Texas Commission on Environmental Quality (TCEQ)

Responses to Public Comments

June 2014
Formaldehyde 24-Hour Air Monitoring Comparison Value Development Support Document

The public comment period on the Development Support Document (DSD) for the proposed 24-hour air monitoring comparison value (AMCV)/reference value (ReV) for formaldehyde ended May 6, 2014. The American Forest & Paper Association/American Wood Council and the American Chemical Council submitted comments on the proposed 24-hour AMCV for formaldehyde. The TCEQ appreciates the effort put forth to provide comments on this proposed DSD for formaldehyde. The goal of the Toxicology Division and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. Comments were divided into sections and are provided below, followed by TCEQ responses.

Comments from the American Forest & Paper Association and the American Wood Council

Comment No. 1:

The American Forest & Paper Association (AF&PA) and the American Wood Council (AWC) appreciate the opportunity to comment on the Texas Commission on Environmental Quality's (TCEQ) proposed 24-Hour Ambient Air Monitoring Comparison Value (AMCV) for formaldehyde.

AF&PA is the national trade association of the forest products industry, representing pulp, paper, packaging and wood products manufacturers, and forest landowners. Our companies make products essential for everyday life from renewable and recyclable resources that sustain the environment. The forest products industry accounts for approximately 5 percent of the total U.S. manufacturing GDP. Industry companies produce about $175 billion in products annually and employ nearly 900,000 men and women, exceeding employment levels in the automotive, chemicals and plastics industries. The industry meets a payroll of approximately $50 billion annually and is among the top 10 manufacturing sector employers in 47 states.

AWC is the voice of North American traditional and engineered wood products, representing over 75% of the industry. From a renewable resource that absorbs and sequesters carbon, the wood products industry makes products that are essential to everyday life and employs about one-third of a million men and women in well-paying jobs. AWC's engineers, technologists,

scientists, and building code experts develop state-of-the-art engineering data, technology, and standards on structural wood products for use by design professionals, building officials, and wood products manufacturers to assure the safe and efficient design and use of wood structural components. AWC also provides technical, legal, and economic information on wood design, green building, and manufacturing environmental regulations advocating for balanced government policies that sustain the wood products industry.

TCEQ Response:

The TCEQ thanks AF&PA and AWC for their comments.

Comment No. 2:

Recently, TCEQ proposed a 24-hour acute AMCV of 24 ppb using based presumably on only one study by Wilhelmsson and Holmstrom (1992) that reports elevated rates of symptoms such as eye, nasal, and lower airway discomfort in workers. Analysis of the acute effects of formaldehyde based solely on one paper is not scientifically robust and is unwise. Furthermore, the decision to make a determination based on one study gives the impression that: (1) this is a unique study in supplying information on these endpoints and, (2) the study is of acceptable quality. Unfortunately, neither of these statements are true. As discussed below, several evaluations have been conducted on the non-cancer health effects of formaldehyde. Indeed, controlled formaldehyde chamber studies provide less possible confounding than occupationally exposed cohorts and a more useful basis for deriving the AMCV. Of interest, there are over 20 published studies and critical reviews of these controlled studies of formaldehyde that provide consistent and convincing outcomes of acceptable exposure concentrations of approximately 0.1 ppm. Moreover, several authoritative bodies have already conducted a review of the formaldehyde literature and have identified the reliance of these studies.

Conversely, at least three reviews of the formaldehyde literature have come to the conclusion that Wilhelmsson and Holmstrom (1992) does not provide sufficient details to be relied upon for determining an acceptable concentration of formaldehyde. Consequently, we urge TCEQ to discard their flawed evaluation and commit to additional review. While we feel several studies are appropriate to provide a satisfactory body of data to support the AMCV, a recent study by Lang et al. (2008) has been chosen by other organizations for a similar exercise and thus we recommend its use. One example is from the World Health Organization that used Lang et al. to derive a protective threshold concentration for sensory irritation in indoor environments at 0.125 ppm.

TCEQ Response:

While the DSD for the proposed 24-hour AMCV cited only one study in consideration of brevity, the study cited was used as the key study only after considering and reviewing the results of other potential key studies as discussed in the 2008 DSD for formaldehyde (TCEQ 2008), which is more explicit about the consideration of other studies. In regard to the key study specifically, while studies commonly have some limitations, the TCEQ and other agencies such as the Agency for Toxic Substances and Disease Registry (ATSDR) and the California Environmental Protection Agency (CalEPA) have deemed studies of this worker cohort (e.g., Wilhelmsson and Holmstrom 1992, Holmstrom 1989) as of acceptable quality for derivation of health-protective inhalation values based on the irritant effects of formaldehyde. The TCEQ certainly recognizes (as do other agencies) that Wilhelmsson and Holmstrom (1992) is not unique and that other studies also supply information on these endpoints, which is why the 2008 DSD for formaldehyde discusses results from other such studies as well. The comments cite approximately 0.1 ppm as an acceptable exposure concentration based on the chamber study literature, which is consistent with the no-observed-adverse-effect-level (NOAEL) of 0.07 ppm (0.09 mg/m^3) from Wilhelmsson and Holmstrom (1992). This NOAEL was used to derive the proposed 24-hour AMCV of 24 ppb, but was not used to derive the final 24-hour AMCV value of 41 ppb.

The comments suggest use of Lang et al. (2008) for derivation of the 24-hour AMCV. This 4-hour study was used as a supporting study for the 1-hour AMCV and is discussed in acute assessment portion of the 2008 formaldehyde DSD (TCEQ 2008). While Lang et al. (2008) does not provide the lowest point-of-departure (POD) identified for the critical effects due to short-term exposure to formaldehyde, it is now included as a supporting study in the final formaldehyde DSD for the 24-hour AMCV, which discusses multiple studies and derives a final 24-hour AMCV of 41 ppb (as opposed to the proposed value of 24 ppb). This value is equal to the 1-hour AMCV as the irritant effects of formaldehyde are primarily concentration dependent, and is health protective for the general public. It is similar to (although somewhat lower than) the cited World Health Organization (WHO) indoor air threshold guideline value of 81 ppb (0.1 mg/m^3), which WHO considers a threshold value not to be exceeded during any 30-minute period (see page 141 of WHO 2010). The TCEQ does not set health-based values at thresholds.

Comment No. 3:

<u>The Study Chosen by CEQ for the AMCV is Inadequate for the Prescribed Purpose</u>

Wilhelmsson and Holmstrom (1992) have been reviewed by several authoritative bodies and in several cases the use of the findings for public health considerations has been rejected. For example, the National Academy of Sciences committee in its review of EPA's 2010 draft IRIS file of formaldehyde concluded that Holmstrom and Wilhelmsson (1988) and Holmstrom et al.

(1989) which to our understanding represents the same cohort have “numerous weaknesses, the most important of which is a failure to identify a clear relationship between adverse responses and exposure concentration or exposure duration.” Moreover, the World Health Organization (WHO) Guidelines for Indoor Air Quality (2010) chapter on formaldehyde concluded that Holmstrom et al. (1989) “cannot be used for risk assessment owing to the lack of an exposure-dependent effect.” Finally, the joint DECOS/Nordic group considered Holmstrom and Wilhelmsson a, “not well-documented study” and the recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for Formaldehyde (2008) stated that the publication “neither gives methodological details of the questionnaire used, nor was the way of exposure assessment specified.”

In addition to these concerns, the NAS report also raised questions regarding potential confounding to other chemicals/substances. The NAS report suggested co-exposures including resins and dusts. Certainly the reported finding of deeper airway discomfort does not seem to be attributable to formaldehyde. Also, another paper by Holmstrom et al., (1995) appears to have a similar exposure scenario and reported where exposures to organic solvents and dusts resulted in nasal, pharyngeal, and ocular symptoms of discomfort common among all exposed groups.

TCEQ Response:

The Wilhelmsson and Holmstrom (1992) study is no longer used as the key study. However, the TCEQ notes that despite the alleged limitations, the study NOAEL of 0.07 ppm is remarkably similar to the approximately 0.1 ppm cited in comments above as an acceptable exposure concentration based on the chamber study literature. Please see the previous response.

Comment No. 4:

<u>Determination of the AMCV Should Rely on Controlled Human Studies</u>

Authoritative bodies worldwide have relied on the use of chamber studies precisely because they allow an accurate measure of formaldehyde concentrations associated with ocular and upper airway sensory irritation. Both WHO and SCOEL have utilized chamber studies in deriving appropriate values to protect against sensory irritation. In addition, the NAS has stated that chamber studies, “provide controlled measures of exposure and response.” Therefore, we feel TCEQ should use chamber studies to determine the AMCV.

The Environmental Protection Agency (EPA) also has evaluated these types of studies and has reached similar conclusions. In a critical analysis of controlled human volunteer exposure studies to derive human health effects criteria for sensory irritation EPA noted that, “an important advantage of this approach is that all relevant data can be used in the derivation as opposed to a NOAEL for the critical effect. The benefit of doing so allows health risks to be

estimated across various exposure levels (EPA, 2005)." This modeling process which was endorsed by the EPA's Science Advisory Board showed a clear threshold at 0.5 ppm for any symptoms of sensory irritation for formaldehyde and an effective concentration at 1.5 ppm for moderate effects.

TCEQ Response:

The final formaldehyde DSD for the 24-hour AMCV now utilizes as a key study the same chamber study that ATSDR used to derive their acute inhalation MRL (Pazdrak et al. 1993), as well as another key study and supporting studies (including Lang et al. 2008). The TCEQ does not set health-based AMCVs at thresholds. However, it is noted that the supposed threshold of 0.5 ppm cited above for formaldehyde-induced sensory irritation is: (1) considerably higher than the acceptable concentration of 0.1 ppm based on the chamber study literature cited in comments previously (farther above); (2) not a clear threshold as it is above the lowest-observed-adverse-effect-levels (LOAELs) for irritant effects in short-term exposure chamber studies such as Pazdrak et al. (1993) and Krakowiak et al. (1998), both of which had LOAELs of 0.4 ppm (also see Table 2-1 of ATSDR 1999); and (3) above even the occupational short-term exposure limits (STELs) recommended by ACGIH (STEL of 0.3 ppm) and NIOSH (STEL of 0.1 ppm). While such potential thresholds may be more appropriately considered for setting occupational worker guideline values, again, the TCEQ does not set health-based values at thresholds for the protection of the general public.

Comment No. 5:

With regard to adjustment factors or uncertainty terms we generally agree with the decisions made by TCEQ. We recognize that the volunteer studies are not 24 hour exposures and that for many chemicals a risk-based adjustment to convert to a 24 hour exposure would be appropriate. However, we concur with TCEQ's treatment of the data based on the knowledge that formaldehyde-induced sensory irritation is strongly dependent on concentration and not the traditional function of concentration multiplied by time. We also note that not performing this duration adjustment is consistent with other agencies. As to intraspecies variability, however, it is our opinion that while the scientific literature reports on a broad range of reported human susceptibility to the irritating properties of airborne formaldehyde, the threshold of effect appears consistent across the human volunteer studies and a database uncertainty factor does not appear to be warranted. Finally, TCEQ supports this uncertainty term based, in part, on occupational cohorts where the healthy worker affect may underestimate an effect in the sometimes include asthmatic individuals (a sensitive subpopulation) showing no distinct difference from non-asthmatics, an intraspecies uncertainty factor does not appear to be supported by the underlying facts.

TCEQ Response:

The TCEQ acknowledges the comments agreement with not performing a duration adjustment (i.e., formaldehyde-induced irritation is strongly dependent on concentration and not the traditional function of concentration multiplied by time) and with TCEQ using a database uncertainty factor of 1. However, the TCEQ disagrees with the comment that an intraspecies (i.e., intrahuman) uncertainty factor is not needed. Asthmatics are not the only potentially sensitive subpopulation (e.g., children, contact lens wearers). For example, ocular irritation was significantly ($p < 0.001$) higher among wearers of contact lenses compared with students without contacts in Tanaka et al. 2003 (as cited by CalEPA 2008). Additionally, the comments acknowledge, "the scientific literature reports on a broad range of reported human susceptibility to the irritating properties of airborne formaldehyde." Thus, although the key studies (Pazdrak et al. 1993, Krakowiak et al. 1998) in the final formaldehyde DSD for the 24-hour AMCV included potentially sensitive subpopulations (e.g., potentially sensitized individuals), some uncertainty about intraspecies differences in sensitivity remains and use of an intrahuman uncertainty factor greater than 1 (e.g., 3) is justified.

Comment No. 6:

<u>Lang et al. (2008) Would Provide Useful Information to Develop the AMCV</u>

As noted earlier, there are several published studies describing health effects of formaldehyde using controlled conditions with humans. Some precedent has been established by WHO and SCOEL in the use of Lang et al. (2008) to derive a threshold value for sensory irritation which should be considered the critical endpoint for the evaluation of the AMCV. Based on this study, it is notable that symptoms of sensory irritation are unlikely to occur at levels below around 0.1 ppm. Many authoritative organizations have reached this same conclusion. Consequently, we recommend the WHO derived protective threshold concentration of 0.125 ppm as the AMCV.

TCEQ Response:

As the basis for the 24-hour AMCV, the comments suggest use of the Lang et al. (2008) study and/or the WHO indoor air threshold guideline value, which is actually 81 ppb (0.1 mg/m^3) (see page 141 of WHO 2010). As indicated previously, while Lang et al. (2008) does not provide the lowest POD identified for critical (i.e., the most sensitive) effects due to short-term exposure to formaldehyde, it is now included as a supporting study in the final formaldehyde DSD for the 24-hour AMCV. Concerning the WHO indoor air threshold guideline value of 81 ppb (0.1 mg/m^3), WHO considers this value a threshold value not to be exceeded during any 30-minute period (see page 141 of WHO 2010). The TCEQ does not set health-based values at thresholds. The final DSD derives a final 24-hour AMCV of 41 ppb (as opposed to the proposed value of 24 ppb), which is equal to the 1-hour AMCV as the irritant effects of formaldehyde are primarily concentration dependent. This 24-hour AMCV is health protective for the general public and is

similar to (although somewhat lower than) the WHO indoor air threshold guideline value of 81 ppb (0.1 mg/m^3).

American Chemistry Council Comments Regarding the DSD for the Proposed 24-Hour Formaldehyde AMCV

Comment 1:

The American Chemistry Council's Formaldehyde Panel (the Panel) is pleased to submit the following comments on the Texas Commission on Environmental Quality's (TCEQ) proposed 24-Hour Ambient Air Monitoring Comparison Value (AMCV) for formaldehyde. The Panel represents US producers, suppliers and users of formaldehyde and formaldehyde products. The TCEQ proposes a 24-hour acute Reference Value (ReV) of 30 ug/m^3 (24 ppb) and identifies the critical effects as "elevated rates of symptoms such as eye, nasal, and lower airway discomfort in workers." The TCEQ has chosen Wilhelmsson and Holmstrom (1992) as the key study for development of the AMCV for formaldehyde. As discussed in the comments below, however, the Wilhelmsson and Holmstrom (1992) study does not represent the most up-to-date scientific information to characterize the association between formaldehyde exposure and irritation and includes critical confounding factors. Therefore, it should not be relied upon to derive the AMCV for formaldehyde.

Controlled formaldehyde chamber studies provide a more reliable basis from which to derive the AMCV, and there are in fact over 20 published studies and critical reviews of controlled studies of formaldehyde that provide consistent findings (many of which were reviewed in the World Health Organization (WHO) 2010 Guidelines for Indoor Air Quality - Formaldehyde). (Golden et al., 2011) In addition, many authoritative bodies have chosen to rely on these chamber studies to identify thresholds for sensory irritation. For example, the WHO used Lang et al. (2008) to derive a threshold for workers at 0.1 mg/m^3 and for indoor environments at 0.125 mg/m^3. The Lang et al. (2008) study is a well conducted study of 21 volunteers, and was selected by WHO to be one of the key studies in this derivation because the corrected lowest observed effect level (LOEL; 0.63 mg/m^3) from Lang et al. (2008) was in agreement with no observed adverse effect levels (NOAELs) from studies in both humans and animals, including Kulle et al. (1987) and Nielson et al. (1999).

Accordingly, the TCEQ also should consider the Lang et al. (2008) study to derive the AMCV. Moreover, based on the weight of the available scientific evidence, symptoms of sensory irritation are unlikely to occur and would be insignificant at levels below 0.1 ppm (Golden et al., 2011; Mueller et al., 2013). Therefore, the WHO guidelines, based on the higher quality chamber studies, appear to be accurate.

TCEQ Response:

While studies commonly have some limitations, the TCEQ and other agencies such as the ATSDR and CalEPA have deemed studies of the worker cohort in Wilhelmsson and Holmstrom (1992) and Holmstrom (1989) as of acceptable quality for derivation of health-protective inhalation values based on the irritant effects of formaldehyde. While the Wilhelmsson and Holmstrom (1992) study is no longer used as the key study for derivation of the 24-hour AMCV, the TCEQ notes that the study NOAEL of 0.07 ppm is remarkably similar to the approximately 0.1 ppm cited in AF&PA and AWC comments above as an acceptable exposure concentration based on the chamber study literature, as well as the 0.1 ppm cited above as a concentration where symptoms of sensory irritation are unlikely. The final formaldehyde DSD for the 24-hour AMCV now utilizes the same chamber study that ATSDR used to derive their acute inhalation MRL (Pazdrak et al. 1993).

As the basis for the 24-hour AMCV, the comments suggest use of the Lang et al. (2008) study and/or the WHO indoor air threshold guideline value, which is actually 81 ppb (0.1 mg/m^3) (see page 141 of WHO 2010). As indicated previously, while Lang et al. (2008) does not provide the lowest POD identified for critical (i.e., the most sensitive) effects due to short-term exposure to formaldehyde, it is now included as a supporting study in the final formaldehyde DSD for the 24-hour AMCV. Concerning the WHO indoor air threshold guideline value of 81 ppb (0.1 mg/m^3), WHO considers this value a threshold value not to be exceeded during any 30-minute period (see page 141 of WHO 2010). The TCEQ does not set health-based values at thresholds. The final DSD derives a final 24-hour AMCV of 41 ppb (as opposed to the proposed value of 24 ppb), which is equal to the 1-hour AMCV as the irritant effects of formaldehyde are primarily concentration dependent. This 24-hour AMCV is health protective for the general public and is similar to (although somewhat lower than) the WHO indoor air threshold guideline value of 81 ppb (0.1 mg/m^3).

Comment 2:

<u>The Key Study Chosen for Setting the AMCV Should Not Be Used for Risk Assessment Due to Possible Confounders and Lack of An Exposure-Dependent Effect</u>

In the support document for the proposed AMCV, the TCEQ identifies Wilhelmsson and Holmstrom (1992) as the key study chosen for development of the AMCV. This study evaluates reported symptoms of sensory irritation in a cohort of 66 formaldehyde plant workers, and is the same cohort that has been analyzed in the widely cited Holmstrom and Wilhelmsson (1988) and Holmstrom et al. (1989) papers. These studies have drawn significant criticism by a number of authoritative bodies. Most recently, the 1989 and 1988 studies were reviewed by a National Academy of Sciences (NAS) committee in its review of the Environmental Protection Agency's (EPA's) 2010 draft Integrated Risk Information System (IRIS) assessment of formaldehyde (2011) (NAS Report). The NAS Report concluded that the Holmstrom and Wilhelmsson (1988) and

Holmstrom et al. (1989) studies taken together have "numerous weaknesses, the most important of which is a failure to identify a clear relationship between adverse responses and exposure concentration or exposure duration." (pg. 77)

In addition, the NAS Report raised concerns regarding potential confounding due to co-exposures to other respiratory irritants in the workplace. (pg. 76) A careful examination of the Holmstrom and Wilhelmsson (1988) study reveals that despite the claim by the authors that it looked at two groups -one "exposed almost exclusively to formaldehyde as the only nasal irritant" and the other exposed to both wood dust and formaldehyde, workers in both groups were exposed to dusts. The "formaldehyde-only" group consisted of 70 workers "...where formaldehyde and products based on formaldehyde were produced (resins and impregnation of paper for laminate production)... For the group of workers impregnating paper (N=31) dust concentrations of up to 1 mg/m^3 have been measured close to the machines." Therefore, since 44% of the formaldehyde-only workers in this study were exposed to both formaldehyde and paper dust, there is no basis for attributing effects to formaldehyde alone.

Paper dust is a nasal irritant and has also been associated with eliciting symptoms in asthmatic workers (Jaakkola and Jaakkola, 2007; Shusterman, 2007). Based on this association, the significant findings of nasal discomfort, eye discomfort, and deeper airway discomfort in the formaldehyde group should not be attributed to formaldehyde alone. In fact, the 44% frequency of deeper airway discomfort in this group suggests that something other than formaldehyde (or in addition to formaldehyde) was causing this effect since formaldehyde is efficiently scrubbed from the upper airways and does not penetrate into the lower airways and bronchi. (See Golden, 2011, citing Schlosser et al., 2003; Kimbell et al., 1993, 2001; Overton et al., 2001; Garcia et al., 2009). Since, as the NAS Report notes, "the co-exposure could be a confounding factor in the study" (p. 76), this study should not be relied upon to quantify the association specifically between formaldehyde exposure and upper respiratory tract pathology.

In addition, the WHO Guidelines for Indoor Air Quality (2010) chapter on formaldehyde (WHO Guidelines) concluded that Holmstrom et al. (1989) "cannot be used for risk assessment owing to the lack of an exposure-dependent effect." (pg. 116) Similar critiques of this cohort study can be found elsewhere in the scientific literature. (See e.g., Wolkoff and Nielsen, 2010; Golden, 2011).

Given that the Wilhelmsson and Holmstrom (1992) study is essentially the same cohort and has not addressed the concerns identified above, it should be judged of a lesser quality than more recent studies and should not be relied upon to derive the AMCV.

TCEQ Response:

Concerning Wilhelmsson and Holmstrom (1992) as a key study, while studies commonly have some limitations (e.g., potential workplace and personal co-exposures), the TCEQ and other agencies such as the ATSDR and CalEPA have deemed studies of this worker cohort (e.g., Wilhelmsson and Holmstrom 1992, Holmstrom 1989) as of acceptable quality for derivation of

health-protective inhalation values based on the irritant effects of formaldehyde. Regardless, the Wilhelmsson and Holmstrom (1992) study is no longer used as the key study for derivation of the 24-hour AMCV. However, the TCEQ notes that the study NOAEL of 0.07 ppm is remarkably similar to the approximately 0.1 ppm cited in AF&PA and AWC comments above as an acceptable exposure concentration based on the chamber study literature, as well as the 0.1 ppm cited above as a concentration where symptoms of sensory irritation are unlikely. The final formaldehyde DSD for the 24-hour AMCV now utilizes the same chamber study that ATSDR used to derive their acute inhalation MRL (Pazdrak et al. 1993), as well as another key study and supporting studies (including Lang et al. 2008).

Comment 3:

<u>The TCEQ Should Rely on Controlled Human Studies to Determine the AMCV</u>

There are numerous controlled chamber studies using human volunteers that can provide a more appropriate data set for deriving a valid AMCV for sensory irritation. Controlled chamber studies allow for clean air controls that ensure known dose concentrations and preclude confounding by other chemical exposure. This of course allows for a more accurate assessment of a potential threshold specifically attributable to formaldehyde.

The use of controlled formaldehyde chamber studies in developing risk values for sensory irritation has been validated by a number of authoritative bodies. In reviewing the 2010 draft IRIS assessment of formaldehyde, NAS agreed with EPA that eye irritation is the critical outcome upon which to base risk values, but questioned the Agency's rejection of the chamber studies, stating: "The draft IRIS assessment sets aside the chamber studies as less relevant to derivation of candidate RfCs, but the findings from the studies could be useful, and the committee does not concur with EPA's decision to set them aside...." The NAS goes on to state that the utility of chamber studies is that they "provide controlled measures of exposure and response." (NAS Report, at 65, 68)

Indeed, EPA itself has evaluated these types of studies and has reached similar conclusions. In 2005, EPA conducted a critical analysis of six human volunteer controlled exposure studies to derive human health effects criteria for formaldehyde-induced sensory irritation. From these data, mathematical models were used to assess responses. EPA noted that:

> An important advantage of this approach is that all relevant data can be used in the derivation as opposed to a NOAEL for the critical effect. The benefit of doing so allows health risks to be estimated across various exposure levels (USEPA/NCEA 2005).

This approach was supported by the EPA Science Advisory Board reviewing EPA's 2005 report, which observed that the process EPA used in this report:

> makes use of every bit of data available.... The underlying premise of the approach is that the severity of the effect, not the specific measurement or outcome incidence, is the information needed for assessing exposure-response relationships for non-cancer endpoints... (USEPA/NCEA 2005).

EPA's detailed modeling process showed a clear threshold at 0.5 ppm for any symptoms of sensory irritation for formaldehyde and an effective concentration at 1.5 ppm for moderate effects.

Numerous other regulatory and authoritative bodies worldwide have relied upon the large body of data from chamber studies precisely because it permits a more accurate assessment of formaldehyde concentrations associated with sensory irritation than workplace or residential studies. (See e.g., OECD Development Screening Information Data Set, 2002; EU Scientific Committee on Occupational Exposure Limits, 2008; WHO Guidelines, 2010).

The TCEQ 2012 guidance document, TCEQ Guidelines to Develop Toxicity Factors (RG-442), describes using controlled human chamber studies which meet the WHO International Programme on Chemical Safety (IPCS) criteria in Section 3.3.3.3.1.1 for derivation of screening values. The Lang et al. (2008) study clearly meets these criteria. Furthermore, appropriate controlled human chamber studies previously have been used by TCEQ as the "key study" in several Effects Screening Level (ESL) and AMCV derivations, including, acetone, n-butyraldehyde, and methanol.

Therefore, the TCEQ should utilize chamber studies for purposes of developing the AMCV for formaldehyde as well, because these well designed and well described exposures provide greater scientific clarity.

TCEQ Response:

The final formaldehyde DSD for the 24-hour AMCV now utilizes as the key study the same chamber study that ATSDR used to derive their acute inhalation MRL (Pazdrak et al. 1993), as well as another key study and supporting studies. As previously indicated, while Lang et al. (2008) does not provide the lowest POD identified for critical (i.e., the most sensitive) effects due to short-term exposure to formaldehyde, it is now included as a supporting study in the final formaldehyde DSD for the 24-hour AMCV. The TCEQ does not set health-based AMCVs at thresholds. However, it is noted that the supposed threshold of 0.5 ppm cited above for formaldehyde-induced sensory irritation is: (1) considerably higher than the acceptable concentration of 0.1 ppm based on the chamber study literature cited in AF&PA and AWC comments above; (2) not a clear threshold as it is above the LOAELs for irritant effects in short-term exposure chamber studies such as Pazdrak et al. (1993) and Krakowiak et al. (1998), both of which had LOAELs of 0.4 ppm (also see Table 2-1 of ATSDR 1999); and (3) above even the occupational short-term STELs recommended by ACGIH (STEL of 0.3 ppm) and NIOSH (STEL of 0.1 ppm). While such potential thresholds may be more appropriately considered for setting

occupational worker guideline values, the TCEQ does not set health-based values at thresholds for the protection of the general public.

Comment 4:

We recognize that controlled studies are often criticized for focusing on acute effects, and therefore they do not capture potential effects from longer term exposures. The Proposed TCEQ Guidelines to Develop 24-Hour Inhalation Reference Values suggests that exposure duration adjustments should be made for studies that are less than 24 hours. It is important to note; however, that formaldehyde does not follow traditional "concentration x time" principles consistent with Haber's law. Therefore, it is the concentration, not the time or duration, of the exposure that is relevant to the observed health outcomes. Scientists, including some within EPA, report that, for formaldehyde-induced sensory irritation, there is essentially no meaningful difference between short-term and longer-term exposure (EPA, 2004; NAS, 2007; Shusterman et al., 2006). In fact, NAS (2007) concluded:

> Formaldehyde irritation does not appear to follow Haber's law (concentration [c] x exposure time [t] = response [k]) for extrapolating between short-term and long-term toxicity levels. Generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure.... The degree of sensory and irritant effects at lower exposure levels depends on concentration rather than duration (NAS, 2007, at 105-06,118).

This conclusion is based on test results derived from human chamber studies which show that once symptoms are produced at a certain concentration they are not enhanced with additional exposure time. As such, the estimated point of departure (PODHEC) that would be relied upon for the derivation of the 24-hour formaldehyde AMCV would need no duration adjustment if the Lang et al. (2008) study is used as the basis.

TCEQ Response:

The TCEQ acknowledges the comments agreement with not performing a duration adjustment since formaldehyde-induced irritation is strongly dependent on concentration and not the traditional function of concentration multiplied by time consistent with Haber's law.

Comment 5:

<u>The TCEQ Should Use Lang et al. (2008) to Support the Derivation of the AMCV</u>

As noted above, there are over 20 published studies and critical reviews of controlled studies of formaldehyde. The TCEQ should consider Lang et al. (2008) as the key study to derive the

AMCV. Firstly, the Lang et al. (2008) study presents new data, possibly rendering the previous 2009 derivations obsolete and warranting re-evaluation; secondly, there is precedent for the use of this study to derive a risk value for sensory irritation. The WHO did so in developing the final threshold value for objective sensory irritation.

Essentially, the TCEQ is using the same justification and study for development of the 24-hour AMCV as it did for the formaldehyde acute and chronic ESLs and AMCVs. These values were derived in 2008, which was prior to the publication of Lang et al. (2008). In August, 2008, the TCEQ responded to public comments on the proposed formaldehyde acute and chronic ESLs and AMCVs (Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the Proposed Development Support Document for Formaldehyde, August 7, 2008). In that response, the TCEQ included the Lang et al. (2008) study in the acute section of the formaldehyde assessment. In both the August 2008 response to comments and the 2012 TCEQ Guidelines for Development of Toxicity Factors, the TCEQ states that it will update ESLs and AMCVs when new scientific evidence supports a re-review. The Lang et al. (2008) study and its supportive peer-reviewed studies (e.g., Triebig et al., 2012; Mueller et al., 2013) create a substantial body of new evidence. The 2008 assessment which provides the basis for the proposed 24-hour AMCV is scientifically out of date and should be re-evaluated.

In Lang et al. (2008), the authors examined 21 volunteers over a 10 week period and each participant was exposed to 10 exposure conditions on 10 consecutive working days, each for 4 hours. During 4 of the 10 sessions, ethyl acetate (12-16 ppm) was used as a masking agent for formaldehyde exposure. Measurements were related to conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function and reaction times. Subjective assessments included discomfort, and the influence of personality factors on subjective scoring was also evaluated.

Blinking frequency and conjunctival redness, ranging from slight to moderate, were significantly increased by short-term peak exposures of 1.0 ppm that occurred at a baseline exposure of 0.5 ppm formaldehyde. Nasal irritation was reported at concentrations of 0.5 ppm plus peaks of 1.0 ppm, as well as at levels of 0.3 ppm and 0.5 ppm with co-exposure to ethyl acetate. In this case, the ethyl acetate exposure was also perceived as irritating. No significant treatment effects were noted regarding nasal flow and resistance, pulmonary function and reaction times. When negative affectivity was introduced as a covariate, the level of 0.3 ppm was no longer an effect level, but 0.5 ppm with peaks of 1.0 ppm was. The authors concluded that eye irritation was the most sensitive parameter recorded, and that the NOAEL for objective eye irritation was 0.5 ppm.

TCEQ Response:

The final formaldehyde DSD for the final 24-hour AMCV now utilizes as the key study the same chamber study that ATSDR used to derive their acute inhalation MRL (Pazdrak et al. 1993), as well as another key study and supporting studies. As previously indicated, while Lang et al. (2008) does not provide the lowest POD identified for critical (i.e., the most sensitive) effects

due to short-term exposure to formaldehyde, it is now included as a supporting study in the final formaldehyde DSD for the 24-hour AMCV. Lang et al. (2008) was also included as a supporting study for the 1-hour AMCV in the acute assessment portion of the formaldehyde DSD (TCEQ 2008), but was not selected as the key study. In regard to whether the new scientific articles cited necessitate the reopening the 2008 assessment, the new studies cited do not justify reopening the 2008 formaldehyde DSD (TCEQ 2008). As a TCEQ response to comments on the 2008 formaldehyde DSD indicated, "The DSD will be updated if TS determines that new scientific information would significantly affect the critical acute or chronic ReVs/ESLs." This would be particularly true if after critical evaluation of all relevant information, new scientifically conclusive data clearly demonstrated a need to significantly reduce an AMCV/ESL (e.g., > 10-fold) in order to protect public health. After careful review, the TCEQ has determined that evaluation of the information contained in the new articles cited and not considered in TCEQ (2008) (e.g., Mueller et al. 2013, Golden 2011) would not significantly affect the critical acute or chronic ReVs/ESLs (e.g., different acute PODs/AMCVs are unlikely to be proposed and final acute AMCVs are unlikely to be significantly different than current AMCVs).

Comment 6:

The WHO relied upon the Lang et al. (2008) study to set a NOAEL of 0.63 mg/m^3 (0.5 ppm) for the determination of the Indoor Air Quality Guideline, to which was applied what we believe was an overly conservative uncertainty factor of 5, to take into account nasal pungency thresholds. (pgs. 115-116) This resulted in a derived value of 0.125 mg/m^3 (0.1 ppm), which the Guidelines provided "was considered safe for the entire population against sensory irritation, including chronic sensory irritation." (pg. 116) In spite of our concern regarding the uncertainty factor applied by the WHO, we believe that the WHO threshold value for sensory irritations is based on the best available science, and the TCEQ should consider the approach reflected in the WHO Guidelines in developing the AMCV for formaldehyde.

TCEQ Response:

As the basis for the 24-hour AMCV, the comments suggest use of the Lang et al. (2008) study and/or the WHO indoor air threshold guideline value, which is actually 81 ppb (0.1 mg/m^3) (see page 141 of WHO 2010). To reiterate, Lang et al. (2008) does not provide the lowest POD identified for critical (i.e., the most sensitive) effects due to short-term exposure to formaldehyde, although it is now included as a supporting study in the final formaldehyde DSD for the 24-hour AMCV. In regard to the indoor air threshold guideline value of 81 ppb (0.1 mg/m^3), WHO considers this value a threshold value not to be exceeded during any 30-minute period (see page 141 of WHO 2010). The TCEQ does not set health-based values at thresholds. The final DSD derives a final 24-hour AMCV of 41 ppb (as opposed to the proposed value of 24 ppb), which is equal to the 1-hour AMCV as the irritant effects of formaldehyde are primarily concentration dependent. This 24-hour AMCV will protect the general public against potential

symptoms of sensory irritation and is similar to (although somewhat lower than) the cited WHO indoor air threshold guideline value of 81 ppb (0.1 mg/m^3).

Comment 7:

Symptoms of sensory irritation are unlikely to occur and would be insignificant at levels below 0.1 ppm

As we noted above, the WHO concluded that an objective threshold for sensory irritation is about 1 mg/m^3 (0.81 ppm) for workers and that a value of 0.125 mg/m^3 (0.1 ppm) is considered safe for the entire population, including chronic sensory irritation and children, exposed in an indoor environment 24 hours per day (WHO, 2010, pgs. 115-16).

TCEQ Response:

WHO considers the indoor air threshold guideline value of 81 ppb (0.1 mg/m^3) as a threshold value not to be exceeded during any 30-minute period (see page 141 of WHO 2010). The TCEQ does not set health-based values at thresholds. The final formaldehyde DSD for the 24-hour AMCV does use Lang et al. (2008) study as a supporting study and derives a 24-hour AMCV of 41 ppb, which is similar to (although somewhat lower than) the WHO indoor air threshold guideline value.

Comment 8:

Other evidence-based reviews conclude that 0.3 ppm is a reasonable and appropriate level below which symptoms of sensory irritation are unlikely to occur:

- "[S]ymptoms of eye and mucous membrane irritation at that concentration were not increased above control conditions in controlled chamber studies" (NAS, 2007).
- "Studies in the literature have reported a variety of responses induced by exposure to gaseous formaldehyde, generally beginning in the range of 0.3 to 0.5 ppm for eye irritation, the most sensitive endpoint. However, the severity of response at these levels is generally mild, and only a small portion of the population may respond" (The Organisation for Economic Cooperation and Development (OECDJ/SIDS, 2002).
-

Many other authoritative bodies have reached these same conclusions. (Agency for Toxic Substances and Disease Registry (ATSDR), 1999, 2007; WHO, 2002; American Conference of Industrial Hygienists (ACGIH), 2001; MAK, 2006; National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 2006).

TCEQ Response:

This comment cites 0.3 ppm formaldehyde as a threshold concentration since eye irritation occurs "generally beginning in the range of 0.3 to 0.5 ppm." While such potential thresholds may be more appropriately considered for setting occupational worker guideline values, the TCEQ does not set health-based values at thresholds for the protection of the general public and notes that this concentration corresponds to the occupational STEL recommended by ACGIH (STEL of 0.3 ppm) and exceeds that recommended for workers by NIOSH (STEL of 0.1 ppm).

Comment 9:

In a recent human exposure study, Mueller et al. (2013) examined chemosensory effects of formaldehyde in 41 hypo- and hypersensitive male volunteers. Individuals were exposed on five days, for four hours, at four different concentrations (0.3 ppm, 0.3 ppm + 4 x 0.6 ppm peaks, 0.4 ppm + 4 x 0.8 ppm peaks, 0.5 ppm, and 0.7 ppm). The results indicate no chemosensory effects on hypo- and hyper-sensitive males at formaldehyde exposures to 0.7 ppm for 4 hours and to 0.4 ppm for 4 hours with peaks of 0.8 ppm for 15 minutes. The measured endpoints included conjunctival redness, eye-blinking frequency (EBF), tear film break-up time (sBUT), nasal flow, and several subjective symptoms. This study supports the conclusions of the Lang et al. (2008) study and indicates sensory irritation is unlikely to occur below 0.1 ppm, even for hypersensitive individuals.

The WHO Guidelines and conclusions of other authoritative bodies make clear that sensory irritation is unlikely to occur below 0.1 ppm. The most recent controlled studies in humans support this conclusion. Therefore, we strongly believe that the TCEQ should consider 0.1 ppm as the lowest, most conservative value from which to derive its AMCV.

TCEQ Response:

Please see previous comments regarding the use of Lang et al. (2008) as a supporting study and the WHO indoor air threshold guideline value (a 30-minute not to be exceeded value) of 81 ppb (0.1 mg/m^3). In regard to Mueller et al. (2013), seemingly spurious statistically significant differences such as those for all three "objective" measures of eye irritation in volunteers identified as sensitive under the control condition of 0 ppm (e.g., statistically significant increases in the percent of hyper-sensitives with decreased conjunctival redness and decreased eye blinking frequency at 0 ppm) as well as other paradoxical results such as tear film breakup time actually being prolonged in both groups (hypo-/hyper-sensitive) after all exposures to formaldehyde, achieving statistical significance in most cases, gives rise to TCEQ concerns about use of this study. Regarding the suggestion to use of 0.1 ppm as the lowest, most conservative value from which to begin to derive the 24-hour AMCV, the TCEQ notes that this comment discusses 0.1 ppm like a NOAEL to be used as the POD (e.g., a "value from which to derive its

AMCV") and that the final 24-hour DSD uses a NOAEL estimated from the key studies that is actually slightly higher (i.e., LOAEL of 0.4 ppm / UFL of 3 = estimated NOAEL of 0.133 ppm). Despite using different key studies than suggested, the final 24-hour AMCV of 41 ppb is similar to, although somewhat lower than, the WHO indoor air guideline threshold value of 81 ppb. The 24-hour AMCV will protect the general public, including sensitive subpopulations, against potential formaldehyde-induced sensory irritation.

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APPENDIX 1

American Forest & Paper Association/American Wood Council Comments

May 6, 2014

Texas Commission on Environmental Quality
Toxicology Division
MC-168
P.O. Box 13087
Austin, TX 78711-3087

RE: Formaldehyde 24-Hour Ambient Air Monitoring Comparison Value

To Whom It May Concern:

The American Forest & Paper Association (AF&PA) and the American Wood Council (AWC) appreciate the opportunity to comment on the Texas Commission on Environmental Quality's (TCEQ) proposed 24-Hour Ambient Air Monitoring Comparison Value (AMCV) for formaldehyde.

AF&PA is the national trade association of the forest products industry, representing pulp, paper, packaging and wood products manufacturers, and forest landowners. Our companies make products essential for everyday life from renewable and recyclable resources that sustain the environment. The forest products industry accounts for approximately 5 percent of the total U.S. manufacturing GDP. Industry companies produce about $175 billion in products annually and employ nearly 900,000 men and women, exceeding employment levels in the automotive, chemicals and plastics industries. The industry meets a payroll of approximately $50 billion annually and is among the top 10 manufacturing sector employers in 47 states.

AWC is the voice of North American traditional and engineered wood products, representing over 75% of the industry. From a renewable resource that absorbs and sequesters carbon, the wood products industry makes products that are essential to everyday life and employs about one-third of a million men and women in well-paying jobs. AWC's engineers, technologists, scientists, and building code experts develop state-of-the-art engineering data, technology, and standards on structural wood products for use by design professionals, building officials, and wood products manufacturers to assure the safe and efficient design and use of wood structural components. AWC also provides technical, legal, and economic information on wood

1101 K Street NW, Suite 700 • Washington, DC 20006 • 202 463-2700 Fax: 202 463-2785 • www.afandpa.org

222 Catoctin Circle SE, Suite 201 • Leesburg, VA 20175 • 202-463-2766 Fax: 202-463-2791 • www.awc.org •

design, green building, and manufacturing environmental regulations advocating for balanced government policies that sustain the wood products industry.

Recently, TCEQ proposed a 24-hour acute AMCV of 24 ppb using based presumably on only one study by Wilhelmsson and Holmstrom (1992) that reports elevated rates of symptoms such as eye, nasal, and lower airway discomfort in workers. Analysis of the acute effects of formaldehyde based solely on one paper is not scientifically robust and is unwise. Furthermore, the decision to make a determination based on one study gives the impression that: (1) this is a unique study in supplying information on these endpoints and, (2) the study is of acceptable quality. Unfortunately, neither of these statements are true. As discussed below, several evaluations have been conducted on the non-cancer health effects of formaldehyde. Indeed, controlled formaldehyde chamber studies provide less possible confounding than occupationally exposed cohorts and a more useful basis for deriving the AMCV. Of interest, there are over 20 published studies and critical reviews of these controlled studies of formaldehyde that provide consistent and convincing outcomes of acceptable exposure concentrations of approximately 0.1 ppm. Moreover, several authoritative bodies have already conducted a review of the formaldehyde literature and have identified the reliance of these studies.

Conversely, at least three reviews of the formaldehyde literature have come to the conclusion that Wilhelmsson and Holmstrom (1992) does not provide sufficient details to be relied upon for determining an acceptable concentration of formaldehyde. Consequently, we urge TCEQ to discard their flawed evaluation and commit to additional review. While we feel several studies are appropriate to provide a satisfactory body of data to support the AMCV, a recent study by Lang et al. (2008) has been chosen by other organizations for a similar exercise and thus we recommend its use. One example is from the World Health Organization that used Lang et al. to derive a protective threshold concentration for sensory irritation in indoor environments at 0.125 ppm.

The Study Chosen by CEQ for the AMCV is Inadequate for the Prescribed Purpose

Wilhelmsson and Holmstrom (1992) have been reviewed by several authoritative bodies and in several cases the use of the findings for public health considerations has been rejected. For example, the National Academy of Sciences committee in its review of EPA's 2010 draft IRIS file of formaldehyde concluded that Holmstrom and Wilhelmsson (1988) and Holmstrom et al. (1989) which to our understanding represents the same cohort have "numerous weaknesses, the most important of which is a failure to identify a clear relationship between adverse responses and exposure concentration or exposure duration." Moreover, the World Health Organization (WHO) Guidelines for Indoor Air Quality (2010) chapter on formaldehyde concluded that Holmstrom et al. (1989) "cannot be used for risk assessment owing to the lack of an exposure-dependent effect." Finally, the joint DECOS/Nordic group considered Holmstrom and Wilhelmsson a, "not well-documented study" and the recommendation from the Scientific Committee

on Occupational Exposure Limits (SCOEL) for Formaldehyde (2008) stated that the publication "neither gives methodological details of the questionnaire used, nor was the way of exposure assessment specified."

In addition to these concerns, the NAS report also raised questions regarding potential confounding to other chemicals/substances. The NAS report suggested co-exposures including resins and dusts. Certainly the reported finding of deeper airway discomfort does not seem to be attributable to formaldehyde. Also, another paper by Holmstrom et al., (1995) appears to have a similar exposure scenario and reported where exposures to organic solvents and dusts resulted in nasal, pharyngeal, and ocular symptoms of discomfort common among all exposed groups.

Determination of the AMCV Should Rely on Controlled Human Studies

Authoritative bodies worldwide have relied on the use of chamber studies precisely because they allow an accurate measure of formaldehyde concentrations associated with ocular and upper airway sensory irritation. Both WHO and SCOEL have utilized chamber studies in deriving appropriate values to protect against sensory irritation. In addition, the NAS has stated that chamber studies, "provide controlled measures of exposure and response." Therefore, we feel TCEQ should use chamber studies to determine the AMCV.

The Environmental Protection Agency (EPA) also has evaluated these types of studies and has reached similar conclusions. In a critical analysis of controlled human volunteer exposure studies to derive human health effects criteria for sensory irritation EPA noted that, "an important advantage of this approach is that all relevant data can be used in the derivation as opposed to a NOAEL for the critical effect. The benefit of doing so allows health risks to be estimated across various exposure levels (EPA, 2005)." This modeling process which was endorsed by the EPA's Science Advisory Board showed a clear threshold at 0.5 ppm for any symptoms of sensory irritation for formaldehyde and an effective concentration at 1.5 ppm for moderate effects.

With regard to adjustment factors or uncertainty terms we generally agree with the decisions made by TCEQ. We recognize that the volunteer studies are not 24 hour exposures and that for many chemicals a risk-based adjustment to convert to a 24 hour exposure would be appropriate. However, we concur with TCEQ's treatment of the data based on the knowledge that formaldehyde-induced sensory irritation is strongly dependent on concentration and not the traditional function of concentration multiplied by time. We also note that not performing this duration adjustment is consistent with other agencies. As to intraspecies variability, however, it is our opinion that while the scientific literature reports on a broad range of reported human susceptibility to the irritating properties of airborne formaldehyde, the threshold of effect appears consistent across the human volunteer studies and a database uncertainty factor does not appear to be warranted. Finally, TCEQ supports this uncertainty term based, in part, on occupational cohorts where the healthy worker affect may underestimate an effect in the

general population. As these human volunteer studies do not include workers and sometimes include asthmatic individuals (a sensitive subpopulation) showing no distinct difference from non-asthmatics, an intraspecies uncertainty factor does not appear to be supported by the underlying facts.

Lang et al. (2008) Would Provide Useful Information to Develop the AMCV

As noted earlier, there are several published studies describing health effects of formaldehyde using controlled conditions with humans. Some precedent has been established by WHO and SCOEL in the use of Lang et al. (2008) to derive a threshold value for sensory irritation which should be considered the critical endpoint for the evaluation of the AMCV. Based on this study, it is notable that symptoms of sensory irritation are unlikely to occur at levels below around 0.1 ppm. Many authoritative organizations have reached this same conclusion. Consequently, we recommend the WHO derived protective threshold concentration of 0.125 ppm as the AMCV.

Again, AF&PA and AWC appreciate the opportunity to provide these comments on the derivation of the proposed AMCV for formaldehyde. If you have any questions regarding these comments, please contact Stewart Holm, Chief Scientist, at (202) 463-2709 or at stewart_holm@afandpa.org.

Sincerely,

Paul Noe
Vice President, Public Policy
AF&PA

Robert Glowinski
President & CEO
AWC

APPENDIX 2

American Chemistry Council (Formaldehyde Panel) Comments

May 6, 2014

Texas Commission on Environmental Quality
Toxicology Division
MC-168
P.O. Box 13087
Austin, TX 78711-3087

RE: Proposed Formaldehyde 24-Hour Ambient Air Monitoring Comparison Value

Dear Sir or Madam:

The American Chemistry Council's Formaldehyde Panel (the Panel) is pleased to submit the following comments on the Texas Commission on Environmental Quality's (TCEQ) proposed 24-Hour Ambient Air Monitoring Comparison Value (AMCV) for formaldehyde. The Panel represents US producers, suppliers and users of formaldehyde and formaldehyde products.

The TCEQ proposes a 24-hour acute Reference Value (ReV) of 30 µg/m^3 (24 ppb) and identifies the critical effects as "elevated rates of symptoms such as eye, nasal, and lower airway discomfort in workers." The TCEQ has chosen Wilhelmsson and Holmstrom (1992) as the key study for development of the AMCV for formaldehyde. As discussed in the comments below, however, the Wilhelmsson and Holmstrom (1992) study does not represent the most up-to-date scientific information to characterize the association between formaldehyde exposure and irritation and includes critical confounding factors. Therefore, it should not be relied upon to derive the AMCV for formaldehyde.

Controlled formaldehyde chamber studies provide a more reliable basis from which to derive the AMCV, and there are in fact over 20 published studies and critical reviews of controlled studies of formaldehyde that provide consistent findings (many of which were reviewed in the World Health Organization (WHO) 2010 Guidelines for Indoor Air Quality – Formaldehyde). (Golden et al., 2011) In addition, many authoritative bodies have chosen to rely on these chamber studies to identify thresholds for sensory irritation. For example, the WHO used Lang et al. (2008) to derive a threshold for workers at 0.1 mg/m^3 and for indoor environments at 0.125 mg/m^3. The Lang et al. (2008) study is a well conducted study of 21 volunteers, and was selected by WHO to be one of the key studies in this derivation because the corrected lowest observed effect level (LOEL; 0.63 mg/m^3) from Lang et al. (2008) was in agreement with no observed adverse effect levels (NOAELs) from studies in both humans and animals, including Kulle et al. (1987) and Nielson et al. (1999).

Accordingly, the TCEQ also should consider the Lang et al. (2008) study to derive the AMCV. Moreover, based on the weight of the available scientific evidence, symptoms of sensory irritation are unlikely to occur and would be insignificant at levels below 0.1 ppm (Golden et al., 2011; Mueller et al., 2013). Therefore, the WHO guidelines, based on the higher quality chamber studies, appear to be accurate.

The Key Study Chosen for Setting the AMCV Should Not Be Used for Risk Assessment Due to Possible Confounders and Lack of An Exposure-Dependent Effect.

In the support document for the proposed AMCV, the TCEQ identifies Wilhelmsson and Holmstrom (1992) as the key study chosen for development of the AMCV. This study evaluates reported symptoms of sensory irritation in a cohort of 66 formaldehyde plant workers, and is the same cohort that has been analyzed in the widely cited Holmstrom and Wilhelmsson (1988) and Holmstrom et al. (1989) papers. These studies have drawn significant criticism by a number of authoritative bodies. Most recently, the 1989 and 1988 studies were reviewed by a National Academy of Sciences (NAS) committee in its review of the Environmental Protection Agency's (EPA's) 2010 draft Integrated Risk Information System (IRIS) assessment of formaldehyde (2011) (NAS Report). The NAS Report concluded that the Holmstrom and Wilhelmsson (1988) and Holmstrom et al. (1989) studies taken together have "numerous weaknesses, the most important of which is a failure to identify a clear relationship between adverse responses and exposure concentration or exposure duration." (pg. 77)

In addition, the NAS Report raised concerns regarding potential confounding due to co-exposures to other respiratory irritants in the workplace. (pg. 76) A careful examination of the Holmstrom and Wilhelmsson (1988) study reveals that despite the claim by the authors that it looked at two groups – one "exposed almost exclusively to formaldehyde as the only nasal irritant" and the other exposed to both wood dust and formaldehyde, workers in both groups were exposed to dusts. The "formaldehyde-only" group consisted of 70 workers "...where formaldehyde and products based on formaldehyde were produced (resins and impregnation of paper for laminate production) . . . For the group of workers impregnating paper (N=31) dust concentrations of up to 1 mg/m^3 have been measured close to the machines." Therefore, since 44% of the formaldehyde-only workers in this study were exposed to both formaldehyde and paper dust, there is no basis for attributing effects to formaldehyde alone.

Paper dust is a nasal irritant and has also been associated with eliciting symptoms in asthmatic workers (Jaakkola and Jaakkola, 2007; Shusterman, 2007). Based on this association, the significant findings of nasal discomfort, eye discomfort, and deeper airway discomfort in the formaldehyde group should not be attributed to formaldehyde alone. In fact, the 44% frequency of deeper airway discomfort in this group suggests that something other than formaldehyde (or in addition to formaldehyde) was causing this effect since formaldehyde is efficiently scrubbed from the upper airways and does not penetrate into the lower airways and bronchi. (See Golden, 2011, citing Schlosser et al., 2003; Kimbell et al., 1993, 2001; Overton et al., 2001; Garcia et al., 2009). Since, as the NAS Report notes, "the co-exposure could

be a confounding factor in the study," (p. 76), this study should not be relied upon to quantify the association specifically between formaldehyde exposure and upper respiratory tract pathology.

In addition, the WHO Guidelines for Indoor Air Quality (2010) chapter on formaldehyde (WHO Guidelines) concluded that Holmstrom et al. (1989) "cannot be used for risk assessment owing to the lack of an exposure-dependent effect." (pg. 116) Similar critiques of this cohort study can be found elsewhere in the scientific literature. (See e.g., Wolkoff and Nielsen, 2010; Golden, 2011).

Given that the Wilhelmsson and Holmstrom (1992) study is essentially the same cohort and has not addressed the concerns identified above, it should be judged of a lesser quality than more recent studies and should not be relied upon to derive the AMCV.

The TCEQ Should Rely on Controlled Human Studies to Determine the AMCV.

There are numerous controlled chamber studies using human volunteers that can provide a more appropriate data set for deriving a valid AMCV for sensory irritation. Controlled chamber studies allow for clean air controls that ensure known dose concentrations and preclude confounding by other chemical exposure. This of course allows for a more accurate assessment of a potential threshold specifically attributable to formaldehyde.

The use of controlled formaldehyde chamber studies in developing risk values for sensory irritation has been validated by a number of authoritative bodies. In reviewing the 2010 draft IRIS assessment of formaldehyde, NAS agreed with EPA that eye irritation is the critical outcome upon which to base risk values, but questioned the Agency's rejection of the chamber studies, stating: "The draft IRIS assessment sets aside the chamber studies as less relevant to derivation of candidate RfCs, but the findings from the studies could be useful, and the committee does not concur with EPA's decision to set them aside...." The NAS goes on to state that the utility of chamber studies is that they "provide controlled measures of exposure and response." (NAS Report, at 65, 68)

Indeed, EPA itself has evaluated these types of studies and has reached similar conclusions. In 2005, EPA conducted a critical analysis of six human volunteer controlled exposure studies to derive human health effects criteria for formaldehyde-induced sensory irritation. From these data, mathematical models were used to assess responses. EPA noted that:

> An important advantage of this approach is that all relevant data can be used in the derivation as opposed to a NOAEL for the critical effect. The benefit of doing so allows health risks to be estimated across various exposure levels (USEPA/NCEA 2005).

This approach was supported by the EPA Science Advisory Board reviewing EPA's 2005 report, which observed that the process EPA used in this report:

> makes use of every bit of data available.... The underlying premise of the approach is that the severity of the effect, not the specific measurement or outcome incidence, is the information needed for assessing exposure-response relationships for non-cancer endpoints... (USEPA/NCEA 2005).

EPA's detailed modeling process showed a clear threshold at 0.5 ppm for any symptoms of sensory irritation for formaldehyde and an effective concentration at 1.5 ppm for moderate effects.

Numerous other regulatory and authoritative bodies worldwide have relied upon the large body of data from chamber studies precisely because it permits a more accurate assessment of formaldehyde concentrations associated with sensory irritation than workplace or residential studies. (See e.g., OECD Development Screening Information Data Set, 2002; EU Scientific Committee on Occupational Exposure Limits, 2008; WHO Guidelines, 2010).

The TCEQ 2012 guidance document, *TCEQ Guidelines to Develop Toxicity Factors* (RG-442), describes using controlled human chamber studies which meet the WHO International Programme on Chemical Safety (IPCS) criteria in Section 3.3.3.3.1.1 for derivation of screening values. The Lang et al. (2008) study clearly meets these criteria. Furthermore, appropriate controlled human chamber studies previously have been used by TCEQ as the "key study" in several Effects Screening Level (ESL) and AMCV derivations, including, acetone, n-butyraldehyde, and methanol.

Therefore, the TCEQ should utilize chamber studies for purposes of developing the AMCV for formaldehyde as well, because these well designed and well described exposures provide greater scientific clarity.

We recognize that controlled studies are often criticized for focusing on acute effects, and therefore they do not capture potential effects from longer term exposures. The *Proposed TCEQ Guidelines to Develop 24-Hour Inhalation Reference Values* suggests that exposure duration adjustments should be made for studies that are less than 24 hours. It is important to note; however, that formaldehyde does not follow traditional "concentration x time" principles consistent with Haber's law. Therefore, it is the concentration, not the time or duration, of the exposure that is relevant to the observed health outcomes. Scientists, including some within EPA, report that, for formaldehyde-induced sensory irritation, there is essentially no meaningful difference between short-term and longer-term exposure (EPA, 2004; NAS, 2007; Shusterman et al., 2006). In fact, NAS (2007) concluded:

> Formaldehyde irritation does not appear to follow Haber's law (concentration [c] x exposure time [t] = response [k]) for extrapolating between short-term and long-term toxicity levels. Generally, concentrations that do not produce short-term sensory irritation also do not produce

> sensory irritation after repeated exposure.... The degree of sensory and irritant effects at lower exposure levels depends on concentration rather than duration (NAS, 2007, at 105-06, 118).

This conclusion is based on test results derived from human chamber studies which show that once symptoms are produced at a certain concentration they are not enhanced with additional exposure time. As such, the estimated point of departure (POD_{HEC}) that would be relied upon for the derivation of the 24-hour formaldehyde AMCV would need no duration adjustment if the Lang et al. (2008) study is used as the basis.

The TCEQ Should Use Lang et al. (2008) to Support the Derivation of the AMCV.

As noted above, there are over 20 published studies and critical reviews of controlled studies of formaldehyde.[1] The TCEQ should consider Lang et al. (2008) as the key study to derive the AMCV.[2] Firstly, the Lang et al. (2008) study presents new data, possibly rendering the previous 2009 derivations obsolete and warranting re-evaluation; secondly, there is precedent for the use of this study to derive a risk value for sensory irritation. The WHO did so in developing the final threshold value for objective sensory irritation.

Essentially, the TCEQ is using the same justification and study for development of the 24-hour AMCV as it did for the formaldehyde acute and chronic ESLs and AMCVs. These values were derived in 2008, which was prior to the publication of Lang et al. (2008). In August, 2008, the TCEQ responded to public comments on the proposed formaldehyde acute and chronic ESLs and AMCVs (*Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the Proposed Development Support Document for Formaldehyde, August 7, 2008*). In that response, the TCEQ included the Lang et al., (2008) study in the acute section of the formaldehyde assessment. In both the August 2008 response to comments and the 2012 TCEQ *Guidelines for Development of Toxicity Factors*, the TCEQ states that it will update ESLs and AMCVs when new scientific evidence supports a re-review. The Lang et al. (2008) study and its supportive peer-reviewed studies (e.g., Triebig et al., 2012; Mueller et al., 2013) create a substantial body of new evidence. The 2008 assessment which provides the basis for the proposed 24-hour AMCV is scientifically out of date and should be re-evaluated.

In Lang et al. (2008), the authors examined 21 volunteers over a 10 week period and each participant was exposed to 10 exposure conditions on 10 consecutive working days, each for 4 hours. During 4 of the 10 sessions, ethyl acetate (12-16 ppm) was used as a masking agent for formaldehyde exposure. Measurements were related to conjunctival redness, blinking frequency, nasal flow and resistance,

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[1] See Golden (2011), citing e.g., Andersen (1979); Andersen and Molhave (1983); Bender et al. (1983); Day et al. (1984); Gorski et al. (1992); Green (1987); Krakowiak et al. (1998); Kulle (1993); Kulle et al. (1987); Lang et al. (2008); Pazdrak et al. (1993); Schachter (1986, 1987); Weber-Tschopp et al. (1977); Witek (1987).

[2] Recent controlled chamber studies by Triebig et al. (2012) and Mueller et al. (2013) confirm the outcomes from Lang et al. (2008).

pulmonary function and reaction times. Subjective assessments included discomfort, and the influence of personality factors on subjective scoring was also evaluated.

Blinking frequency and conjunctival redness, ranging from slight to moderate, were significantly increased by short-term peak exposures of 1.0 ppm that occurred at a baseline exposure of 0.5 ppm formaldehyde. Nasal irritation was reported at concentrations of 0.5 ppm plus peaks of 1.0 ppm, as well as at levels of 0.3 ppm and 0.5 ppm with co-exposure to ethyl acetate. In this case, the ethyl acetate exposure was also perceived as irritating. No significant treatment effects were noted regarding nasal flow and resistance, pulmonary function and reaction times. When negative affectivity was introduced as a covariate, the level of 0.3 ppm was no longer an effect level, but 0.5 ppm with peaks of 1.0 ppm was. The authors concluded that eye irritation was the most sensitive parameter recorded, and that the NOAEL for objective eye irritation was 0.5 ppm.

The WHO relied upon the Lang et al. (2008) study to set a NOAEL of 0.63 mg/m^3 (0.5 ppm) for the determination of the Indoor Air Quality Guideline, to which was applied what we believe was an overly conservative uncertainty factor of 5, to take into account nasal pungency thresholds.[3] (pgs. 115-116) This resulted in a derived value of 0.125 mg/m^3 (0.1 ppm), which the Guidelines provided "was considered safe for the entire population against sensory irritation, including chronic sensory irritation." (pg. 116) In spite of our concern regarding the uncertainty factor applied by the WHO, we believe that the WHO threshold value for sensory irritations is based on the best available science, and the TCEQ should consider the approach reflected in the WHO Guidelines in developing the AMCV for formaldehyde.

Symptoms of sensory irritation are unlikely to occur and would be insignificant at levels below 0.1 ppm.

As we noted above, the WHO concluded that an objective threshold for sensory irritation is about 1 mg/m^3 (0.81 ppm) for workers and that a value of 0.125 mg/m^3 (0.1 ppm) is considered safe for the entire population, including chronic sensory irritation and children, exposed in an indoor environment 24 hours per day (WHO, 2010, pgs. 115-16). Other evidence-based reviews conclude that 0.3 ppm is a reasonable and appropriate level below which symptoms of sensory irritation are unlikely to occur:

- "[S]ymptoms of eye and mucous membrane irritation at that concentration were not increased above control conditions in controlled chamber studies" (NAS, 2007).

[3] Arguably, the application of any uncertainty factor is an unnecessarily conservative approach, since the data relied upon was derived largely from controlled human exposures studies, and therefore there is no need for further "adjustments" by the use of uncertainty factors. Moreover, there is such a rich database of controlled chamber studies that have produced fairly consistent results, which should negate the need for applying a default uncertainty factor. See Golden (2011), pg. 12.

- "Studies in the literature have reported a variety of responses induced by exposure to gaseous formaldehyde, generally beginning in the range of 0.3 to 0.5 ppm for eye irritation, the most sensitive endpoint. However, the severity of response at these levels is generally mild, and only a small portion of the population may respond" (The Organisation for Economic Co-operation and Development (OECD)/SIDS, 2002).

Many other authoritative bodies have reached these same conclusions. (Agency for Toxic Substances and Disease Registry (ATSDR), 1999, 2007; WHO, 2002; American Conference of Industrial Hygienists (ACGIH), 2001; MAK, 2006; National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 2006).

In a recent human exposure study, Mueller et al. (2013) examined chemosensory effects of formaldehyde in 41 hypo- and hypersensitive male volunteers. Individuals were exposed on five days, for four hours, at four different concentrations (0.3 ppm, 0.3 ppm + 4 x 0.6 ppm peaks, 0.4 ppm + 4 x 0.8 ppm peaks, 0.5 ppm, and 0.7 ppm). The results indicate no chemosensory effects on hypo- and hyper-sensitive males at formaldehyde exposures to 0.7 ppm for 4 hours and to 0.4 ppm for 4 hours with peaks of 0.8 ppm for 15 minutes. The measured endpoints included conjunctival redness, eye-blinking frequency (EBF), tear film break-up time (sBUT), nasal flow, and several subjective symptoms. This study supports the conclusions of the Lang et al. (2008) study and indicates sensory irritation is unlikely to occur below 0.1 ppm, even for hypersensitive individuals.

The WHO Guidelines and conclusions of other authoritative bodies make clear that sensory irritation is unlikely to occur below 0.1 ppm. The most recent controlled studies in humans support this conclusion. Therefore, we strongly believe that the TCEQ should consider 0.1 ppm as the lowest, most conservative value from which to derive its AMCV.

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We appreciate the opportunity to provide these comments on the proposed AMCV for formaldehyde. We thank you in advance for considering our comments, which we hope will inform the final development of an AMCV that reflects the best available science and advances public health. Should you have any questions, please feel free to contact me.

Sincerely,

Jackson Morrill
Director
ACC Formaldehyde Panel

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