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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 I of IV

Introduction, Background, and Toxicokinetics

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(Stenton and Hendrick, 1994; Hendrick et al., 1982). Stenton and Hendrick (1994) concluded that these studies "provide clear evidence of formaldehyde's ability to induce asthma" but no indication of the exposure concentrations to induce it. In a follow-up study of dialysis unit staffers exposed to formaldehyde as a sterilizing agent, 8/28 people reported respiratory symptoms and a prolonged increase in circadian rhythm of peak expiratory flow rate was seen in one subject (Hendrick and Lane, 1983) implying an increase in airway responsiveness (Stenton and Hendrick, 1994). It should be noted, however, that while there did appear to be a clear response to formalin, it is not known what contribution to the response was attributable to formaldehyde and what contribution might have been attributable to methanol. Other cases of formaldehyde asthma have been described. Nordman et al. (1985) describe 12 cases and refers to several other case reports (Popa et al., 1965; Sakula 1975; Alanko et al. 1977). While the evidence of a causal association between formaldehyde and asthma is clear, the above studies do not offer information on the concentrations at which adverse effects would be expected in a population. While formaldehyde exposure is generally considered an etiologic factor for the development of asthma in occupational settings it appears to be a rare occurrence.

Numerous epidemiologic studies have investigated adverse effects in populations. Decreased peak expiratory flow rates (PEFR) are an important component in the diagnosis of asthma and there is extensive evidence of formaldehyde-induced decrements in PEFR (see Section 4.1.1.2). However, the diagnosis of asthma is both a more serious health condition and diagnostically more complex than decreased PEFR alone and is evaluated here as a distinct endpoint. While epidemiologic studies have investigated the potential association between formaldehyde exposure and a continuum of adverse health effects from pulmonary function to asthma, few nonoccupational studies have evaluated the potential effects of formaldehyde exposure on the risk of asthma onset (Delfino 2002).

However, residential formaldehyde exposure was reported to be associated with an increased risk of incident asthma in a population-based case-control study of 192 children aged 6 months to 3 years (Rumchev et al., 2002). The study was comprised of 88 children discharged from the emergency department of a children's hospital in Perth, Australia, with a primary diagnosis of asthma and 104 controls from the same community identified through the health department. Information about the child's respiratory condition and risk factors for asthma was obtained via a questionnaire compiled by the parent. Seasonal (winter, summer) 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 diagnosis by formaldehyde exposure level category (10-29, 30-49, 50-59 and >60 $\mu g/m^3$) were adjusted for measured indoor air pollutants, allergy levels of house dust mite, relative humidity, indoor

temperature, family history of asthma, atopy, 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 (ORs of 1.09, 2.57, and 2.66, respectively). Coexposures to other indoor air pollutants were also controlled for including benzene, toluene and ethylbenzene (Rumchev et al., 2004).

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 $\mu g/m^3$ (49 ppb) (OR of 1.39) (Rumchev et al., 2002). 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. The paper states this effect as OR 1.003 (95% CI 1.002-1.004) which appears at odds with a 3% increased in risk per every 10 $\mu g/m^3$ but this must be the effect per 1 $\mu g/m^3$ and can be confirmed by comparing the per unit effect to the plotted results[1]. All analyses controlled for other indoor air pollutants, allergen levels, relative humidity, and indoor temperature as well as other risk factors.

While the study by Rumchev et al. (2002) focused on formaldehyde controlling for other indoor air pollutants, a subsequent report described the specific effects of those indoor air pollutants (Rumchev et al., 2004). This paper evaluated the risk of asthma incidence with 10 VOCs. The highest odds ratios were increased risks of asthma diagnosis associated with benzene, toluene, and ethylbenzene and were statistically significant associations. Compared to the effects observed for formaldehyde, the strength of the associations appear to be stronger on a per 10 $\mu g/m^3$ basis. The strength of these effects is an important consideration as the relative strength of the VOC effects appears to be larger than that attributable to formaldehyde if the effects of the measured indoor air pollutants had not been controlled for in the formaldehyde analysis (Rumchev et al., 2002). However, as these indoor air pollutants had been controlled for, the reported effect of formaldehyde should be independent of the effect of benzene and other VOCs in the absence of residual confounding. If two factors both cause the same outcome and are statistically associated, then they may mutually confound. In Rumchev et al. (2004) on page 750, the investigators assessed whether the effect of the VOCs were confounded by formaldehyde and stated that the results showed that exposure to VOCs still had a highly significant effect on asthma even when formaldehyde was controlled for. This finding further substantiates the formaldehyde finding since mutual confounding was not identified.

[1] In order to confirm that the effect size is 1.003 per unit change in exposure and 1.03 per 10 units, EPA compared these results to the plotted results in Rumchev et al. (2002). A line drawn across the plot at OR = 1.003 per one unit change in exposure estimates the non-linear categorical results well. At 60 $\mu g/m^3$, the extrapolated linear effect would be OR = 1.2.

Several other nonoccupational studies have evaluated the association between formaldehyde exposure and the prevalence of asthma among children (Garrett et al., 1999; Tavernier et al., 2006; Gee et al., 2005; Krzyzanowski et al., 1990; Palczynski et al., 1999). Three studies (Tavernier et al., 2006; Gee et al., 2005; Garrett et al., 1999) were performed by matching children with and without asthma and comparing the levels of formaldehyde in their homes. Gee et al. (2005) selected 100 cases with current asthma and 100 controls from 2 primary care facilities in an area of England with low socioeconomic status. Cases were identified through a screening questionnaire that had been validated with diagnoses by physicians. Cases and controls (aged 4–16 years) were matched by age and sex. Median formaldehyde levels were 0.03 ppm in living rooms and 0.04 ppm in bedrooms. Univariate comparisons found no differences in formaldehyde levels between cases of current asthma and controls without asthma. Notably, no association was observed for pollutant indicators of environmental tobacco smoke and current asthma, a recognized risk factor. A subsequent study of the same children in the same homes conducted a more thorough evaluation of risk factors (Tavernier et al. (2006). Again, a one-week average formaldehyde concentration in the living room or bedroom was not found to be associated with current asthma in multivariate analyses adjusted for several indoor variables. Respirable particulates, tobacco specific particles, volatile organic compounds, and nitrogen dioxide also were not associated with current asthma. Tavernier et al. (2006) did not report the measured levels of formaldehyde, but gave the OR for the highest tertile of exposure in the bedroom compared with the lowest tertile of exposure as 0.99 (95% CI: 0.39–2.50). The odds ratio for the second tertile compared to the lowest tertile was 1.22 (95% CI: 0.49-3.07). The width of the confidence intervals indicates that study did not have adequate statistical power to detect low level risks and suggests that these findings would still be consistent with a two-fold increase in risk.

Garrett et al. (1999) reported on the risk of allergy and asthma-like respiratory symptoms due to formaldehyde exposure in a cross-sectional survey of 80 households in rural Victoria, Australia with children, aged 7–14 years, with (n = 53) or without (n = 88) doctor-diagnosed asthma. Households were recruited via schools, medical centers, and advertisements in the local press. The study was designed to include asthmatic children in half of the households and the study recruited 43 households with at least one child with asthma diagnosed by a doctor and 37 households with no asthmatic children. Formaldehyde exposure was characterized by 4 seasonal in-home sampling events in 1994 and 1995 (4-day passive samples) in bedrooms of all participating children and in living rooms, kitchens, and outdoors. Median indoor formaldehyde concentrations were 15.8 $\mu g/m^3$ (12.6 ppb) with a maximum of 139 $\mu g/m^3$ (111 ppb). The median outdoor concentration was 0.7 $\mu g/m^3$ with a range of < 0.3–15.3 $\mu g/m^3$.

Information on asthma respiratory symptoms during the previous year was obtained through an interview with a parent after sampling was completed. An erratum to the original paper reported that the column headers in two tables were switched but that the summary statistical and conclusions in the 1999 report were correct as published. The proportion of asthmatic children by the highest formaldehyde level measured over four seasons was 0.16, 0.39, and 0.44 for <20 μg/m^3, 20-50 μg/m^3, and >50 μg/m^3, respectively (test for trend, $p < 0.02$). However, in logistic regression models, the ORs for the association did not remain statistically significant after controlling for parental allergy and asthma (ORs and 95% CIs were not provided).

A large, representative 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 physician-diagnosed asthma was 45.5% for those with measured levels of formaldehyde in the kitchen >60 ppb ($N = 11$). The prevalence of asthma dropped to 0% for levels 41–60 ppb ($N = 12$) and 15.1% for levels ≤40 ppb ($N = 106$) (chi-squared trend test $p < 0.05$). No trend in asthma prevalence was seen for children who were not exposed to environmental tobacco smoke (Krzyzanowski et al., 1990).

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 did show an increased risk. For example, the reported risk ratio for having new construction or remodeling performed in the house in the past 4 months was 2.5 (95% CI: 1.7–3.9). The risk ratio for having new or upholstered furniture in the house (brought into the house within the past 4 months) was 2.2 (95% CI: 1.2–3.9).

A study in Poland randomly selected 120 households with children 5–15 years of age in 10 year old apartment houses (Palczynski et al., 1999). Using self-reported asthma prevalence as an outcome, study investigators found no association with levels of formaldehyde (mean 25.9 μg/m^3, range 2.0–66.8 μg/m^3) measured using 24-hour samples in the children. Among adults, the authors reported a higher prevalence of allergic diseases in the highest formaldehyde exposure group but that the group was too small for statistical evaluation. However, the prevalence of allergic asthma was higher among adults exposed to 25.1-50 μg/m^3 compared to <25 μg/m^3 and exposed to environmental tobacco smoke ($p = 0.03$).

Delfino et al. (2003) conducted a panel study of 22 Hispanic children with a minimum one year history of doctor diagnosed asthma, aged 10–16 years, and living in Los Angeles. The participants were nonsmokers from nonsmoking households, and lived and went to school within 3 miles of a central site monitor. The children recorded the severity of asthma symptoms in daily diaries for 3 months. The mean outdoor 24-hour levels of formaldehyde were 7.21 ppb (range 4.27–14.02 ppb). A positive association between asthma symptom scores (comparing children