism to the behavioral changes seen in the other studies, including the learning deficits and developmental findings, has not been evaluated. Although there are data supporting stimulation of the trigeminal nerve by formaldehyde (and documenting the relevance of this interaction to the sensory irritation caused by formaldehyde), there are no data supporting a causal relationship between irritant properties of formaldehyde and the behavioral and neurodevelopmental effects in humans that occur following formaldehyde exposure. In summary, none of the available data provide sufficient information to allow a determination of the mode of action for effects of formaldehyde on the adult or developing nervous system.

6.1.3.7. *Reproductive and Developmental Effects*

Formaldehyde inhalation exposure has been associated with adverse developmental and reproductive outcomes in both epidemiologic studies and experimental animal studies. Observed developmental outcomes include fetal loss, structural alterations, growth retardation, and delays in functional development.

Several occupational studies found an increased risk of spontaneous abortions among formaldehyde-exposed women (Taskinen et al., 1999, 1994; John et al., 1994; Seitz and Baron, 1990; Axelsson et al., 1984). The Taskinen et al. (1999) study examined several reproductive outcomes in women employed in the wood-processing industry, with a range of average daily

formaldehyde exposures. The authors found that formaldehyde was associated with a more than three-fold increased risk of spontaneous abortion, and with a nearly 50% decrease in a measure of delayed conception indicating reduced fertility, an increased time to pregnancy, and an increased risk for endometriosis in this study. In experimental animal studies, early fetal death was noted following maternal formaldehyde exposures (Kitaev et al., 1984; Sheveleva, 1972), supporting the epidemiologic findings that the spontaneous abortion is likely related to formaldehyde exposure. Kitaev et al. (l984) hypothesized that formaldehyde may affect reproductive function by stimulating the hypothalamus-pituitary-gonadal (HPG) axis, based on their observations of increased ovary weight, increased number of ovulating cells, and changes in blood levels of gonadotropins (LH and FSH) in female rats. Additionally, Maronpot et al. (l986) reported endometrial hypoplasia with a lack of ovarian luteal tissue in formaldehyde-exposed female rats. This finding may be relevant to the increased risk for endometriosis noted in the Taskinen et al. (1999) study. However, additional human and animal studies are needed to better understand the effects of inhalation exposure to formaldehyde on developmental outcomes after early gestational windows of exposure or on the female reproductive system.

The findings of some occupational studies have suggested formaldehyde-related associations with congenital malformations and low birth weight. In numerous experimental animal studies, developmental effects have been noted following inhalation exposures to formaldehyde (see Table 4-68). Exposure of rat dams to formaldehyde during pregnancy has been shown to result in significantly decreased fetal weight gain (Martin, 1990; Saillenfait et al., 1989; Kilburn and Moro, 1985). Other studies have noted changes in relative organ weight, undescended testes, biochemical changes (e.g., ascorbic acid), and blood acidosis (Senichenkova and Chebotar, 1996; Senichenkova, 1991; Kilburn and Moro, 1985; Gofmekler and Bonashevskaya, 1969; Gofmekler, 1968; Pushkina et al., 1968).

Studies designed to assess adult male reproductive system toxicity in rats following repeated inhalation exposures to formaldehyde have found concentration-dependent decreases in Leydig cell number and quality, degeneration of seminiferous tubules, decreases in testes weight, alterations in sperm measures, decreased testosterone levels, alterations in trace metals in the testes, and/or dominant lethal effects (Guseva, 1972; Özen et al., 2002, 2005; Sarsilmaz et al., 1999; Xing et al., 2007; Zhou et al., 2006) (see Table 4-71).

6.1.3.8. *Effects on General Systemic Toxicity*

Extrapulmonary effects such as changes in liver function enzymes and focal, chronic inflammation in the heart and kidney have been observed due to formaldehyde exposure in experimental animal studies. Most of these changes occurred at exposures of 20 ppm, and those

that occurred at lower formaldehyde exposures (3.7 ppm) were confounded by coexposures. The underlying modes of action of liver, kidney, and cardiac effects have not been elucidated, and the human relevance is unknown.

6.1.3.9.*Summary*

Formaldehyde-induced eye, nose and throat irritation, decreased pulmonary function, decreased mucociliary clearance and histopathological lesions have been extensively documented in human and laboratory animal studies. These health effects are commonly noted at the portal of entry as expected for exposure to a reactive gas. In addition, effects on immune system responses and on the nervous and reproductive systems, including developmental effects, have also been reported. An association between formaldehyde exposure and increased incidence and severity of response to allergens (i.e., asthma and atopy) has been noted in humans. This effect, which has also been studied in laboratory animals, might occur via a neurogenic mode of action. A limited database of information that evaluates neurological effects in humans following formaldehyde exposure demonstrates a potential for adverse outcomes, and studies in laboratory animals have reported a variety of formaldehyde-induced neurobehavioral and neurodevelopmental effects. Formaldehyde has also been associated with adverse reproductive outcomes. Epidemiology studies have reported an association between formaldehyde exposure and decreased fertility as well as an increased risk of spontaneous abortions. Other epidemiology studies have suggested formaldehyde-related associations with congenital malformations, low birth weight, and endometriosis. Animal studies have noted a variety of developmental effects, including fetal death, structural alterations, and growth retardation (e.g., delayed fetal skeletal ossification and decreased fetal body weight) following inhalation exposure to formaldehyde, and adverse reproductive effects have been observed in both males and females.

6.1.4. Carcinogenicity in Humans and Laboratory Animals

6.1.4.1.*Carcinogenicity in Humans*

Upper respiratory tract cancers:

Epidemiologic studies of formaldehyde-exposed workers provide sufficient evidence of a causal association between formaldehyde exposure and nasopharyngeal cancer (see Section 4.1.2.1.1) as well as nasal and paranasal cancers (see Section 4.1.2.1.2). The epidemiologic evidence of association between formaldehyde exposure and other upper

respiratory tract cancers (see Section 4.1.2.1.3) is consistent with, and supportive of, a causal association but insufficient on its own to reach a causal conclusion. However, taken together with the causal evidence of an association between formaldehyde and nasopharyngeal cancer and sinonasal cancer in neighboring tissues of the upper respiratory tract and sites of first contact with inhaled formaldehyde, along with the strongly supportive evidence of association in animals, the evidence is sufficient to conclude that formaldehyde is causally related to cancers of the upper respiratory tract as a group.

Based on the total weight of evidence, including the results from a large and well-followed longitudinal cohort study of 25,619 industrial workers and several case-control studies, the epidemiologic evidence is sufficient to characterize the association between formaldehyde nasopharyngeal cancer as causal in humans (Hauptmann et al., 2004; Hildesheim et al., 2001; Vaughan et al., 2000). As further evaluated below, the evidence supporting a positive association between formaldehyde exposure and NPC is unlikely due to chance, bias or confounding. However, it should be noted that other smaller studies of formaldehyde-exposed workers did not document increased NPC mortality (e.g., Coggon et al., 2003; Pinkerton et al., 2004). These smaller study sizes yielded effect estimates with wide confidence intervals that were not statistically inconsistent with the increased risk of mortality from nasopharyngeal cancer reported in Hauptmann et al. (2004).

Luce et al. (2002) evaluated pooled data from 12 case-control studies conducted in seven countries using a common job-exposure matrix and demonstrated a statistically significant increased risk between formaldehyde exposure and sinonasal cancer exhibiting a concentration-response relationship providing further causal evidence of carcinogenicity. This analysis was based on a very large dataset of 930 cases and 3,136 controls, enabling the investigators to control for multiple potential sources of bias and confounding and to conduct separate analyses by histological type. These results are particularly convincing, as the association was consistently seen for a rare subtype of sinonasal cancer which normally accounts for only 10% of the reported cases.

In addition to the evidence of formaldehyde carcinogenicity in the nasopharynx, nose and sinuses, other upper respiratory tract sites of direct contact with formaldehyde upon inhalation (i.e., larynx, mouth and salivary gland) also showed evidence of increasing relative risk with increasing average intensity and peak exposure in a large cohort study with exposure estimates for the individual workers, although these trends did not reach the level of statistical significance (Hauptmann et al., 2004). However, Hauptmann and colleagues (2004) concluded that in spite of the small numbers of deaths from these rare cancers of the upper respiratory tract, the positive associations of increased cancer risk with increased formaldehyde exposure were consistent with

the carcinogenicity of formaldehyde at these sites of first contact. Case-control studies also provide evidence of an association between formaldehyde exposure and oral squamous cell carcinoma (SCC), esophageal, and laryngeal cancers, and hypopharyngeal cancer (Gustavsson et al., 1998; Laforest et al., 2000.)

The finding that formaldehyde inhalation causes nasal squamous cell carcinoma in rodents (see Section 4.2.1.2) further supports the determination of a causal association of formaldehyde exposure and increased risk of upper respiratory tract cancer in humans. Both humans and animals developed tumors within the upper respiratory tract, the site expected to receive direct exposure to formaldehyde.

Several researchers have argued that the relationship between formaldehyde exposure and nasopharyngeal cancer based on existing studies has not been determined. Several limitations, such as the rarity of the cancer and the imprecise estimates of exposure, are often inherent in epidemiologic methods and exposure assessment. These constraints limit the ability of epidemiologic studies to statistically detect associations and can lead to false negatives. The results of the largest cohort study of nasopharyngeal cancer (Hauptmann et al., 2004) showed statistically significant concentration-response relationships with increased risk of cancer associated with increased formaldehyde exposure. However, even though this study was based on 25,619 workers, only 9 cases of nasopharyngeal cancer were observed, compared to an expected number of 5 cases, for a relative rate of 2.1 (with a confidence interval of 1.05−4.21) (Hauptmann et al., 2004).

The next largest cohort study of nasopharyngeal cancer was based on 14,014 workers (Coggon et al., 2003) and reported only 1 case compared to an expected number of 2 cases, for a relative risk of 0.5 (with an estimated 95% confidence interval of 0.07 − 3.55; see Bosetti et al., 2008). To put this finding into perspective, it is helpful to note not only the relative risk but also that this effect estimate is highly unstable due to a lack of statistical power. The large width of this interval (0.07 − 3.55) indicates that the range of possible true values includes both increased and decreased NPC mortality and therefore does not contradict the evidence of elevated risk of nasopharyngeal cancer mortality associated with formaldehyde exposure reported by Hauptmann et al. (2004). The even smaller study of 11,039 textile workers by Pinkerton et al. (2004) reported no cases of nasopharyngeal cancer compared to an expected number of one case—yielding an effective relative risk of zero with a highly unstable 95% confidence interval estimated at 0 − 3.00 (see Bosetti et al., 2008). While true that Pinkerton et al. (2004) did not report an increased risk of nasopharyngeal cancer, this study did not have sufficient statistical power to rule out a true association with less than a 3-fold increase in risk and therefore is likewise not inconsistent with the finding by Hauptmann et al. (2004). Thus, results from these

cohort studies, with limited power to detect the relatively rare upper respiratory tract cancers (e.g., NPC), are given less weight in the overall evaluation.

The largest occupational cohort study, conducted by the NCI (Hauptman et al., 2004), did report statistically significant associations of formaldehyde exposure with carcinogenicity at the sites of first contact with sufficient statistical power to rule out the null hypothesis of no association. The NCI investigations controlled for potential selection bias due to the healthy worker effect and for several potential confounders, including calendar year, age, sex, race, and pay category. However, other potential sources of bias or confounding have been suggested with respect to the strength of these data to support a causal conclusion.

Following reports of increased risk of NPC associated with formaldehyde exposure, a series of analyses of similar data were undertaken by Marsh and coworkers (Marsh et al., 2007a, b, 2002, 1996; Marsh and Youk, 2005). Briefly, these studies focused on the specific findings from a single plant in the NCI cohort (Wallingford, Connecticut) that generated the majority of the NPC cases. Marsh et al. (1996) confirm a significant adverse association of formaldehyde with nasopharyngeal cancer but note the effects are predominantly among workers at the Wallingford plant with less than one year employment. Marsh et al. (2002) report a five-fold excess in risk of nasopharyngeal cancer associated with formaldehyde in both short-term and long-term workers but note that the increase was concentrated among workers hired during 1947−1956. Marsh and Youk (2005) re-evaluated the same Wallingford workers and reported a regional rate-based standardized mortality ratio (SMR) of 10.32 (95% CI = 3.79 − 22.47) compared to 0.65 (95% CI = 0.08 − 2.33) for workers at the nine other plants combined. However, Marsh and Youk (2005) also show that rate-based mortality ratios standardized to both United States and local populations were elevated (nonsignificantly) not only at the Wallingford plant but individually at each of the four other plants at which a single case of nasopharyngeal cancer was reported: Plant 2 (SMR_{US} = 5.35), Plant 3 (SMR_{US} = 1.99), Plant 7 (SMR_{US} = 1.06), and Plant 10 (SMR_{US} = 1.44). It should be noted that Plant 1 (Wallingford) and Plant 2 had both the two highest median formaldehyde exposures and the two highest reported excess risks (Marsh and Youk, 2005).

In another reanalysis of the NCI cohort data on the workers at the Wallingford plant, Marsh and coworkers (2007a) suggested that an imprecise assessment of formaldehyde exposure and an inability of the study to separate formaldehyde exposure from other potential chemical or particulate exposures may have confounded the observed association between formaldehyde and cancer. However, there was no evidence of any differential measurement error that could have produced the observation of a spurious association. Any nondifferential exposure measurement error (i.e., random error in the exposure assessment) would likely have led to an attenuated

observed effect of formaldehyde that was less than that which would otherwise have been observed in the absence of measurement error.

The potential for confounding by particulates was explicitly examined by Hauptmann et al. (2004) and it was shown that there was an exposure-response relationship with formaldehyde among individuals with high particulate exposures—alleviating the potential for confounding and thereby strengthening the causal interpretation of the formaldehyde relationship with an increased risk of NPC. Marsh and coworkers (Marsh et al., 2007b) later suggested the reported formaldehyde association was confounded by an association between silversmithing and NPC. However, careful examination of that analysis (Marsh et al., 2007a) suggests that multiple comparisons may have led to the reported observation with silversmithing. Additionally, the reported effect was inconsistently reported between the results and the abstract sections using different confidence intervals, and both sets of confidence intervals around the reported association were extremely unstable spanning up to several hundred-fold. No prior studies identified an associated between silversmithing and NPC. Thus it may be that silversmithing is an artifactual potential confounder.

The increased NPC mortality observed in the NCI cohort (Hauptmann et al., 2004) has been thoroughly examined for sources of bias and confounding by both the primary researchers and Marsh and coworkers (Marsh et al., 2007a, b, 2002, 1996; Marsh and Youk, 2005). Despite the extensive scrutiny of these results, no convincing and consistent alternative hypothesis of causation has been identified. Taken together with the statistically significant association demonstrating an exposure-response relationship within exposed workers, these data support the conclusion that the association between formaldehyde exposure and increased risk of NPC is causal.

Therefore, after a thorough examination of potential confounders, the association between formaldehyde exposure and NPC mortality in the NCI cohort remains significant and provides a positive exposure-response relationship. Additionally, case-control studies, which have greater statistical power than cohort studies for rare diseases, provide strong additional evidence in support of a causal association between formaldehyde exposure and the incidence of NPC (Hildesheim et al., 2001; Vaughan et al., 2000). As these studies draw from different demographic groups, regions of the world, and evaluate various confounding factors, there is little potential for these consistently reported associations to be artifactual, confounded by common exposures, or a result of bias or chance.

Lymphohematopoietic cancers:

Numerous epidemiologic studies have also reported an association between formaldehyde-exposed workers, especially "professional" workers (e.g., pathologists, embalmers, and funeral directors), and increased risk of lymphohematopoietic cancers (see Table 4-90). Positive associations between formaldehyde exposure and lymphohematopoietic cancers have been reported for chemical workers (Wong et al., 1983; Bertazzi et al., 1986), embalmers (Walrath and Fraumeni, 1983, 1984; Hayes et al., 1990), anatomists and pathologists (Harrington and Shannon 1975; Hall et al., 1991; Levine at al., 1984; Stroup et al., 1986; Matanoski et al., 1989). However, clear associations (in terms of overall standardized mortality ratios (SMRs) or proportional mortality ratios (PMRs) were not reported in analyses for garment workers, iron-foundry workers, and a large US industrial cohort (Pinkerton et al., 2004; Andjelkovich et al., 1995; Beane Freeman et al., 2009; Marsh et al., 1996), although associations were observed in some of these studies when exposure-response relationships were considered. Several published meta-analyses are available which more formally assess the strength of association between formaldehyde exposure and mortality from all lymphohematopoietic cancers (see Section 4.1.2.2.1.3). Pooled SMRs indicate stronger associations for professional workers (embalmers, anatomists and pathologists) than industry workers (see Table 4-90). Bosetti et al. (2008) found similar relationships, with a pooled SMR of 1.31 (95% CI 1.16-1.47) for 'professionals' (i.e., embalmers, anatomists and pathologists) versus a pooled estimate of 0.85 (95% CI 0.74-0.96) for industrial workers. A recent metaanalysis by Zhang et al. (2009) reports a summary relative risk of 1.25 (95% CI 1.09−1.43) for both professional and industry workers for all lymphohematopoietic cancers (ICD 9 codes 200−209).

Two well-designed cohort studies found significant positive associations between formaldehyde-exposed professional workers and lymphohematopoietic cancer, particularly leukemia, using cumulative exposure measures not previously used and using internal comparison groups. The largest cohort study of industrial workers exposed to formaldehyde (N=25,619), with the most extensive exposure assessment (Blair et al., 1986; Stewart et al., 1986) and with the cohort followed for a median duration of 35 years (Hauptmann et al., 2003) demonstrated that formaldehyde was a risk factor for lymphohematopoietic cancers, independent of other risk factors, such as benzene exposure and smoking. This finding was reconfirmed with an additional 10 years of follow-up (Beane Freeman et al., 2009). Another industrial cohort study reported a significant increase in the risk of leukemia in garment workers 20 years after their initial exposure and in workers with 10 or more years of exposure to formaldehyde (Pinkerton et al. 2004). A third large occupational cohort study (Coggon et al., 2003) that did not evaluate their findings with regard to latency reported somewhat lower mortality from

leukemia and other lymphatic and hematopoietic cancers than expected compared to national rates.

The associations between myeloid leukemia and formaldehyde exposure are strong and consistent (see Table 4-92). Of the four studies which formally assess myeloid leukemia mortality, all are positive, including cohorts of both professional and industrial workers (Beane Freeman et al., 2009; Hayes et al., 1990; Pinkerton at al., 2003; Stroup et al., 1986). Although few cases exist for further subtype analysis, the available data indicate either no differences in SMRs for acute myeloid leukemia (AML) versus chronic myeloid leukemia (CML) (Hayes et al., 1990; Pinkerton et al., 2003) or suggest CML is more prominent (Blair et al., 2000; Stroup et al., 1986). The association between formaldehyde exposure and myeloid leukemia in embalmers has recently been confirmed in a large nested case control study by Hauptman et al (2009) which includes cases identified from the previous studies of Hayes et al. (1990) and Walrath and Fraumeni (1983 and 1984). Exposure estimates were based on interviews with next-of kin for duration of job actively embalming and total number of embalmings performed. Strong and statistically significant exposure-response relationships are demonstrated for duration of exposure, total number of embalmings performed and estimated cumulative exposure to formaldehyde with odds ratios of 13.6 (1.6−119.7), 12.7(1.4−112.8) and 13.2(1.5−115.4) respectively (Hauptmann et al., 2009).

The reported associations between formaldehyde exposure and lymphohematopoietic cancers in general, and leukemia (especially myeloid leukemia) in particular, were in workers exposed in very different environments (i.e., mortuary, chemical industry and garment industry). Since coexposures to other agents are considerably different between these work environments, it is unlikely that influence of confounding exposures plays a role in the observed associations. There is no evidence of bias in the published reports, and the consistency across numerous studies over time is sufficient to conclude that the results are not due to chance. Additionally, where data are available for analysis, increased myeloid leukemia is not the sole driver of increased leukemia and all lymphohematopoietic cancers (see Table 4-91). An evaluation of the epidemiologic evidence for solid tumors of lymphoid origin indicates an association between formaldehyde exposure and both Hodgkins lymphoma and multiple myeloma, but not non-Hodkins lymphoma in general (see Section 4.1.2.2.1.4 and Section 4.5.2.6).

It has been argued that it is biologically implausible for a highly reactive agent such as formaldehyde, whose primary action is expected to be at the portal of entry, to cause acute lymphoid or myeloid leukemias (ALL and AML, respectively), which are both commonly believed to arise from transformation of stem cells in the bone marrow. The modes of action (MOAs) by which formaldehyde may induce these observed cancers are unknown, although it

has been postulated that circulating stem cells (Hauptmann et al., 2003) (e.g., early progenitor cells in circulating blood or pluripotent cells in nasal/oral passages) may travel to bone marrow where they become leukemic stem cells (Zhang et al., 2010a, b). In contrast, the mechanism for the chronic lymphatic leukemia, lymphomas, multiple myelomas (from plasma B-cells) and unspecified lymphohematopoietic cancers may involve an etiology in peripheral tissues, such as cells, cell aggregates, germinal centers and lymph nodes. An association of these cancers to a reactive exogenous agent primarily acting at the point of entry is biologically plausible.

6.1.4.2.*Carcinogenicity in Laboratory Animals*

The carcinogenic potential of formaldehyde is well documented in numerous animal bioassays, especially for sites of first contact. Inhalation exposure of formaldehyde induced primarily squamous cell carcinomas (SCC) in nasal passages of rats (Feron et al., 1988; Holmström et al., 1989a; Woutersen et al., 1989; Tobe et al., 1985; Kamata et al., 1997; Albert et al., 1982; Sellakumar, 1985; Kerns et al., 1983; Monticello et al., 1996) and mice (Battelle Columbus Laboratories, 1981; Swenberg et al., 1980; Kerns et al., 1983; CIIT, 1982). Formaldehyde given as 0.5% formalin orally in drinking water to adult rats induced higher incidences of papillomas in the forestomach, adenomatous hyperplasia in the fundus, and adenocarcinomas in the pylorus in a 40-week study using an initiation-promotion protocol in rats (Takahashi et al., 1986). Formaldehyde is toxic at the portal of entry in rodents, causing increased cell proliferation, DPX formation, and focal lesions in the GI tract or upper respiratory tract (depending on the route of exposure). The portal of entry toxicity of formaldehyde further supports a finding of formaldehyde induced POE cancer in animal bioassays.

Direct support for lymphohematopoietic cancers in animal bioassays is less convincing. Although many of the available chronic studies did not examine lymphoma/leukemia incidence, four studies allow for some evaluation of the leukemic potential of formaldehyde. Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985).

6.1.4.3.*Carcinogenic Mode(s) of Action*

Multiple plausible modes of action (MOAs) are presented in the document so as to explore ways in which a combination of factors may contribute to cancer incidence in a population exposed to formaldehyde. Multiple MOAs for formaldehyde-induced cancer can be reasonably supported based on various known biological actions of formaldehyde (e.g.,

mutation, cell proliferation, cytotoxicity and regenerative cell proliferation). Additionally, alternative actions, such as immunosuppression or viral reactivation, are possible, although few data exist to evaluate their potential relevance. Rather than a single MOA, it is plausible that a combination of these factors contribute to cancer incidence in an exposed population. Considering multiple factors may help to better understand the biological and mechanistic basis for the increases in cancer incidence observed in exposed human populations. Unlike animal bioassays, results in human epidemiological studies reflect not only the effects of the agent of concern but also numerous other risk factors (e.g., viral status, diet, smoking, etc.). Additionally, human studies may be impacted by biological human variability across individuals, cancer biology (subtypes) and wide variability in exposure regimens in human populations.

The overall weight of evidence supports a role of mutagenic activity in formaldehyde's carcinogenic MOA both for respiratory tract cancer and lymphohematopoietic cancers. As reviewed in Section 4.3 and summarized in Section 4.5.3.1, numerous studies provide evidence of formaldehyde's direct mutagenic activity and supports the relevance these data to formaldehyde's carcinogenicity. It can be shown that:

1) Formaldehyde directly interacts with DNA, generating DNA-protein cross-links and DNA adducts (in vitro, in vivo) in multiple species,
2) DNA-protein cross-links exhibit a dose-response relationship to formaldehyde exposure in respiratory tract of laboratory animals and are observed at exposure concentrations of relevance to some people (0.3 ppm, 0.7 ppm),
3) Formaldehyde-induced DNA-protein cross-links have been associated with formaldehyde-induced micronuclei and chromosomal aberrations (in vitro),
4) Mutations induced by formaldehyde due to small deletions and rearrangements in DNA in various experimental systems are consistent with formaldehyde's observed clastogenic effects (micronuclei and chromosomal aberrations) (in vitro, in vivo),
5) Formaldehyde-induced mutations and clastogenic effects occur at levels below where significant cytotoxicity is detected (in vitro),
6) Formaldehyde exposure has been correlated to similar increased micronuclei and chromosomal aberrations in human buccal and oral cells corresponding to sites where formaldehyde-induced tumors arise, and
7) Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been documented in formaldehyde exposed workers including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells.

In addition, mutations may arise indirectly from formaldehyde-induced DNA damage during cell proliferation or due to errors in DNA repair mechanisms. Therefore, formaldehyde's DNA reactivity on a population of proliferating cells strengthens the role of formaldehyde-induced mutagenicity in its carcinogenic MOA. The nasal and gut mucosa are tissues which are continually sloughing and regenerating cells (Junqueira et al., 1992). Mucosal cells proliferate in response to environmental challenges in order to repair cell damage, increase adaptive response and remodel tissue. Additionally, since the pseudostratified epithelium of the respiratory tract is only 1−2 cells in depth, cells with proliferative capacity would be directly impacted by formaldehyde during exposure. Formaldehyde-induced clastogenic effects have been demonstrated in these tissues (e.g., nasal) in humans, as well as in tissues which possess stratified epithelium (e.g., buccal). Therefore, formaldehyde would not need to transport beyond the portal of entry to directly impact and induce DNA mutations in routinely proliferating cells.

In regards to generating the observed clastogenic effects (micronuclei and chromosomal aberrations in peripheral blood lymphocytes, aneuploidy in circulating hematopoietic stem cells), it is less clear as to where formaldehyde is making contact with components of the immune system. Mature lymphocytes present in nasal and gut tissues, and would be vulnerable to the direct toxic actions of formaldehyde including genotoxicity. Since mature lymphocytes routinely traffic through the body and clonally respond in response to an immune challenge, the observed effects in peripheral blood lymphocytes (micronuclei and chromosomal aberrations) are consistent with direct action on these cells. Lymphohematopoietic cancers are known to arise from mature lymphocytes including: Hodgkin lymphoma, multiple myeloma some leukemia and non-Hodgkin lymphoma (Greaves 2004, Harris et al., 2000).

Formaldehyde may also be directly acting upon circulating stem cells or more mature progenitor cell in the peripheral blood (Zhang et al., 2010a). Any genetic damage sustained by circulating cells could contribute to a broad spectrum of lymphohematopoietic cancers if those cells returned to the bone marrow and contributed to hematopoiesis. Evidence of bone marrow toxicity and stem cell aneuploidy has been reported in formaldehyde exposed workers (Zhang et al., 2010b). Finally, formaldehyde is readily hydrated in aqueous systems, existing in equilibrium with its hydrated form methylene glycol, which is able to transport through the blood. It has been hypothesized that this hydration reaction may allow formaldehyde to act systemically and therefore on the bone marrow directly (Zhang et al., 2010a.) Formaldehyde-induced DNA damage, and resulting mutation in the bone marrow and circulating stem cells could contribute to any of the lymphohematopoietic cancers including leukemia (both lymphoid and myeloid) as well as myeloproliferative disorders.

Cell replication allows unrepaired DNA damage to be "fixed" into heritable changes to the genome. Therefore, increased cell proliferation could serve not only to increase the mutagenic effects of formaldehyde on a given tissue but also to enhance the mutagenic effects of other agents in the diet or in the environment. Since epidemiological studies include humans exposed to a range of agents in the environment, increased cell proliferation could contribute to increased cancer incidence. The promotion studies in animal bioassays, though limited in number, support the relevance of formaldehyde's ability to enhance the actions of other agents (initiators) on tumor formation.

Although the other biologic effects discussed above have not been explicitly tested in animal systems, the available data are consistent with these actions contributing to the carcinogenic potential of formaldehyde. For example, localized immunosuppression by formaldehyde may serve to increase viral reactivation (e.g., EBV, HPV etc.) or decrease tissue surveillance and immune activity against preneoplastic cells. Both these actions could contribute to increased cancer risk in a human population, which may not be evident in animal bioassays, where the animals are not subject to the many risk factors for human cancer. Even the simple action of the breakdown of the mucociliary apparatus could increase cancer incidence by increasing toxic insult to the URT and increasing URT infections. Again, these actions may be relevant to human populations, but they have not been adequately tested in animal bioassays.

Animal bioassays suggest a role for regenerative proliferation in contributing to formaldehyde's carcinogenicity. However, these data are not evidence against a role of direct mutagenic action either in the observed tumorigenicity or in the potential low-dose carcinogenicity of formaldehyde. As reviewed, a role for mutagenic action is also consistent with the results of the animal bioassays (Crump et al, 2008; Subramaniam et al., 2007, USEPA 2008). The mutagenic effects of formaldehyde are well-documented to occur below levels of significant cytotoxicity. This observation is important for the relevance of formaldehyde-induced mutagenicity to human health risk. Given the above sequence of evidence—from the nature of formaldehyde's DNA reactivity through clastogenic effects observed in human cells from the various tumor sites—there is an adequate weight of evidence (WOE) to consider formaldehyde-induced mutations relevant to human carcinogenic risk. Although occupational exposures may have resulted in high episodic exposures (especially historically), it is unlikely that any worker would have endured repeated exposures which resulted in gross focal lesions to the upper respiratory tract (URT) or oro-digestive tract as seen in the animal bioassays. It is noteworthy that even without these gross formaldehyde-induced lesions, cancer incidence is increased from occupational (and perhaps nonoccupational) exposures to formaldehyde.

Therefore, we believe formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA.

6.1.5. Cancer Hazard Characterization

Formaldehyde is Carcinogenic to Humans by the Inhalation Route of Exposure. Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, myeloid leukemia and lymphohematopoietic cancers as a group. Epidemiological evidence is also strongly supportive of, but in itself not sufficient for, a conclusion of causal association for other upper-respiratory tract cancers, Hodgkins lymphoma, or multiple myeloma. Animal bioassays consistently demonstrate formaldehyde-induced nasal cancers in rodents which provide strong support for the observed upper respiratory tract cancers in humans. Limited evidence from animal bioassays is available to support the conclusion from human epidemiologic data that formaldehyde causes some types of lymphohematopoietic cancers.

6.2. DOSE-RESPONSE CHARACTERIZATION

6.2.1. Noncancer Toxicity: Reference Concentration (RfC)

The portals of entry are major targets for formaldehyde, as can be seen in many studies, because formaldehyde is highly reactive and water soluble. Human and laboratory animal studies demonstrate that formaldehyde also causes systemic effects, including neurotoxicity, reproductive toxicity, developmental toxicity, and immunotoxicity, although the data are less extensive than those supporting the sensory irritation and respiratory tract effects. Critical data gaps have been identified and uncertainties associated with data deficiencies are more fully discussed in Chapter 5 and summarized below.

6.2.1.1. *Assessment Approach Employed*

RfC values for noncancer effects are derived using EPA's RfC methodologies (U.S. EPA, 1994, 1993, 2002b). EPA reviewed the existing literature and identified health effects associated with formaldehyde exposure, defining health effect categories where evidence was sufficient: sensory irritation, respiratory tract pathology, pulmonary effects, asthma, increased allergic sensitization, immune function, neurological and behavioral effects and reproductive and developmental effects. Specific key studies were identified within each health effects category which provided adequate exposure-response information to support RfC derivation (see Table 5-4). Although not all identified endpoints are represented by these studies, at least one study was identified for each category. A screening process (described in Section 5.1.3.1) was

used to identify key studies for a variety of health effects that would best inform the derivation of the RfC. For each selected key study, a candidate RfC (cRfC) was derived. In several cases more than one alternative was considered for application of the uncertainty factor (UF) addressing human variability (see Table 5-6).

6.2.1.2. *Derivation of Candidate Reference Concentrations*

Seven studies were selected as key studies for further consideration in RfC derivation (see Section 5.3.1, Table 5-4). Candidate RfCs from these studies address various health effects including: sensory irritation, respiratory effects, asthma, increased allergic sensitization, and decreased fecundity (see Table 5-6). From these studies three cocritical studies were selected which provide similar cRfCs for related health effects (Rumchev et al., 2002; Garrett et al., 1999 a,b; Krzyzanowski et al., 1999). These three studies identify serious health effects in residential populations including children: increased asthma incidence, decreased pulmonary function, increase in respiratory symptoms, and increased allergic sensitization (Rumchev et al., 2002; Garrett et al., 1999 a,b; Krzyzanowski et al., 1999). Asthma, allergic sensitization, altered pulmonary function, and symptoms of respiratory disease are not only clinically related, but etiologically related, and it is reasonable that they should be considered together. These health effects are observed below the exposure levels that result in sensory irritation, and the resulting cRfCs are correspondingly lower—ranging from 2.8 to11 ppb—depending on the study, endpoint considered, and the application of alternative uncertainty factors for human variability (see Table 6-1). Additionally, these cRfCs are considered protective of the decreased fecundability density ratio (FDR) reported by Taskinen et al. (1999) which yielded a cRfC of 8.6 ppb. One of the uncertainties in the cRfC for decreased FDR is the use of a time-weighted exposure metric which does not address possible contributions of peak exposure levels to the observed health effect thus; it is possible that a cRfC of 8.6 ppb is lower than is needed for protection against decreased FDR.

As discussed in Section 6.2.1.4, there are uncertainties in establishing an RfC which are not fully captured in the quantitative process or the standard uncertainty factors. The range of RfCs from the critical studies (even with various alternative considered for the human variability uncertainty factor are in close agreement spanning only ½ order of magnitude.) Therefore EPA is considering a simple mean of these cRfCs as adequately representative of the three cocritical studies. Alternatives are to take the median as a different way to represent the three studies together, or the lowest cRfC as most protective. There is little numerical difference in the result of these decisions.

6.2.1.3.*Adequacy of Overall Data Base for RfC Derivation*

The database of available laboratory animal studies, clinical and epidemiological studies, and supporting mechanistic information for formaldehyde is substantial. Many of the health effects are well studied in animals and humans, especially those endpoints related to sensory irritation and respiratory effects at the portal of entry, such as impacts on respiratory tract pathology, asthma and reduced pulmonary function. This is reflected in the number and high quality of human studies presented in Table 5-4 and supporting data summarized in Chapter 4.

The data also indicate effects in other health effect categories, specifically neurotoxic effects, reproductive toxicity, and developmental toxicity (see Section 5.1.2). These nonportal-of-entry effects are areas where additional research may be warranted to reduce uncertainty and better characterize the potential for health effects and the formaldehyde concentrations at which they might occur in humans.

EPA guidance indicates that an uncertainty factor for database deficiencies should be applied where there is an indication that the existing studies may not completely characterize the hazard of a specific agent. This may be the result of lacking studies to assess toxicity to key functional areas or organ systems, or where "… a review of existing data may also suggest that a lower reference value might result if additional data were available." (U.S. EPA 2002b)

Table 6-1. Summary of candidate reference concentrations (RfC) for cocritical studies

Endpoint	Study	Study size	Homes	Children	POD (ppb)	Application of study-specific UF			cRfC [1] (ppb)
						UF_L	UF_S	UF_H	
Respiratory effects/asthma and sensitization									
Reduction of PEFR in children (10%)	Krzyzanowski et al. (1990)	208	Yes	Yes	$BMCL_{10}$ = 17	1	1	[3]	**5.6**
Asthma prevalence	Rumchev et al. (2002)	192	Yes	Yes	NOAEL = 33	1	3	**Alternative A**	
								[3]	**3.3**
								Alternative B	
								[1]	**11**
Asthma, atopy and severity of allergic sensitization	Garrett et al. (1999 a,b)	148	Yes	Yes	LOAEL = 28	3	1	**Alternative A**	
								[3]	**2.8**
								Alternative B	
								[1]	**9.3**

Notes: 1: The final RfC will be rounded to one significant digit per EPA policy. Since the Candidate RfC is an interim calculation, two-significant digits are retained as is common practice in mathematics {i.e., one significant diget more that the final result, to avoid rounding errors compounding across multiple mathematical manipulations.

Application of an uncertainty factor of 3 was considered by EPA based on the lack of a satisfactory two-generation study to fully evaluate the effects of formaldehyde exposure on reproductive and developmental endpoints and limitations of the available studies evaluating neurotoxic effects. An uncertainty factor of 3 rather than 10 was considered given the relative completeness of the database across all major health effect categories such that it is believed all major health effects have been identified at least qualitatively. The observed adverse health effect levels (LOAELs) for those endpoints where the database is not adequate for alternative RfC derivation are above the range of candidate RfCs; however, it is unclear if the candidate RfCs would be protective of these other health effects (neurotoxic, reproductive and developmental) since NOAELs were not identified for several observed health effects.

Therefore EPA is considering several options to address database deficiencies in the final RfC.

Approaches to the application of a database uncertainty factor:
Options EPA is considering include:

(1) Provide an RfC derived from studies of respiratory and allergenic responses and protective of sensory irritation effects with a database uncertainty factor of one given significant data on formaldehyde, but noting that further research reproductive, developmental and neurotoxic effects would be valuable.

(2) Provide an RfC with a database uncertainty factor of one, with this RfC explicitly identified as being protective of the well-studied effects.

(3) Apply a database UF of 3 to the RfC derived from studies of respiratory and allergenic responses to reflect the potential that reproductive, developmental, or neurotoxic effects might occur at lower doses:

(4) Provide both an RfC identified as protective of the better-studied effects and an RfC with a database uncertainty factor of 3 incorporated to account for limits to the data on reproductive, developmental and neurotoxic effects.

It is unclear what uncertainty factors are appropriate to account for human variability and deficiencies in the overall database. For this reason, several alternatives have been presented.

6.2.1.4. *Uncertainties in the Reference Concentration (RfC)*

A number of uncertainties that underlie the RfC for formaldehyde are discussed in this section. A fundamental uncertainty in an RfC is that the critical study(ies) and endpoint(s)

selected reflect an actual hazard, i.e., a chemically related effect. As summarized in Section 6.1.3, there is strong and consistent evidence, from both human and laboratory animal studies, for the critical effects that form the basis of the RfC for formaldehyde. This section pertains to uncertainties in the quantitative derivation of the RfC.

6.2.1.4.1. ***Point of departure (POD).***

Most of the studies considered for RfC derivation did not provide enough data to support benchmark dose modeling. Rather, the PODs for most studies were LOAELs or NOAELs, which have a number of shortcomings relative to a POD obtained from benchmark dose-response modeling (i.e., a benchmark concentration or dose):

- LOAELs and NOAELs are a reflection of the particular exposure/dose levels used in a study, contributing some inaccuracy to the POD determination.
- LOAELs and NOAELs are often determined based on statistical significance and, thus, reflect the number of study subjects or test animals. Studies are typically dissimilar in detection ability and statistical power, with smaller studies tending to identify higher exposure levels as NOAELs relative to larger, but otherwise similarly designed, studies.
- Different LOAELs and NOAELs represent different response rates, so direct qualitative and quantitative comparisons are not possible.

PODs identified from benchmark dose models overcome some of the deficiencies associated with LOAELs and NOAELs. Benchmark models were used for two inhalation data sets—Hanrahan et al. (1984) and Krzyzanowski et al. (1990).

It should also be noted, however, that even for benchmark concentrations/doses there is often uncertainty, in particular for continuous responses, about what response level to select as the benchmark response, i.e., where to define the cut-point between a level of change that is not adverse and one that is adverse. In addition, benchmark dose models currently in use are purely mathematical models and are not intended to accurately reflect the biology of the effect being modeled.

Another source of uncertainty in the POD is the adjustment for continuous exposure. RfCs are meant to apply to continuous (24 hour/day) exposures. Exposure patterns in human and laboratory animal inhalation studies are typically not for continuous exposures, and assumptions must be made in converting reported exposure levels to equivalent continuous exposures. Similarly, there are uncertainties about potential dose rate effects, in particular the effect of peak exposures in occupational studies.

6.2.1.4.2. ***Extrapolation from laboratory animal data to humans.***

Because the inhalation database for formaldehyde contains many human studies for a variety of health effects, it was not necessary to rely on animal data for the endpoints from which the RfC was derived. Thus, unlike for most RfCs, this is *not* a source of uncertainty in the RfC for formaldehyde.

6.2.1.4.3. ***Human variation.***

Heterogeneity among humans is another uncertainty associated with extending results observed in a limited human study population or laboratory animal experiment to a larger, more diverse human population.

For three of the studies used to derive the RfC, a value of 3 was used for the human variability UF (rather than the default value of 10) because the studies had an apparent over-representation of populations expected to have increased susceptibility (see Section 5.5.3.1):

- The residential study by Ritchie and Lehnen (1987) evaluated eye, nose, and throat irritation in a large number of subjects, including children and the elderly. As a result of the study's participation criteria, individuals with greater sensitivity were potentially over-represented.
- Thirty percent of the subjects in the residential study by Krzyzanowski et al. (1990) are children, who are more sensitive to formaldehyde-associated decreases in peak expiratory flow rates (PEFR) than adults. The candidate RfC determination for this study focused on the results in the children, among which asthmatics were over-represented (roughly 3-times) compared to the national average.
- Garrett et al. (1999 a,b) conducted a cross-sectional survey of allergy and asthma-like symptoms in children with or without a doctor's diagnosis of asthma. The study was designed to include a high proportion of asthmatic children, a sensitive population for the effects being studied.

EPA notes, however, that, while a human variability UF of 3 rather than 10 was used to attempt to account for certain special attributes of these studies/effects, there is still uncertainty about how much of the overall population heterogeneity is actually reflected even in these relatively diverse residential studies.

6.2.1.4.4. ***Subchronic-to-chronic extrapolation.***

RfCs are intended to apply to chronic lifetime exposures. If a study is subchronic (typically less than 10% of lifetime), an UF for subchronic-to-chronic extrapolation is generally applied to the candidate RfC for that study. For the human residential and occupational studies comprising the key studies for the RfC in this assessment, the average durations of exposure in

the households or workplaces under study is unknown. In this assessment, these studies were considered chronic in nature and no subchronic-to-chronic UF was applied. However, there is uncertainty about whether or not the responses observed fully reflected the potential effects of chronic exposure, especially for effects in children, where effects on the developing respiratory and immune systems, for example, could be predisposing the children to further health effects later in life.

6.2.1.5.*Conclusions*

Seven different noncancer health effects were identified from formaldehyde inhalation exposure studies, including: 1) sensory irritation of the eyes, nose, and throat, 2) upper respiratory tract pathology, 3) pulmonary function, 4) asthma and atopy, 5) neurologic and behavioral toxicity, 6) reproductive and developmental toxicity, and 7) immunological toxicity. Of note, epidemiological evidence is available for most of these noncancer effects. EPA has derived candidate RfCs for critical effects based on seven key studies. Three cocritical studies were selected which provide similar cRfCs for related adverse health effects observed in residential populations including children i.e., increased asthma incidence, decreased pulmonary function, increase in respiratory symptoms, and increased allergic sensitization (Rumchev et al., 2002; Garrett et al., 1999 a,b; Krzyzanowski et al., 1999). The resulting cRfCs fall in a range between 2.8 and 11 ppb, depending on the study, or endpoints considered, and the application of alternative uncertainty factors for human variability (see Table 6-1). The RfC is taken as the average of the cRfCs from the three cocritical studies (See Section 6.2.1.2).

EPA has assessed the adequacy of the overall database for RfC derivation, and although the database is quite large, and provides significant information on well studied POE effects. There are remaining uncertainties in the database. Most notably, there is a need for additional exposure-response information for observed neurotoxic effects, reproductive and developmental effects as well as a two-generation study to evaluate the effects of formaldehyde exposure on reproductive and developmental endpoints. EPA is considering 4 options to address database uncertainties in the final RfC (see Section 6.2.1.3). It is unclear what uncertainty factors are appropriate to account for human variability and deficiencies in the overall database. For this reason, several alternatives have been presented. EPA is seeking advice from the NAS and the public on this matter.

6.2.2. Cancer Risk Estimates

6.2.2.1. *Choice of Data*

As explained above, the human epidemiologic data and the animal bioassay data indicate multiple sites of concern, remote as well as at the portal of entry. The quantitative cancer risk derivations in this document consider the risks of lymphohematopoietic cancers and solid cancers of the respiratory tract. When adequate human data are available, as is the case with formaldehyde, it is generally preferable to base cancer risk estimates on the human data rather than on data from experimental animals because of the inherent uncertainties associated with interspecies extrapolation. Sufficient exposure-response data from a large, high-quality epidemiologic study for the quantitative estimation of risk were available for some lymphohematopoietic cancers and for nasopharyngeal cancer.[15] Risk estimates based on nasal tumors in rats were also derived for comparison with the estimates based on human data. The data used for the quantitative risk assessment are as follows:

1. Nasopharyngeal cancer (NPC): The dose-response modeling of NPCs is based on results from a large NCI cohort study of over 25,000 workers in 10 U.S. plants producing or using formaldehyde (Hauptmann et al., 2004).
2. Lymphohematopoietic cancers: The dose-response modeling of select lymphohematopoietic cancers is based on results from a more recent follow-up study (of lymphohematopoietic malignancies only) of the same NCI cohort (Beane Freeman et al., 2009).
3. Squamous cell carcinoma (SCC) in the upper and lower respiratory tract: An increased incidence of nasal SCC was seen in two large long-term bioassays using F344 rats (Kerns et al., 1983; Monticello et al., 1996). Although other studies in laboratory animals exist, these two studies, when combined, provided the most robust data for analyses. The nasal tumor incidence data from these rat bioassays is used for extrapolating the risk of SCC to the entire human respiratory tract.[16]

[15] Only two other epidemiological studies were available with quantitative exposure estimates for the individual workers. One was a much smaller study (it focused on one of the ten plants covered in the selected study), and it evaluated only pharyngeal cancers. The second was a study of lymphohematopoietic and brain cancers in funeral industry workers which, as discussed in detail in Section 5.1.1, had serious limitations in the exposure assessment, precluding its use for quantitative risk assessment.

[16] That is, we do not assume site concordance between rat and human. This is reasonable because the respiratory and transitional cell types considered to be at risk of SCC in the upper respiratory tract are also prevalent in the lower human respiratory tract. Greater fractional penetration of formaldehyde is thought to occur posteriorly in the human respiratory tract compared to the rat (Kimbell et al. 2001, Overton et al. 2001). Furthermore, some epidemiological studies reported an increase in lung cancer with formaldehyde exposure (Gardner et al. 1993, Blair et al. 1990, 1986), and lesions were seen in the lower respiratory tract of rhesus monkeys exposed to formaldehyde (Monticello et al. 1989).

6.2.2.2.*Analysis of Epidemiologic Data*

The NCI cohort consisted of 25,619 workers employed in 10 plants prior to 1966. A follow-up through 1994 presented exposure-response analyses for 9 NPC deaths, as well as analyses of deaths from other solid cancers (Hauptmann et al., 2004). The most recent follow-up (through 2004; lymphohematopoietic cancers only) analyzed 319 deaths attributed to lymphohematopoietic malignancy from a total of 13,951 deaths (Beane Freeman et al., 2009). A detailed exposure assessment was conducted for each worker, based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986). Exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure. Respirator use and exposures to formaldehyde-containing particulates and other chemicals were also considered. Relative Risks (RRs) were estimated using log-linear Poisson regression models stratified by calendar year, age, sex, and race and adjusted for pay category (salary/wage/unknown). The NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics."

Although other upper respiratory tract cancers were also identified as being causally associated with formaldehyde exposure in the weight-of-evidence analysis in Section 4.5, NPC was the only upper respiratory tract cancer with exposure-response data adequate for the derivation of unit risk estimates in the Hauptmann et al. (2004) follow-up study of solid tumors. Similarly, the weight-of evidence analysis in Section 4.5 concluded that there were causal relationships between formaldehyde exposure and all lymphohematopoietic cancers as a group as well as leukemias as a group (with the strongest evidence for myeloid leukemia). However, from the Beane Freeman et al. (2009) follow-up study of lymphohematopoietic malignancies, only all leukemias combined and Hodgkin lymphoma were judged to have exposure-response data adequate for the derivation of unit risk estimates.

For the NPCs, significant trends were observed for the cumulative and peak exposure metrics. The cumulative exposure metric provides a good fit to the data (p trend = 0.029 for all person-years). Since this is generally the preferred metric for quantitative risk assessment for environmental exposure to carcinogens, cumulative exposure is chosen as the exposure metric for the risk estimate calculations for NPC in this assessment. For the latency of solid cancers, including nasopharyngeal tumors, a 15-year lag interval was used by Hauptmann et al. (2004).

For the lymphohematopoietic cancers, using the peak exposure metric, statistically significant log-linear trends were observed for all lymphohematopoietic cancers, Hodgkin lymphoma, and leukemia (the latter only when the unexposed person-years were included)

(Beane Freeman et al., 2009). Using the average exposure metric, there was a significant trend for Hodgkin lymphoma. Similar results were seen with the cumulative exposure metric, although the trends were not statistically significant, with *p*-values slightly greater than 0.05 (Hodgkin lymphoma *p* trends = 0.06 and 0.08 with and without the unexposed person-years, respectively; leukemia *p* trends = 0.08 and 0.12 with and without the unexposed person-years, respectively). For the latency of lymphohematopoietic cancers, a 2-year lag interval was used by Beane Freeman et al. (2009).

Although the peak exposure metric provides the most statistically robust dose-response relationship, it is not clear how to extrapolate RR estimates based on the peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures. The average exposure metric is also problematic because it suggests that duration of exposure is not important, i.e., exposure to a given exposure level for one year conveys the same amount of risk as exposure to the same level for 70 years.

Cumulative exposure is generally the preferred metric for quantitative risk assessment for environmental exposure to carcinogens. Given the consistency of increased mortality from Hodgkin lymphoma and leukemia overall (exposed versus unexposed) and for each exposure metric (see Table 5-12), indicating risk from these cancers is more than chance, a determination was made that the cumulative exposure results for these two cancer types constituted the best data sets from which to calculate unit risk estimates for lymphohematopoietic cancers from the NCI cohort.

Regression coefficients from the NCI log-linear trend test models for the NPCs (Hauptmann et al., 2004) and the various lymphohematopoietic cancers (Beane Freeman et al., 2009) were provided by Drs. Hauptmann and Beane Freeman, respectively. These trend tests were of the form $RR = e^{\beta * exposure}$. The coefficients (i.e., β) were used in lifetable analyses to calculate lifetime extra cancer risks from formaldehyde exposure (see Section 5.2). Extra risk estimates for cancer incidence for the three cancer types were approximated by assuming that cancer incidence and cancer mortality have the same dose-response relationships and then using background cause-specific incidence rates instead of mortality rates in the lifetable analysis.

Points of departure (PODs) based on the dose-response modeling of these cancers were calculated as the exposure concentration at which the 95% upper confidence bound on extra risk was 0.0005 (i.e., 0.05%) for NPC and for Hodgkin lymphoma and 0.005 (i.e., 0.5%) for leukemia (see Sections 5.2.2 and 5.2.3). These values approximate the lower confidence bounds on dose at these extra risk levels. The values for these extra risk levels, 0.0005 and 0.005, were chosen because they are near the lower end of the observable range of the data. Having such low response levels associated with the points of departure is warranted because of the low

background lifetime risks for these cancer types (e.g., 0.00022 for NPC mortality). Higher extra risk levels would entail extrapolation above the range of the bulk of the observable data to obtain PODs. The resulting effective concentration values for the selected extra risk values for cancer incidence are presented in Table 6-2.

Table 6-2. Effective concentrations (lifetime continuous exposure levels) predicted for specified extra cancer risk levels for selected formaldehyde-related cancers[a]

Cancer type	Extra risk level	EC[b](ppm)	LEC[c] (ppm)
NPC	0.0005	0.074	0.046
Hodgkin lymphoma	0.0005	0.052	0.030
Leukemias	0.005	0.16	0.088

[a]calculated including all person-years (see Section 5.2)
[b]effective concentration.
[s]95% lower confidence bound on the EC; this value is the POD.

Linear low-dose extrapolation from the PODs was used to derive unit risk estimates for NPC, Hodgkin lymphoma, and leukemia, as discussed in Section 6.2.2.4. To obtain an approximate (upper bound) unit risk estimate of the total cancer risk from formaldehyde exposure, risk estimates for these three cancer types (NPC, Hodgkin lymphoma, and leukemia) were combined assuming a normal distribution (see Section 5.2.4). This was considered the most reasonable approach for estimating total cancer risk from the available data; however, it should be noted that this estimate may not reflect all of the cancer types associated with formaldehyde exposure.

6.2.2.3.*Analysis of Laboratory Animal Data*

Various bioassays have been conducted studying the effects of formaldehyde on rats, mice, and rhesus monkeys and have been discussed at length earlier in this document. Of these, two inhalation bioassays of rats, when combined, allow for the most robust characterization of the long-term dose-response relationship in a laboratory species. These long-term bioassays found an increased incidence of nasal SCCs in rats exposed to formaldehyde by the inhalation route (Monticello et al., 1996; Kerns et al., 1983). In the combined data, rats were exposed to 0, 0.7, 2.0, 6.0, 9.93, and 14.96 ppm (0, 0.86, 2.5, 7.4, 12.2, and 18.4 mg/m^3) exposure

concentrations of formaldehyde (Monticello et al. 1996; Kerns et al. 1983). SCCs were observed only at 6 ppm and higher exposure concentrations.

A large amount of mechanistic information relevant to the dose-response relationship of formaldehyde in the respiratory tract has been generated either following or in conjunction with these two bioassays, as reviewed in Chapter 3, 4 and 5. This information includes the following:

1. Measurements of DNA-protein cross-links (DPXs) formed by formaldehyde in F344 rats and rhesus monkeys (Casanova et al., 1989, 1994). Several PBPK models have been developed in the literature based on these data. Some of these efforts integrated the data in both species (Casanova et al., 1991; Conolly et al., 2000; Klein et al., 2010).
2. Measurements of cell proliferation in F344 rats and rhesus monkeys (Monticello et al., 1989, 1990, 1991, 1996).
3. Simulations of airflow in anatomically realistic representations of the upper respiratory tract of the F344 rat, rhesus monkey and human, and in an idealized representation of the human lower respiratory tract, using computer and physical models (Kimbell et al., 1993, 1997a; Kepler et al., 1998; Subramaniam et al., 1998). These simulations were used to predict regional formaldehyde dosimetry in the corresponding sections of the respiratory tract of these three species (Kimbell et al., 2001a, b; Overton et al., 2001).

The combined nasal tumor incidence data in the two inhalation bioassays (Kerns et al. 1983, Monticello et al. 1996) were analyzed using a multistage-weibull time-to-tumor approach as well as models derived from the biologically based dose-response (BBDR) modeling approach in Conolly et al. (2003) [see Crump et al. (2005), Subramaniam et al. (2007), Section 5.3, and Appendix E for details]. The BBDR approach enabled integration of the mechanistic information and the time-to-tumor incidence data within a single conceptual framework.

6.2.2.4.*Extrapolation Approaches*

An EPA inhalation unit risk is developed to estimate cancer risk from environmental exposures or in order to determine exposure levels corresponding with cancer risks as low as 1 excess cancer in 10,000 or 1 excess cancer in 1 million. As neither data from animal studies, nor human epidemiological studies, provide direct observation of these low level risks, the observed exposure response relationship is extrapolated to estimate low dose risk. The model used to extrapolate below the range of exposures clearly associated with increased risk of health effects has a great influence on the inhalation unit risk, as there may be several orders of magnitude difference between the observed risk and the target risk range. In the absence of empirical data or a biologically-informed model, the EPA applies a simple straight line extrapolation from the point of departure to zero exposure (U.S. EPA, 2005a). The Mode of

Action evaluation reviews available data and determines if an MOA can be sufficiently established and whether it informs the shape of the exposure-response relationship.

6.2.2.4.1. ***Low-dose extrapolation for Lymphohematopoietic cancers.***

Formaldehyde is a mutagen, and known to act directly on cells at the site of first contact. Clastogenic effects have been documented in formaldehyde-exposed workers including peripheral blood lymphocytes and circulating stem cells (Zhang et al., 2010a). Thus a mutagenic MOA has been hypothesized for lymphohematopoeitic cancers, and supports a linear low-dose extrapolation of human cancer risk. Additionally, formaldehyde may also induce some form of bone marrow toxicity, as suggested by observed pancytopenia in exposed workers (Tang et al., 2008, Zhang et al., 2010b). However, as the mechanism of transport to the bone marrow, and biological activity leading to the observed toxicity are unknown, this information does not inform the low-dose extrapolation. Although the mechanisms underlying formaldehyde-induced leukemia and lymphoma are still largely speculative, there is little doubt of an association between formaldehyde exposures and lymphohematopoeitic cancer mortality, especially for myeloid leukemia. Therefore, without a known MOA which would justify an alternative approach, and with a hypothesized mutagenic MOA under consideration which supports a simple straight line extrapolation from the point of departure to zero risk at zero exposure, this is applied when estimating human cancer risk from both leukemia and Hodgkin lymphoma from the NCI cohort.

6.2.2.4.2. ***Low-dose extrapolation for cancer of the upper respiratory tract.***

There are multiple plausible MOAs for formaldehyde carcinogenesis regarding upper respiratory tract cancers (see Section 4.5.3), however they may not be necessarily relevant to describing the lower end of the exposure response curve. For example, although regenerative cell proliferation associated with focal and gross tissue lesions due to cell death may contribute to the high incidence of rat nasal tumor in F344 rats, these mechanisms may not be operative in the low exposure region expected for human environmental exposure (e.g., less than 1ppm) and therefore may not inform low-dose extrapolation. There are MOAs which are more appropriate to the low-dose region. Specifically, formaldehyde is a known mutagen, may inhibit DNA repair activity and may have additional activity as a tumor promoter. Finally, other effects such as formaldehyde-induced cell proliferation, immunosuppression and disruption of the mucociliary apparatus may influence both the level of tissue damage and ultimately cancer incidence.

EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) recommend using biologically based dose-response (BBDR) models for extrapolation when data permit. Conolly

et al. (2003, 2004) developed BBDR models to predict squamous cell carcinoma risk in the rat and human respiratory tract at exposures well below the range of the observed animal data. The primary conclusion from their modeling effort was that human exposure standards protective of effects of formaldehyde-induced cytotoxicity should be sufficient to protect from the potential carcinogenic effects of formaldehyde. The authors assessed that such a conclusion was conservative in the face of model uncertainties.[17] The current assessment evaluated the uncertainties and alternative parameterizations of the modeling in Conolly et al. (2003, 2004) extensively, and concluded that the human cancer risk values computed by Conolly et al. (2004) were not conservative estimates. Models resulting from alternative parametrizations were as consistent with the experimental data as the original model but resulted in maximum likelihood estimates of added human risk that ranged from negative to large positive values at environmental exposure concentrations. Model uncertainty far exceeded statistical uncertainty (see Table E-4 in Appendix E). Each of these models, including the modeling in Conolly et al.,

1. was judged to be just as biologically plausible given the available data,
2. described the rat tumor incidence data equally well,
3. was based on different characterizations of the same empirical cell kinetic data, and
4. was based on the same empirical data on DPX measurements.

This assessment's evaluation[18] (detailed in Section 5.3) of the above models concluded that these models, including alternative implementations of those in Conolly et al. (2003, 2004), were too uncertain to be useful for low-dose extrapolation of risk. In particular:

- When used for the purpose of extrapolating risk, the BBDR models did not appear to reasonably constrain either
  - risk estimates extrapolated from the F344 rat to the human, regardless of whether the extrapolation was carried out at low or comparable exposures, or
  - risk estimates for the F344 rat when extrapolated outside the range of observable data.

[17] Based on their modeling, Conolly et al. (2003, 2004) concluded that the directly mutagenic action of formaldehyde does not play a significant role in formaldehyde carcinogenicity. Respiratory cancer risks associated with inhaled formaldehyde were predicted to be *de minimis* (10^{-6} or less) at relevant human exposure levels when an upper bound on the model estimate for the directly mutagenic action of formaldehyde was used.

[18] The scope of this evaluation was informed by views provided by several experts convened by EPA in October 2004. The participants were Drs. Rory Conolly, Kenny Crump, Linda Hanna, Dale Hattis, Julia Kimbell, George Lucier, Christopher Portier and Fred Miller (guest participant). The meeting agenda and summary are provided in Appendix H.

- Human risk calculated from these BBDR models was numerically unstable when certain parameter conditions were realized (see Section 5.3.3 and Appendix F).

It may be noted that the sensitivity analyses on the basis of which these conclusions were reached have been criticized as resulting in implausible risk estimates (given the epidemiologic data) as a consequence of implementing model variations that are not biologically reasonable (Conolly et al. 2009). This criticism was rebutted by Crump et al. (2009) on biological and epidemiological grounds. These debates have been discussed fully in Appendix F.

However, using the BBDR model to characterize the dose-response in the range of the available data has the advantage of utilizing the available biological and dosimetry data on formaldehyde in an integrated manner as well as providing statistically sound descriptions of the empirical tumor incidence data. Therefore, this assessment uses the BBDR modeling of the rat data to derive multiple PODs (for SCC in the respiratory tract) in the range of the observed data and uses model-derived internal dose estimates. For the reasons detailed above, the BBDR modeling is not used to extrapolate far below the observed data.

The lowest observed incidence of SCC in the bioassays used in the dose-response assessment was equal to 0.0087 (at 6 ppm exposure). In addition, the BBDR modeling of the tumor data was informed by its use of data on cell proliferation and formation of DPXs at the lower exposure concentrations of 0.7 and 2.0 ppm. Thus, the available data supported estimation of response levels below the 10% response level commonly used in BMD analyses of tumor data. Therefore, points of departure corresponding to 95% statistical upper bound levels of extra risk of 0.005, 0.01 and 0.1 were estimated when the BBDR modeling was used.

6.2.2.4.3. ***Summary.***

As discussed earlier in the hazard characterization, formaldehyde is a direct-acting mutagen, and its genotoxic effects have been observed following human occupational exposures.[19] Furthermore, a low-dose nonlinear MOA for formaldehyde-induced lymphohematopoietic cancers, NPCs, or cancers in other regions of the respiratory tract has not been established. In particular, the formation of DPXs by formaldehyde, considered a dose surrogate for the molecular dose associated with formaldehyde's mutagenic action, has been observed at doses well below those considered cytotoxic. Therefore, linear low-dose extrapolation from the suitably chosen PODs was considered most appropriate for all the cancers

[19] While formaldehyde may also contribute to mutations indirectly, such an effect is likely to be relevant only at the higher doses.

(whether the PODs were based on epidemiological data or rodent bioassay data), which is also in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a).

6.2.2.5. *Inhalation Unit Risk Estimates for Cancer*

The epidemiological and rodent inhalation data indicate multiple sites of concern. Unit risk estimates calculated separately from these data are summarized in Table 6-3.

As can be seen in the Table 6-3, the unit risk estimate based on human data for NPC is in the range of the estimates calculated for respiratory tract cancer from the rodent nasal cancer data. Experimental animal data were inadequate for estimating risk of lymphohematopoietic cancers. The unit risk estimate for Hodgkin lymphoma is also in the same range, while the unit risk estimate for leukemia and the total cancer unit risk estimate are up to 4-fold higher.

As documented in EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), when high-quality human data are available, they are generally preferred over laboratory animal data for quantitative risk assessment. Thus, the preferred (plausible upper bound) unit risk estimate in this assessment is the value of **8.1×10^{-2} per ppm (6.6×10^{-5} per µg/m^3)** based on (**adult**) human data for NPC, Hodgkin lymphoma, and leukemia. Note that, as discussed in Section 6.2.2.6 below, if there is early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b).

6.2.2.6.*Early-Life Susceptibility*

There are no chemical-specific data for quantitatively addressing the susceptibility of different life stages to carcinogenicity from inhalation exposure to formaldehyde. As documented in Section 4.5, formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA. Therefore, increased early-life susceptibility should be assumed and, if there is early-life exposure, the ADAFs should be applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). See Section 5.4.4 for details on the application of the ADAFs.

Accordingly, **for *full lifetime* exposures, the overall (plausible upper bound) unit risk estimate is 0.13 per ppm (1.1×10^{-4} per µg/m^3)** for the three cancer types (NPC, Hodgkin lymphoma, and leukemia) combined (see Table 5-26 for calculations).

Table 6-3. Inhalation unit risk estimates based on epidemiological and experimental animal data

Cancer type[a]	Dose metric	Unit Risk Estimate[b] (ppm^{-1})
Based on epidemiological data		
Nasopharyngeal	Cumulative exposure	0.011
Hodgkin lymphoma	Cumulative exposure	0.017
Leukemia	Cumulative exposure	0.057
All three cancer sites combined:		**0.081**[c]
Based on Experimental Animal Data		
Squamous cell carcinoma of the respiratory tract	Local dose (flux) of formaldehyde in $pmol/mm^2/hour$	0.011–0.022[d]

[a] the unit risk estimates are all for cancer incidence.
[b] these unit risk estimates do not include ADAFs (see Section 6.2.2.6 below).
[c] this total cancer unit risk estimate is an estimate of the upper bound on the sum of risk estimates calculated for the 3 individual cancer types (nasopharyngeal cancer, Hodgkin lymphoma, and leukemia); it is not the sum of the individual (upper bound) unit risk estimates (see Section 5.2.4).
[d] values are similar to estimates from Schlosser et al. (2003). These authors determined their PODs based on tumor and cell proliferation as endpoints, and extrapolated benchmark exposure concentrations to humans using formaldehyde flux to the tissue and DPX concentrations as internal dose metrics.

6.2.2.7. *Uncertainties in the Quantitative Risk Estimates*

Uncertainties in the risk estimates based on the human data are discussed in detail in Sections 5.2.2.4 and 5.2.3.4. Major uncertainties inherent in the NPC, Hodgkin lymphoma, and leukemia risk estimates are

- the retrospective exposure estimation,
- the appropriateness of the dose-response model and exposure metric, and
- the extrapolation from occupational exposures to lower environmental exposures.

In addition, the NPC and Hodgkin lymphoma estimates are limited by the sparse data for these cancers in the NCI cohort study (estimates are based on the exposure-response modeling of only 9 NPC deaths and 27 Hodgkin lymphoma deaths).

Of note, Marsh et al. (2002, 1996) independently studied one of the 10 plants that was in the NCI study, and there were large differences in the exposure estimates for that plant from the two different studies. If the exposure estimates of Marsh et al. (2002) are closer to the true

exposures, then the potency of formaldehyde could be greater than reflected in the risk estimates derived from the NCI data.

The linear low-dose extrapolation (see Section 6.2.2.4) from the 95% lower bound on the exposure level associated with the benchmark response is generally considered to provide a plausible upper bound on the risk at lower exposure levels. Although the linear low-dose extrapolation used here is supported by the mutagenicity of formaldehyde, nonlinearities in the exposure-response relationship may be present below, as well as above, the POD. The strong association with peak exposures for all 3 cancer types in the NCI study suggests that dose-rate effects may be operative (i.e., the risk from peak occupational exposures may be greater than the [linearly] proportional risks from lower exposures and, similarly, the risk from an occupational cumulative exposure may be greater than the proportional risk from a lower environmental cumulative exposure).[20] Any such dose-rate effects would not be reflected in the cumulative exposure metric used for the exposure-response modeling in the range of the occupational exposures nor in the linear low-dose extrapolation approach used in this assessment. Actual low-dose risks may be lower to an unknown extent.

Other significant uncertainties may also remain. For example, risk estimates could not be derived from the NCI cohort study for rare upper respiratory tract cancers other than NPC. In addition, although unit risk estimates were derived for Hodgkin lymphoma and leukemia because they exhibited the strongest trend results of the lymphohematopoietic cancers using the cumulative exposure metric, it is uncertain which specific lymphohematopoietic cancer subtypes are associated with formaldehyde exposure. Furthermore, the potential role of particulates in the NPC risk is unclear. Moreover, as for all occupational epidemiology studies, there is uncertainty in extrapolating risk from an adult worker population (in this case predominantly white males) to the more diverse general population.

Despite inevitable uncertainties, it is important not to lose sight of the strengths of the estimates, which are based on human data from a high-quality NCI study. In addition to the use of internal analyses and the extensive exposure assessment and consideration of potential confounding or modifying variables, the NCI study has a large cohort that has been followed for a long time. With the additional follow-up through 2004, reflected in the lymphohematopoietic cancer results of Beane Freeman et al. (2009), the median duration of follow-up was 42 years, and the 25,619 cohort members had accrued 998,106 person-years of follow-up.

[20] Dose-rate effects are also suggested by the very steep, nonlinear exposure-response relationships observed in the rodent cancer bioassays, although, in the rodents, this steep increase in tumor incidence at high exposures is thought to be due to the contribution of cytotoxicity and regenerative proliferation, which is not apparent with the human exposures (Section 4.5).

Significant uncertainties also exist in the risk estimates derived from the rodent bioassay data. In general, the difficulties in extrapolating from experimental animal bioassays are considerable, and the use of human data is preferred, while recognizing the different uncertainties that are present in risk estimates based on epidemiological data.

In the case of formaldehyde, this general uncertainty associated with extrapolation from rodent data is increased due to the highly curvilinear nature of the dose-response relationships associated with DPX formation, labeling index data, and tumor responses. The mechanistic interpretation of these observed data has provided grounds for arguments in the literature that formaldehyde tumorigenicity (at exposures ≥ 6 ppm) should be uncoupled from its potential carcinogenicity in the low-dose region.

Quantitative models have been used in the literature to further argue that the observed risk in animal experiments is entirely due to cell proliferation induced by regenerative hyperplasia in response to cell injury at cytotoxic doses, i.e., without a relevant role for the direct mutagenic action of formaldehyde. In the context of using these data for quantitative risk assessment, this document notes that such an inference of the data has been found to be extremely uncertain. A quantitative analysis of the uncertainties in interpreting the available data has shown that the directly mutagenic action of formaldehyde could be very important in explaining the high-dose effect (Subramaniam et al., 2007).

While acknowledging these substantial difficulties, the quantitative dose-response modeling of the rat data does allow inference about upper bound risks for respiratory cancer, consistent with the observed experimental tumorigenicity. These upper bound risk estimates are consistent with those estimated from the epidemiological data; however, such a consistency may be entirely artifactual. As noted earlier, the BBDR modeling helped characterize some of the uncertainty associated with extrapolating from the rodent data to the environmental risk in people. The actual risk may be substantially lower or higher than the reasonable upper bound risk estimated from the animal data.

6.2.2.8. *Conclusions*

Cancer unit risk estimates for formaldehyde inhalation exposure were derived from both human and laboratory animal data. As documented in EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), when high-quality human data are available, they are generally preferred over laboratory animal data for quantitative risk assessment. Thus, the preferred unit risk estimate in this assessment is based on human data for NPC, Hodgkin lymphoma, and leukemia from a high-quality NCI occupational cohort study (Hauptmann et al., 2004; Beane Freeman et al., 2009). (The qualitative hazard assessment suggests causal associations between

formaldehyde exposure and other cancer types as well [e.g., other upper respiratory tract cancers and possibly other lymphohematopoietic cancers; see Section 4.5], but quantitative data from the NCI cohort study were not amenable for deriving quantitative risk estimates for those cancer types. Because there were not clear exposure-response data for these cancer types in that cohort study [based on cumulative exposure], any contributions to the total cancer risk from environmental formaldehyde exposure for these cancers are not expected to be large; however, this is a source of uncertainty.)

The unit risk estimate for the total cancer incidence extra risk for these three cancer types combined based on the (adult) human data is 8.1×10^{-2} per ppm (6.6×10^{-5} per μg/m^3). As documented in Section 4.5, formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA. Therefore, as there are no chemical-specific inhalation data on cancer susceptibility at different life-stages, increased early-life susceptibility is assumed and ADAFs should be applied in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). Applying the ADAFs, the overall (upper bound) unit risk estimate for *full lifetime* exposure is 0.13 per ppm (1.1×10^{-4} per μg/m^3) for the three cancer types (NPC, Hodgkin lymphoma, and leukemia) combined. Using this lifetime unit risk estimate, the upper bound estimate of the cancer risk at the RfC of 1 ppb is 1×10^{-4}.

6.3. SUMMARY AND CONCLUSIONS

Seven different noncancer health effects were identified from formaldehyde inhalation exposure studies, including: 1) sensory irritation of the eyes, nose, and throat, 2) upper respiratory tract pathology, 3) pulmonary function, 4) asthma and atopy, 5) neurologic and behavioral toxicity, 6) reproductive and developmental toxicity, and 7) immunological toxicity. Of note, epidemiological evidence is available for most of these noncancer effects. EPA has derived candidate RfCs for critical effects based on seven key studies. Three cocritical studies were selected which provide similar cRfCs for related adverse health effects observed in residential populations including children i.e., increased asthma incidence, decreased pulmonary function, increase in respiratory symptoms, and increased allergic sensitization (Rumchev et al., 2002; Garrett et al., 1999 a,b; Krzyzanowski et al., 1999). The resulting cRfCs fall in a range between 2.8 and 11 ppb, depending on the study, or endpoints considered, and the application of alternative uncertainty factors for human variability (see Table 6-1). The representative RfC for the cocritical studies is taken as the average of the cRfCs (see Section 6.2.1.2).

EPA has assessed the adequacy of the overall database for RfC derivation, and although the database is quite large, and provides significant information on well studied POE effects. There are remaining uncertainties in the database. Most notably, there is a need for additional exposure-response information for observed neurotoxic effects, reproductive and developmental effects as well as a two-generation study to evaluate the effects of formaldehyde exposure on reproductive and developmental endpoints. EPA is considering 4 options to address database uncertainties in the final RfC (see Section 6.2.1.3). It is unclear what uncertainty factors are appropriate to account for human variability and deficiencies in the overall database. For this reason, several alternatives have been presented. EPA is seeking advice from the NAS and the public on this matter.

Formaldehyde is Carcinogenic to Humans by the Inhalation Route of Exposure. Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, myeloid leukemia and lymphohematopoietic cancers as a group. Epidemiological evidence is also strongly supportive of, but in itself not sufficient for, a conclusion of causal association for other upper-respiratory tract cancers, Hodgkins lymphoma, or multiple myeloma. Animal bioassays consistently demonstrate formaldehyde-induced nasal cancers in rodents which provide strong support for the observed upper respiratory tract cancers in humans. Limited evidence from animal bioassays is available to support the conclusion from human epidemiologic data that formaldehyde causes some types of lymphohematopoietic cancers.

The (upper bound) unit risk estimate for the total cancer incidence based on (adult) human data is 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu g/m^3$). Applying the age-dependent adjustment factors for increased early-life susceptibility, the overall combined cancer unit risk estimate for full lifetime exposure is 0.13 per ppm (1.1×10^{-4} per $\mu g/m^3$).

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