Background

In 2011, the NAS completed its review of the EPA's draft IRIS assessment[1] and made recommendations for improving the evaluation of carcinogenicity, toxicity and dose-response modeling in the IRIS assessment. The American Chemistry Council Formaldehyde Panel has been committed to generating new science that directly addresses the specific recommendations made by the NAS. The below summary provides an overview of some of the available scientific evidence that illustrate a lack of causal association of formaldehyde and leukemia; and a need to integrate all the available formaldehyde data to reach conclusion.

Epidemiological Evidence

The NAS report recommended reviewing determinations of causality for specific lymphohematopoietic (LHP) cancers, and reviewing the criteria that were used to weigh evidence and assess causality. In addition, because the draft IRIS assessment relies heavily on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas) is also needed, as well as clarification of the basis of EPA's interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. Additionally, the NAS also recommended resolving the conflicting statements in the IRIS assessment concerning which upper respiratory cancer sites were found to be causally associated with formaldehyde exposure. Below are several studies that focus on these areas.

- **Mundt, K., Gallagher, A., Dell, L., Natelson, E., Boffetta, P., and Gentry, R. Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? (2017) Critical Reviews in Toxicology. Aug;47(7):592-602.** Conducted additional and refined analysis on the key underlying data (including specifically exposure information which had not been previously provided) utilized in a study relied upon in the draft IRIS assessment (e.g. Zhang et al. 2010). The analysis evaluates exposed and unexposed populations and any potential correlations between formaldehyde exposure and aneuploidy among the exposed populations. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Additionally, among formaldehyde-exposed workers, no association was observed between individual formaldehyde exposure estimates and frequency of aneuploidy, which the original study authors suggested were indicators of myeloid leukemia risk. *Work Supported by the ACC Formaldehyde Panel members.

- **Marsh, G., Morfeld, P., Zimmerman, S., Liu, Y., and Balmert, L. (2016). An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study." Journal of Occupational Medicine and Toxicology 11, no. 1: 1.** The reanalysis provided little or no evidence to support NCI's suggestion of a persistent association between formaldehyde exposure and mortality from nasopharyngeal cancer. Specifically, the findings led to: (1) reduced standardized mortality ratios and relative risks in the remaining nine study plants in unaffected exposure categories, (2) attenuated exposure-response relations for formaldehyde and nasopharyngeal cancer for all the formaldehyde metrics considered and (3) strengthened and expanded evidence that the earlier NCI internal analyses were non-robust and mis-specified as they did not account for a statistically significant interaction structure between

[1] NAS 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. National Research Council. ISBN: 0-309-21194-8, 194 pages. Available at: http://www.nap.edu/catalog/13142.html.

plant group (Plant 1 vs. Plants 2-10) and formaldehyde exposure. *Work supported by the ACC Formaldehyde Panel members.

- **Checkoway, H., Dell, L.D., Boffetta, P., Gallagher, A.E., Crawford, L., Lees, P.S., and Mundt, K.A. (2015). Formaldehyde exposure and mortality risks from acute myeloid leukemia and other Lymphohematopoietic Malignancies in the US National Cancer Institute cohort study of workers in Formaldehyde Industries. Journal of Occupational and Environmental Medicine, 57(7), 785-794.** Authors obtained the data from the NCI cohort study via a Technology Transfer Agreement to replicate the findings reported by Beane Freemen et al. (2009) and to conduct additional analysis of associations of specific leukemias and lymphomas, especially acute myeloid leukemia, with formaldehyde exposure. Analyses were conducted including peak exposure as defined by Beane Freeman et al. (2009), as well as using an alternative more standard definition of peak exposure. The findings from this re-analysis fail to support the hypothesis that formaldehyde causes acute myeloid leukemia. Specifically, the results indicated: Acute myeloid leukemia was unrelated to "peak" or any other formaldehyde metric including the conventional cumulative exposure (also as reported in Beane Freeman (2009)). In fact, very few cohort members had any peak exposure within 20 years of death due to AML. There were suggestive associations with peak exposure only for chronic myeloid leukemia, albeit based on very small numbers. No other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. *Work supported by the ACC Formaldehyde Panel members. Work recognized by the American College of Occupational and Environmental Medicine (ACOEM's) Journal of Occupational and Environmental Medicine (JOEM) for a 2017 Kammer Merit in Authorship Award.

- **Coggon, D., Ntani, G., Harris, E. C., & Palmer, K. T. (2014). Upper airway cancer, myeloid leukemia, and other cancers in a cohort of British chemical workers exposed to formaldehyde. American Journal of Epidemiology, 179(11), 1301-1311.** Conducted an update of mortality data through 2012 for the UK cohort of 14,008 formaldehyde users and producers and reported no increased mortality from myeloid leukemia (SMR 1.16, 95% CI 0.60 -2.20 for background exposure; SMR=1.46, 95% CI 0.84 - 2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450 -1.82 for high exposure). In a nested case-control analysis of 45 myeloid leukemias (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was increased (non-statistically significant) among workers exposed to high concentrations for < 1 year (OR=1.77, 95% CI 0.45 - 7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24 - 3.82)

- **Talibov, M., Lehtinen-Jacks, S., Martinsen, JI., Kjærheim, K., Lynge, E., Sparén, P., Tryggvadottir, L., Weiderpass, E., Kauppinen, T., Kyyrönen, P., Pukkala, E. (2014). Occupational exposure to solvents and acute myeloid leukemia: a population-based, case–control study in four Nordic countries Scandinavian Journal of Work, Environment & Hhealth 40.5: 511.** Analyzed 15,332 newly diagnosed cases of AML (i.e., not deaths) diagnosed from 1961 to 2005 in Finland, Norway, Sweden, and Iceland, and 76,660 matched controls. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (HR 0.89, 95% CI 0.81 - 0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83 -1.03 for workers

exposed to 0.171 - 1.6 ppm-yrs, and HR=1.17, 95% CI 0.91 - 1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde).

- **Marsh, G., Morfeld, P., Collins, J., Symons, JM. (2014). Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. Journal of Occupational Medicine and Toxicology 9, no. 1: 1.** Evaluation concluded that efforts should be made to re-analyze data from the 2004 follow-up of the National Cancer Institute formaldehyde cohort study. The evaluation also recommended that publications resulting from the National Cancer Institute formaldehyde cohort study which contain incorrect data from the incomplete 1994 mortality follow-up should be retracted entirely or corrected via published errata in the corresponding journals. * Work supported by the ACC Formaldehyde Panel members.

- **Meyers, AR, Pinkerton, LE, Hein, MJ. (2013). Cohort mortality study of garment industry workers exposed to formaldehyde: Update and internal comparisons. AmJ IndMed 56(9):1027-39.** Updated mortality data from 1960 through 2008 for 11,043 US garment workers employed at least three months between 1955 and 1983 at three US factories and exposed to formaldehyde. A total of 36 leukemia deaths were reported (SMR=1.04, 95% CI 0.73 - 1.44, compared to US mortality rates), of which 21 were myeloid leukemia (14 AML, 5 CML, 2 other and unspecified ML). The SMR for AML was 1.22 (95% CI 0.67 - 2.05), noting that "the extended follow-up did not strengthen previously observed associations."

- **Saberi Hosnijeh, F., Christopher, Y., Peeters, P., Romieu, I., Xun, W., Riboli, E., Raaschou-Nielsen, O., Tjønneland, A., Becker, N., Nieters, A., Trichopoulou, A., Bamia, C., Orfanos, P., Oddone, E., Luján-Barroso, L., Dorronsoro, M., Navarro, C., Barricarte, A., Molina-Montes, E., Wareham, N., Vineis, P., and Vermeulen, R. (2013). Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC)Occup Environ Med;70:464–470.** Studied occupational risk factors among 671 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy. Occupational exposures were estimated using a general population exposure matrix that classified occupational codes of study subjects into categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). No increased risk of AML was associated with low exposure to formaldehyde (HR 1.01, 95% CI 0.65 - 1.57) and no AML cases occurred among individuals in the high formaldehyde exposure category.

Toxicological Evidence

The NAS noted the paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. Two studies, as summarized below, have been conducted by the National Toxicology Program to further evaluate the potential for LHPs in animals.

- **Morgan, DL., Dixon, D., Jokinen, MP., King, DH., Price, H., Travlos, G., Herbert, RA., French, JW., and Waalkes, MP. Evaluation of a potential mechanism for formaldehyde-induced leukemia in p53-haploinsufficient mice. (2015). Society of Toxicology Annual Meeting, Abstract #1637.** The research reported on a study testing the hypothesis that formaldehyde may cause leukemia by causing genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. Despite the fact that the study used mice pre-disposed to the development of lymphohematopoietic cancers, the results provided indicated that formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in the mice. (Draft technical report currently under internal NTP review).

- **Morgan, DL., Dixon, D., Jokinen, MP., King, DH., Price, H., Travlos, G., Herbert, RA., French, JE., and Waalkes, MP. Evaluation of a potential mechanism for formaldehyde-induced leukemia in C3B6.129F1-Trp53tm1Brd mice. (2014). Society of Toxicology Annual Meeting, Poster Board -129.** Study found that no cases of leukemia or lymphohematopoietic neoplasia were seen in genetically predisposed C3B6.129F1-Trp53tm1Brd mice exposed to formaldehyde through inhalation.(Draft technical report currently under internal NTP review).

Mechanistic Evidence

The NAS noted that systemic responses are unlikely to arise from the direct delivery of formaldehyde to a distant site in the body and that the experimental evidence is insufficient to support the hypothesis that circulating hematopoietic stem cells may be the target cells for the mutagenic effects that eventually lead to cancers. The NAS also noted a need for improved understanding of exogenous and endogenous formaldehyde concentrations. Below are several studies that focus on these areas.

- **Albertini, R. J., & Kaden, D. A. (2016). Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. Critical Reviews in Toxicology, 1-40.** Research focused on the critical review and integration of the available peer-reviewed literature addressing the potential genotoxicity of formaldehyde. This publication also addresses the potential involvement of chromosome changes in blood cells suggested to be key events in proposed modes of action for the development of leukemia following formaldehyde exposure. The evaluation found reported genetic changes in circulating blood cells do not provide convincing support for formaldehyde classification as a human leukemogen. Specifically, the evaluation notes that no convincing evidence that exogenous exposures to formaldehyde alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically not in the bone marrow. In addition, recent studies reporting changes in human bone marrow or hematopoietic precursor cells either have had confounding exposures or could not distinguish in vivo from in vitro occurrences. *Work supported by the ACC Formaldehyde Panel members.

- **Lai, Y., Yu, R., Hartwell, H. J., Moeller, B. C., Bodnar, W. M., & Swenberg, J. A. (2016). Measurement of Endogenous versus Exogenous Formaldehyde–Induced DNA–Protein Crosslinks in Animal Tissues by Stable Isotope Labeling and Ultrasensitive Mass Spectrometry. Cancer Research, 76(9), 2652-2661.** Examined the formation, accumulation, and hydrolysis of DNA-protein crosslinks of both exogenous and endogenous formaldehyde. The results show that inhaled formaldehyde only reached rat and monkey noses, but not tissues distant to the site of initial contact. *Work supported by the ACC Formaldehyde Panel members.

- **Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W., Starr, T., & Swenberg, J. A. (2015). Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicological Sciences, 146(1), 170-182.** Evaluated the plausibility for inhaled formaldehyde to reach distal sites in rat and monkey models. The study indicated that inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. *Work supported by the ACC Formaldehyde Panel members.

- **Edrissi, B., Taghizadeh, K., Moeller, B., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Dedon, P. (2013). Dosimetry of N 6-Formyllysine Adducts Following [13C2H2]-Formaldehyde Exposures in Rats. Chemical Research in Toxicology 26, no. 10: 1421-1423.** The research found that Exogenous N6-formyllysine was detected in the nasal epithelium, but was not detected in the lung, liver, or bone marrow. Endogenous adducts dominated at all exposure conditions, The results parallel previous studies of formaldehyde-induced DNA adducts. *Work supported by the ACC Formaldehyde Panel members.

- **Gentry, R., Rodricks, J., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A., Albertini, R., and Irons, R. (2013). Formaldehyde exposure and leukemia: Critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. Critical Reviews in Toxicology 43, no. 8: 661-670.** A critical review of the study, as well as a reanalysis of the underlying data, was performed and the results of this reanalysis suggested factors other than formaldehyde exposure may have contributed to the effects reported. Specifically, in the original study the authors did not follow their stated protocol and evaluation of the other study data indicates that the aneuploidy measured could not have arisen in vivo, but rather arose during in vitro culture. The results of the critical review and reanalysis of the data do not support a mechanism for a causal association between formaldehyde exposure and myeloid or lymphoid malignancies. *Work supported by the ACC Formaldehyde Panel members.

- **Rager, J., Moeller, B., Miller, S., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Fry, R. (2014). Formaldehyde-associated changes in microRNAs: tissue and temporal specificity in the rat nose, white blood cells, and bone marrow. Toxicological Sciences: 138(1):36-46. doi:10.1093/toxsci/kft267.** In this study, a multi-tiered approach was employed to enable an understanding of the genome-wide miRNA responses to formaldehyde and to establish how these responses relate to alterations in transcriptional profiles over time and in various tissues. This study found that formaldehyde inhalation exposure induces tissue and time-dependent responses at the genomic and epigenomic level. Formaldehyde exposure disrupts miRNA expression profiles within the rat nose and white blood cells but not within the bone marrow. *Work supported by the ACC Formaldehyde Panel members.

- **Rager, J., Moeller, B., Doyle-Eisele, M., Kracko, D., Swenberg, J., and Fry, R. (2013). Formaldehyde and epigenetic alterations: microRNA changes in the nasal epithelium of nonhuman primates." Environmental Health Perspectives (Online) 121, no. 3: 339.** Research found that Formaldehyde exposure significantly disrupts miRNA expression profiles within the nasal epithelium. These results provide evidence for a relationship between formaldehyde exposure and altered signaling of the apoptotic machinery, likely regulated via epigenetic mechanisms. *Work supported by the ACC Formaldehyde Panel members.

- **Lu, K., Craft, S., Nakamura, J., Moeller, B., and Swenberg, J. (2012). Use of LC-MS/MS and stable isotopes to differentiate hydroxymethyl and methyl DNA adducts from formaldehyde and nitrosodimethylamine." Chemical Research in Toxicology 25, no. 3: 664-675.** Research demonstrated that N(2)-hydroxymethyl-dG is the primary DNA adduct formed in cells following formaldehyde exposure. In addition, the study shows that alkylating agents induce methyl adducts at N(2)-dG and N(6)-dA positions, which are identical to the reduced forms of hydroxymethyl adducts arising from formaldehyde. *Work supported by the ACC Formaldehyde Panel members.

- **Moeller, B., Lu, K., Doyle-Eisele, M., McDonald, J., Gigliotti, A., and Swenberg, J. (2011). Determination of N 2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure. Chemical Research in Toxicology 24, no. 2: 162-164.** Research found that both exogenous and endogenous adducts were readily detected and quantified in the nasal tissues of both exposure groups, with an exposure dependent increase in exogenous adducts observed. In contrast, only endogenous adducts were detectable in the bone marrow, even though ~10 times more DNA was analyzed. * Work supported by the ACC Formaldehyde Panel members.

- **Andersen, M. E., Clewell, H. J., Bermudez, E., Dodd, D. E., Willson, G. A., Campbell, J. L., & Thomas, R. S. (2010). Formaldehyde: Integrating dosimetry, cytotoxicity and genomics to**

understand dose-dependent transitions for an endogenous compound. Toxicological Sciences, kfq303. In this study, concentration and exposure duration transitions in formaldehyde mode of action were examined with pharmacokinetic modeling and with histopathology and gene expression in nasal epithelium from rats exposed to concentrations of up to 15 ppm formaldehyde for up to 13 weeks. The results of the study indicated that formaldehyde concentrations below 1 or 2 ppm would not increase risk of cancer in the nose or any other tissue or affect formaldehyde homeostasis within epithelial cells. * Work supported by the ACC Formaldehyde Panel members.

- **Andersen, M. E., Clewell, H. J., Bermudez, E., Willson, G. A., & Thomas, R. S. (2008). Genomic signatures and dose-dependent transitions in nasal epithelial responses to inhaled formaldehyde in the rat. Toxicological Sciences, 105(2), 368-383.** Research included repeated and acute exposure studies to assess time and concentration-dependencies of nasal responses to formaldehyde and genomic changes. The study noted that the most sensitive gene changes were associated with extracellular components and plasma membrane. There were temporal and concentration-dependent transitions in epithelial responses and genomic signatures between 0.7 and 6 ppm. * Work supported by the ACC Formaldehyde Panel members.

Dose- Response and Modeling Evidence

The NAS noted that the biologically based dose response (BBDR) model for formaldehyde is one of the best developed BBDR models to date and recommended utilizing the BBDR model in the IRIS assessment. Below are a few studies that highlight approaches for dose response analysis in line with the NAS committee recommendation.

- **Van Landingham, C., Mundt, K. A., Allen, B. C., and Gentry, P. R. (2016). The need for transparency and reproducibility in documenting values for regulatory decision making and evaluating causality: The example of formaldehyde. Regulatory Toxicology and Pharmacology, 81, 512-521.** This evaluation was in response to the NAS comment to conduct independent analysis of the dose-response models used in the IRIS assessment to confirm the degree to which the models fit the data appropriately The authors reported that the documentation of the methods applied in the EPA IRIS assessment lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the Beane Freeman et al. (2010). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. *Work supported by the ACC Formaldehyde Panel members.

- **Starr, T. B., & Swenberg, J. A. (2016). The bottom-up approach to bounding potential low-dose cancer risks from formaldehyde: An update. Regulatory Toxicology and Pharmacology, 77, 167-174.** Updated a previously proposed method (Starr and Swenberg 2013). This approach has useful applications for substances, like formaldehyde, where there is a substantial endogenous exposure in potential target tissues and little or no empirical evidence of a positive dose-response at low exogenous exposure levels. It also provides valid bounding estimates of added risk from exposure to all airborne formaldehyde concentrations up to and including 2 ppm. *Work supported by the ACC Formaldehyde Panel members.

- **Schroeter, J., Campbell, J., Kimbell, J., Conolly, R., Clewell, H., and Andersen, M. (2014) "Effects of endogenous formaldehyde in nasal tissues on inhaled formaldehyde dosimetry predictions in the rat, monkey, and human nasal passages." Toxicological Sciences 138, no. 2 (2014): 412-424.** Pharmacokinetic modeling was conducted to evaluate the impact of endogenous concentrations of formaldehyde at the portal of entry. Endogenous formaldehyde in nasal tissues

did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations.

- **Starr, T. B., & Swenberg, J. A. (2013). A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. Regulatory Toxicology and Pharmacology, 65(3), 311-315.** Provided a refined approach for conducted risk extrapolations using a bottom up instead of top-down risk calculation. Results indicate that top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. *Work supported by the ACC Formaldehyde Panel members.

Critical Reviews and Data Integration Evidence

The NAS committee indicated that the IRIS assessment should review the discussion of asthma causation and the selected approach to establish the points of departure. The NAS also recommended that the IRIS program overall should provide more clarity in the evaluation and integration of the scientific evidence. Below are a few articles that inform the formaldehyde science in line with the NAS committee recommendations.

- **Mundt, K., Gentry, PR., Dell, L., Rodricks, J., and Boffetta, P. (2017). Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. Regul Toxicol Pharmacol. 2017 Nov 20. pii: S0273-2300(17)30363-X.** Evaluates the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. Indicated that overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of lymphohematopoietic malignancies (LHM) has increased substantially. The new evidence been published in each of the major streams of evidence (i.e., human, animal and mechanistic) consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the National Research Council (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. *Work Supported by the ACC Formaldehyde Panel members.

- **Golden, R., and Holm, S. (2017). Indoor Air Quality and Asthma: Has Unrecognized Exposure to Acrolein Confounded Results of Previous Studies? Dose Response. Feb 15;15(1).** The evaluation illustrated that there is no evidence that indicates increased sensitivity to sensory irritation to formaldehyde in people often regarded as susceptible such as asthmatics. Suggest that previous studies on potential risk factors and childhood asthma may be confounded by formaldehyde acting as an unrecognized proxy for acrolein. *Work supported by the ACC Formaldehyde Panel members.

- **Nielsen, G.D., Larsen, S.T. and P. Wolkoff. (2016) Re-evaluation of the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Arch. Toxicol. doi:10.1007/s0204-016-7133-8.** Provides a summary of new key studies conducted since 2013, which were evaluated and compared to the WHO guideline. The authors concluded the overall the credibility of the WHO guideline (that recognizes threshold effects for any potential carcinogenic responses) has not been challenged by new studies.

- **Rhomberg, L. (2015). Contrasting directions and directives on hazard identification for formaldehyde carcinogenicity." Regulatory Toxicology and Pharmacology: RTP 73, no. 3: 829-833.** The article examined two separate National Academy of Sciences committee evaluations on whether formaldehyde should be identified as a human carcinogen. It highlighted key differences in the approaches, scientific methods and criteria used by two government agencies in identifying and classifying human carcinogens. It also discussed the importance of clear processes for evaluating science and how the available formaldehyde science illustrates the contrast between the two approaches when evidence is integrated to reach conclusions on hazard. *Work supported by the ACC Formaldehyde Panel members.

- **Swenberg, J., Moeller, B., Lu, K., Rager, J., Fry, R., and Starr, T. (2013). Formaldehyde Carcinogenicity Research 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment. Toxicologic Pathology 41(2):181-189. doi:10.1177/0192623312466459.** Article reviews the data for rodent and human carcinogenicity, early mode of action studies, more recent molecular studies of both endogenous and exogenous DNA adducts, and epigenetic studies. It goes on to demonstrate the power of these research studies to provide critical data to improve our ability to develop science-based cancer risk assessments, instead of default approaches. *Work Supported by the ACC Formaldehyde Panel members.

- **Checkoway, H., Boffetta, P., Mundt, D., and Mundt, K. (2012). Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies." Cancer Causes & Control 23, no. 11: 1747-1766.** Evaluation found that there is no consistent or strong epidemiologic evidence that formaldehyde is causally related to any of the lymphohematopoietic malignancies. Specifically, the evaluation noted that findings from occupational cohort and population-based case-control studies were very inconsistent for lymphohematopoietic malignancies, including myeloid leukemia. Apart from some isolated exceptions, relative risks were close to the null, and there was little evidence for dose-response relations for any of the lymphohematopoietic malignancies. *Work supported by the ACC Formaldehyde Panel members.

- **Rhomberg, L., Bailey, L., Goodman, J., Hamade, A., and Mayfield, D. (2011). Is exposure to formaldehyde in air causally associated with leukemia?—A hypothesis-based weight-of-evidence analysis. Critical Reviews in Toxicology 41, no. 7: 555-621.** The evaluation concluded that the case for a causal association is weak and strains biological plausibility. *Work Supported by the ACC Formaldehyde Panel members.

- **Golden, R. (2011). Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. Critical Reviews in Toxicology 41, no. 8: 672-721.** The assessment concluded that a formaldehyde indoor air limit of 0.1 ppm should protect even particularly susceptible individuals from both irritation effects and any potential cancer hazard. *Work supported by the ACC Formaldehyde Panel members.