COMMENTS ON ACGIH NOTICE OF INTENDED CHANGE FOR FORMALDEHYDE
# CONTENTS

1 Introduction 1

2 Comments on Cancer Classification 1
   2.1 Comments On ACGIH Classification 1
   2.2 Determinations of Other Regulatory Bodies Who Have Cancer Classifications 1

   2.2.1 Scientific Committee On Occupational Exposure Limits (SCOEL) 1
   2.2.2 World Health Organization (WHO) Guidelines For Indoor Air 2

   2.3 Inconsistencies Among National Academy of Sciences (NAS) National Research Council (NRC) Committees 3

3 Commenting on the Justification in the Changes for the TLV Numbers 3
   3.1 Proposed Changes To The TLV 3
   3.2 Basis Of The TLV Recommendations 4
      3.2.1 Human Studies 4
   3.3 Determinations Of Other Regulatory Bodies Who Have Health-Based Recommendations, Limits, And Guidelines 5
      3.3.1 Scientific Committee On Occupational Exposure Limits (SCOEL) 5
      3.3.2 World Health Organization (WHO) Indoor Air Guidelines 6

4 Additional Comments on the Literature Review 6
   4.1 Biological Plausibility Of Leukemia 6
   4.2 Mechanistic Considerations (Threshold vs Non-Threshold) 8
   4.3 Endogenous Formaldehyde 9

5 Conclusion 9
   5.1 A1 Category "Confirmed Human Carcinogen" Is An Inappropriate Classification, Given The ACGIH Guidance 9
   5.2 The Proposed Recommendations For A 0.1 ppm TLV-TWA Is Without Justification 9
   5.3 The Proposed Recommendation For A 0.3 ppm TLV-STEL Is In Line With The Current 0.3 ppm TLV-CEILING (Established In 1992). However, Even This Value Is Not Justified By Literature 10

Appendix A: References A1
Appendix B: Details of Studies Reviewed for Proposed TLVs B1
COMMENTS ON ACGIH NOTICE OF INTENDED CHANGE FOR FORMALDEHYDE

1 INTRODUCTION
The American Conference of Governmental Industrial Hygienists (ACGIH) published a notice of intended change (NIC) for formaldehyde (CAS RN 50-00-0) on October 22, 2015. The current threshold limit value (TLV) ceiling for formaldehyde is 0.3 ppm, with designations as a respiratory sensitizer (RSEN) and dermal sensitizer (DSEN). The current cancer classification is A2, suspected human carcinogen. This NIC proposes to change the TLV to a set of values: 0.1 ppm for a TLV-TWA and 0.1 ppm for a TLV-STEL. The RSEN and DSEN designation would remain the same, but the cancer classification is proposed to change from A2 suspected human carcinogen to A1 confirmed human carcinogen. The basis for the proposed ACGIH TLV is upper respiratory tract and eye irritation, as well as upper respiratory tract cancer. We therefore focus on those endpoints, and discuss the individual studies (and their interpretation) below. We then comment on the strength of these studies in supporting a change in the classification and TLV. Because the literature discussion in the NIC supporting the change in classification and TLV contains summaries of a number of important studies, we also comment on the accuracy of the portrayal of that literature.

2 COMMENTS ON CANCER CLASSIFICATION
The change of the ACGIH- TLV cancer classification recommendation from A2 “Suspected Human Carcinogen.” to A1 category “confirmed human carcinogen,” as proposed in the NIC requires justification, but none is provided. Given ACGIH guidance for the A1 category “confirmed human carcinogen” (ACGIH 2012), the change to A1 category does not reflect weight-of-evidence based on epidemiology. Given the current epidemiologic evidence that suggests no excess risk of upper respiratory tract cancer among populations of workers exposed at the level causing nasal irritation in humans, the current ACGIH cancer classification category A2 “Suspected Human Carcinogen” is more appropriate. Other regulatory bodies, such as Scientific Committee on Occupational Exposure Limits (SCOEL), the World Health Organization (WHO), and the European Union classify formaldehyde differently based on the same science. For example, formaldehyde is classified by the SCOEL in cancer category Group C “Genotoxic carcinogens for which a practical threshold is supported” (SCOEL 2013). These updates have not provided strong evidence of an association between formaldehyde and nasopharyngeal cancer (NPC) such that formaldehyde should be considered to be a known human carcinogen.

2.1 Comments On ACGIH Classification
The ACGIH is proposing a change in the cancer classification from A2 “suspected human carcinogen” to A1 “confirmed human carcinogen” for “upper respiratory tract cancer.” The ACGIH definition of the A1 classification indicates that the agent is carcinogenic to humans based on the weight-of-evidence from epidemiology studies (ACGIH 2012; Spirtas et al. 2001). Therefore the ACGIH cancer classification of “A1 confirmed human carcinogen” in the NIC suggests there is strong evidence from epidemiological studies. However, epidemiology studies of upper respiratory tract cancers provide inconsistent results. Occupational studies reporting NPC/sinonasal cancers provide limited evidence of an association with formaldehyde exposure (Beane Freeman et al. 2013; Meyerset al. 2013; Coggon et al. 2014; Marsh et al. 2014; Marsh et al. 2016). Population-based case-control studies of NPC show more consistent increased risks of NPC but are limited by the exposure assessments, including absence of formaldehyde exposure measurements, and potential for exposure misclassification (Vaughan et al. 2000); and possible confounding or effect modification by other risk factors (Vaughan et al. 2000; Hildesheim et al. 2001; West et al. 1993). These results are inconsistent with industry cohort studies (where formaldehyde exposure was known to occur (Vaughan et al. 2000; Hildesheim et al. 2001)). Animal studies provide evidence of nasal cancers only following inhalation exposure to high concentrations of formaldehyde. For these reasons, it appears that a change in classification to “A1 confirmed human carcinogen” is not justified.

2.2 Determinations of Other Regulatory Bodies Who Have Cancer Classifications
2.2.1 Scientific Committee On Occupational Exposure Limits (SCOEL)
The European Scientific Committee on Occupational Exposure Limits (SCOEL) also classifies chemicals as carcinogens. The SCOEL advises the European Commission by reviewing science and preparing recommendations for occupational Exposure Limit Values (OELVs) for chemicals in the workplace. Its mission parallels the ACGIH, also tasked with developing health-based occupational TLVs. The SCOEL is forward-thinking in that it considers mode-of-action when considering the extrapolation of carcinogenic risk from high- to low- doses. SCOEL, unlike other regulatory agencies, distinguishes between genotoxic and non-genotoxic chemicals and considers the possibility of “practical thresholds” for genotoxic carcinogens. “There is consensus that for non-DNA reactive genotoxicants, such as aneugens, thresholds should be defined. Specific mechanisms of clastogenicity have been repeatedly addressed as also having thresholds, such as topoisomerase II poisons or reactive oxygen species.” (SCOEL 2013, p. 26). Therefore, SCOEL distinguishes carcinogens AND mutagens when setting OELs:
• Group A: non-threshold genotoxic carcinogens (for risk low-dose assessment, the linear non-threshold (LNT) model appears appropriate.
• Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty.
• Group C: Genotoxic carcinogens for which a practical threshold is supported.
• Group D: Non-genotoxic carcinogens and non-DNA reactive carcinogens; for these compounds a true (“perfect”) threshold is associated with a clearly founded NOAEL.

The ACGIH cancer classifications currently do not allow for consideration of a “practical threshold.” However, the ACGIH documentation allows that “human (Beane Freeman et al. 2013) and animal studies (Kerns et al. 1983; Monticello et al. 1996) have indicated nonlinear dose-response relationships for the risk of squamous cell nasal cancer.” (Note, Beane Freeman reported no increased risk of cancer in nose or nasal sinuses related to average, cumulative, or peak formaldehyde exposure. Five deaths were observed; two occurred among those who were not exposed to formaldehyde. Death certificate data did not allow identification of histologic type of nose or nasal cancers).

Based on what is currently understood about formaldehyde and upper respiratory cancers (sinonasal cancers and NPC), SCOEL classified formaldehyde as a Group C, Genotoxic carcinogen for which a practical threshold is supported (SCOEL 2015). This classification as Group C is reasonable and accurately reflects the existing science from in vivo animal studies demonstrating nasal tumors in animals and epidemiology studies showing no excess risk of upper respiratory tract cancer among populations of workers exposed at the level causing nasal irritation in humans. In the absence of such a classification that recognizes a practical threshold for formaldehyde exposure, the appropriate classification, using the existing ACGIH classifications, a more appropriate classification may be A2 “suspected human carcinogen” due to limited evidence of NPC from epidemiology studies and sufficient evidence of carcinogenicity in experimental animals with relevance to humans.

2.2.2 World Health Organization (WHO) Guidelines For Indoor Air

Although the World Health Organization (WHO) indoor air guidelines working group conducted an independent review of the epidemiology literature for formaldehyde carcinogenicity (WHO 2010), they also rely upon the International Agency for Research on Cancer (IARC) classification of formaldehyde as a human carcinogen. IARC based its decision on “sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans” largely based on the National Cancer Institute (NCI) cohort analysis by Hauptmann et al. (2004) (since superseded by Beane Freeman et al. 2013). In addition, IARC found limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans. “Formaldehyde can induce squamous cell carcinoma of the nasal cavity in rats and nasopharyngeal cancer in humans. Long-term exposure to 7.5 mg/m³ formaldehyde and above caused squamous cell carcinoma of the nasal cavity of rats with a non-linear, biphasic concentration–response relationship having the break point at or above 2.5 mg/m³. In humans, no excess nasopharyngeal cancer has been observed at mean exposure levels at or below 1.25 mg/m³ and with peak exposures below 5 mg/m³.”


In Europe, formaldehyde is classified as a Carcinogen Category 1B “presumed human carcinogen” under the CLP Regulation. This harmonized classification was based on “limited evidence of carcinogenicity mainly from the positive association of nasopharyngeal tumours in industrial cohorts.” The French Agency for Food, Environmental and Occupational Health & Safety, on behalf of the France Competent Authority submitted a proposal to classify formaldehyde as a Carcinogen Category 1A “known human carcinogen” and mutagen Category 2 in 2011. The European Chemical Agency Risk Assessment Committee (RAC) rejected a proposal by France Competent Authority to classify formaldehyde exposure as a 1A carcinogen under the European Classification, Labelling and Packaging Regulation. The RAC instead adopted an opinion that classified formaldehyde as a “Carcinogen Category 1B” (presumed human carcinogen) based on an interpretation of weight-of-evidence (RAC

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2012). In their opinion, the RAC cited studies by results of industrial cohorts (a positive study of nasopharyngeal cancers by Hauptmann et al. (2004)) and negative studies of nasopharyngeal cancers in United Kingdom industrial workers cohort (Coggon et al. 2003) and the National Institute for Occupational Safety and Health (NIOSH) garment workers cohort (Pinkerton et al. 2004). The classification was made based on sufficient evidence of NPCs in animals, because the epidemiology data was limited.

These studies have since been updated (Beane Freeman et al. 2013; Coggon et al. 2014; Meyers et al. 2013, respectively). In the NCI cohort, Beane Freeman et al. (2013) reported one additional death from NPC (1.2 expected) in the 10 years of additional follow-up (1995-2004). In addition, the death occurred among a study subject in the lowest category of peak, average intensity and cumulative exposure. In the United Kingdom industry cohort, one death from NPC was reported (1.7 expected among those with average exposure greater than 0.1 ppm) while 0 deaths (1.33 expected) from NPC and 0 deaths from sinonasal cancer (0.95 expected) were reported in the NIOSH cohort. In the NIOSH cohort, formaldehyde exposures were thought to have decreased over time due to reformulations of resins used to treat fabrics. (In the early 1980s, an industrial hygiene survey reported similar formaldehyde levels across all departments and an overall geometric mean of 0.15 ppm [geometric standard deviation of 1.90]). Overall, these updates have not provided strong evidence of an association between formaldehyde and NPC; and formaldehyde should therefore not be considered to be a known human carcinogen.

### 2.3 Inconsistencies Among National Academy of Sciences (NAS) National Research Council (NRC) Committees

The ACGIH NIC Documentation states: “The following discussion will focus primarily on key studies of formaldehyde and nasopharyngeal cancers, which were considered to be strong or moderately strong in study quality in the U.S. National Academy of Sciences review (US NAS, 2014).” It appears clear that the ACGIH Documentation relied extensively (and perhaps solely) on the NRC (2014) review of the formaldehyde assessment for the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP) 12th Report on Carcinogens (RoC). No clear rationale is specified for using the NAS (NRC 2014) as an authoritative source. Relying solely on the NRC (2014) is problematic because the NRC (2014) relied on a “strength of evidence” approach rather than a “weight of evidence” approach advocated by the ACGIH (ACGIH 2012; Spirtas et al. 2001).

Two NRC committees (NRC 2014; NRC 2011) have independently evaluated draft summaries of cancer in relation to formaldehyde. The different approaches taken by these two Committees are detailed in the Appendix; the charges and tasks assigned to the two NRC committees were different, and the approach that the NTP takes for listing carcinogens in its RoC is different from the IARC and the US EPA under the IRIS program. The RoC process relies upon assessing the strength of key human studies. If there are sufficiently strong human studies, a judgment of causality is made without necessarily considering the quality and quantity of "negative" studies (Rhomberg 2015). In contrast, the US EPA relies upon evaluating all types of evidence (human, animal, mechanistic studies) (US EPA 2015; Rhomberg 2015).

In the absence of explicit guidance, the NRC (2014) committee interpreted the RoC listing criteria for sufficient evidence of carcinogenicity as indicated by at least two studies of moderately strong or strong quality that showed an association between formaldehyde exposure for a specific cancer site in two different study designs or populations. In addition, the study results could not be explained by chance, bias, and confounding. The NRC committee identified criteria for strong quality: studies of large populations that had gradients of well characterized exposure and sufficiently long follow-up to detect cancers. The NRC (2014) review did not consider limitations of the studies it identified as strong quality, nor did it consider studies reporting negative results when considering the consistency of findings. ACGIH (2012), in its “Guidelines for Carcinogenicity Classification” states “ACGIH also recommends using the weight-of-evidence approach suggested by the EPA, rather than the strength-of-evidence approach used by IARC. ACGIH is most interested in the predictive relevance to human risk.” (p. iv).

### 3 Commenting on the Justification in the Changes for the TLV Numbers

#### 3.1 Proposed Changes To The TLV

In addition to recommending a change in the cancer designation, the NIC proposes changes to the TLV as well. The proposed ACGIH TLV recommendations are for a 0.1 ppm TLV-TWA; a 0.3 ppm TLV-STEL; maintaining the RSEN and DSEN notation, and changing the cancer designation to A1 Confirmed Human Carcinogen. The ACGIH notes that a combination of TWA and STEL are recommended, as by minimizing repeated irritation to the respiratory tract, the TLV...
should protect against increasing cell proliferation and the risk of upper respiratory tract cancer. The proposed recommendations for a 0.1 ppm TLV-TWA is without justification. The proposed recommendation for a 0.3 ppm TLV-STEL is in line with the current 0.3 ppm TLV-CEILING (established in 1992), but justification for this number is not provided.

3.2 Basis Of The TLV Recommendations
A number of studies, including controlled human exposure (chamber) studies (Lang et al. 2008) and occupational studies (Alexandersson and Hedenstierna 1988; Horvath et al. 1988; Edling et al. 1988), as well as supporting studies in experimental animals (Feron et al. 1988; Kerns et al. 1983; Monticello et al. 1996), are cited as the basis of the TLV-TWA and TLV-STEL recommendations. An important controlled human exposure study (Mueller et al. 2013) is not included in the basis of the TLV-TWA and TLV-STEL recommendations. However, the ACGIH Documentation provides no context for how the actual numerical TLV values are derived based on these studies. Without this context, it is impossible to evaluate the ACGIH reasoning in arriving at these numbers, which appear overly conservative.

3.2.1 Human Studies
The ACGIH Documentation discusses a controlled human exposure study (Lang et al. 2008) as providing a lowest-observed-adverse effect level (LOAEL) for objective measures of irritation (blinking rate and conjunctival redness). The LOAEL from this study was a group exposed for 4 hours per day, for 10 consecutive working days, to 0.5 ppm formaldehyde with a series of four 1.0 ppm peak exposures within the 4 hour exposure. The ACGIH Documentation also cites another controlled human exposure study (Andersen and Molhave 1983) as providing a LOAEL of 0.3 mg/m$^3$ (approximately 0.24 ppm) for decrease mucociliary flow in the anterior region of the nose, and 0.3 mg/m$^3$ (approximately 0.24 ppm) for subjective eye irritation. They do not report on the controlled human exposure study of Mueller et al. (2013) who examined individuals exposed to formaldehyde for 4 hours each day to 0.5 ppm or 0.7 ppm and individuals exposed with baseline exposures to 0.3 ppm or 0.4 ppm formaldehyde with peak exposures of 0.6 ppm or 0.8 ppm, respectively. In the Mueller et al. (2013) study, subjective rating of symptoms and complaints, conjunctival redness, eye-blinking frequency, self-reported tear film break-up time and nasal flow rates were assessed; none of these chemosensory effects were seen at any of the exposure scenarios.

The Documentation also cites a set of two occupational studies of workers as providing a LOAEL of 0.3 ppm (8-hr TWA) with a peak of 0.6 ppm for subjective eye and respiratory tract irritation (Alexandersson and Hedenstierna 1988) and 0.4 ppm (8-hr TWA) for nasal irritation (Horvath et al. 1988).

Looking across the three controlled human exposure studies (Lang et al. 2008; Andersen and Molhave 1983; Mueller et al. 2013), only non-serious effects were observed. Minor eye irritation resulting in increased blink frequency and conjunctival redness was observed at formaldehyde concentrations as low as 0.5 ppm formaldehyde (or 0.3 ppm with peak exposures of 1 ppm) in one study (Lang et al. 2008) but not another (Mueller et al. 2013). Reductions in nasal mucociliary flow rates were observed in the anterior portion of the nose (but not the posterior regions) and subjective eye irritation was reported in one study at formaldehyde concentrations as low as 0.3 mg/m$^3$ (approximately 0.24 ppm) (Andersen and Molhave 1983) but not another with formaldehyde exposures up to 0.7 ppm (or 0.4 ppm with peak exposures of 0.8 ppm) (Mueller et al. 2013).

Importantly, exposures in the two more recent controlled human exposure studies (Lang et al. 2008; Mueller et al. 2013) were complex. Even if the Mueller study is ignored (and it should not be), it is not clear how ACGIH derives a 0.1 ppm TLV-TWA and a 0.3 ppm TLV-STEL from these exposures. In the one study reporting effects (Lang et al. 2008), the LOAEL of 0.5 ppm includes a series of 4 peak exposures to 1 ppm. The stand-alone exposure scenario without peak exposures from this study, at concentrations of 5 ppm, did not show any effects. In fact, the authors identified the 0.5 ppm alone (no 1.0 ppm peak exposure) and the 0.3 ppm plus 0.6 ppm peak exposure as the highest exposures without effects (the no-observed-adverse-effect-level, or NOAEL).

The Anderson and Molhave (1983) study reported on a series of 5 previously published controlled human exposure studies involving formaldehyde, with additional data reported for one of these studies. Providing additional results from a previously reported study by the authors, Anderson and Molhave (1983) reported decreases in nasal flow rates in the

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Details about these studies are provided in the Appendix to these comments.
3.3 Determinations Of Other Regulatory Bodies Who Have Health-Based Recommendations, Limits, And Guidelines

3.3.1 Scientific Committee On Occupational Exposure Limits (SCOEL)

In addition to SCOEL’s conclusion that although formaldehyde acts through a threshold mode-of-action, SCOEL has also derived health-based Occupational Exposure Limit (OELs) of 0.3 ppm (8h TWA) and 0.6 ppm (STEL) (Scientific Committee on Occupational Exposure Limits [SCOEL] 2015). These values were based on the two high quality chamber studies (Lang, Bruckner, and Triebig 2008; Mueller, Bruckner, and Triebig 2013) which measure both subjective reporting, as well as more objective measures of eye and upper respiratory tract irritation. SCOEL derived an OEL from no-observed adverse effect levels (NOAELs) for sensory irritation of 0.7 ppm (or 0.4 ppm exposures with transient peaks of 0.8 ppm). The two studies used somewhat different exposure regimes: the Lang et al. (2008) used constant exposures of 0.3 ppm or 0.5 ppm with 4 superimposed peaks 0.6 ppm or 1 ppm respectively. Objective measures of irritation were only observed at the higher 0.5 ppm constant plus peaks of 1 ppm (Lang, Bruckner, and Triebig 2008). The Mueller et al. (2013) study used constant exposures of 0.5 ppm or 0.7 ppm or exposures with constant exposures to 0.3 ppm or 0.4 ppm with peaks of 0.6 ppm or 0.8 ppm, respectively. No chemosensory effects were seen at any of these exposure concentrations (Mueller, Bruckner, and Triebig 2013). The NOAEL observed in both studies, 0.3 ppm with peaks of 0.6 ppm, therefore served as the basis for the OEL of 0.3 ppm (8 h TWA) with a 0.6 ppm STEL. This contrasts with the proposed ACGIH recommendations of a 0.1 ppm TLV-TWA and a 0.3 ppm TLV-STEL.

ACGIH cites Anderson and Molhave (1983) as demonstrating a lowest-observed-effect-level (LOEL) for decreased mucociliary flow rate in the anterior region of the nose (although in the basis for the TLV section they refer to this as an adverse effect) of 0.3 mg/m³. While true, this statement omits much of the detail showing that this effect did not persist or worsen with prolonged (1-3 hours versus 4-5 hours) or higher (1 or 2 mg/m³) exposures. These findings were interpreted by the authors as showing evidence of adaptation formaldehyde effects, something that should have been discussed in the ACGIH Documentation in applying the results of this study to a TLV-TWA. The Documentation also cites Anderson and Molhave (1983) as demonstrating a LOAEL of 0.3 mg/m³ for eye, nose, or throat irritation. One important limitation to this study is the lack of a control group with a sham exposure, something that ACGIH does not acknowledge. Nevertheless, ACGIH states that these studies provide the justification of both a TLV-TWA (8 hour) of 0.1 ppm and TLV-STE (15 minute) of 0.3 ppm. They state that “By minimizing repeated irritation to the respiratory tract, the TLV should also protect against increasing cell proliferation and the risk of upper respiratory tract cancer.” However, the controlled human exposure studies they identify as the basis of the TLVs examine sensory irritation: eye blinking and conjunctival redness (Lang et al. 2008), mucociliary flow rate (Andersen and Molhave 1983), and subjective indices of eye irritation (Andersen and Molhave 1983). Sensory irritation is not the same as cytotoxic irritation leading to cell proliferation, and occurs at lower formaldehyde concentrations than cytotoxic irritation (Bruning et al. 2014). Thus, these studies do not provide supporting evidence for low-level exposures to formaldehyde, and certainly do not justify establishment of a 0.1 ppm TLV-TWA; a 0.3 ppm TLV-STE. It is also important to note that the type of sensory irritation seen in this study (Lang et al. 2008) is irritation produced by stimulation of the trigeminal nerves receptors (fifth cranial nerve) in the cornea and nasal mucosa. Such sensory irritation is considered to be a compensatory response and not a toxic response in that the sensory irritation effects are rapidly reversible and produce no residual tissue damage or cell injury. This is in contrast to other types of irritation which involves an inflammatory or cytotoxic response characterized by tissue destruction, which is not rapidly reversible. Formaldehyde acts only at the site of contact and is not a systemic toxicant; its irritating properties are transient and fully reversible.

Additional details of these studies are provided in the Appendix of these comments.
COMMENTS ON ACGIH NOTICE OF INTENDED CHANGE FOR FORMALDEHYDE

SCOEL also states that a “skin” notation is not required, noting the exclusively local effects of formaldehyde, a well-known contact allergen to the skin (SCOEL, 2015). Against the background of a widespread use, respiratory sensitization has been reported only in single cases and SCOEL concludes designation as respiratory sensitizer is not warranted. This contrasts with the ACGIH current RSEN and DSEN notations.

3.3.2 World Health Organization (WHO) Indoor Air Guidelines

Based on a review of the formaldehyde health literature, the WHO (2010) developed indoor air guidelines based on the no observed adverse effects level (NOAEL) in controlled human exposure (chamber) studies. The most sensitive health outcomes were sensory irritation of the eyes and upper respiratory tract. A NOAEL for trigeminal stimulation of the eyes (increase blink reflex) was observed for 0.5 ppm (approximately 0.63 mg/m³) alone (no peak exposures) as well as for 0.3 ppm (approximately 0.38 mg/m³) with 0.6 ppm (approximately 0.75 mg/m³) peak exposures (Lang et al. 2008). This NOAEL was adjusted 5-fold to account for variation in sensory irritation (based on the standard deviation for nasal pungency) to arrive at a value of 0.12 mg/m³, which was then rounded down to 0.1 mg/m³. This value was considered protective for short duration (30 minute) exposures, with a statement that because formaldehyde-induced effects did not accumulate, it would also be protective of longer-term exposures.

Similarly, the WHO used the threshold-base dose-response for cancer and the observed NOAEL of 1.25 mg/m³ for cell proliferation (seen as being an essential step in nasopharyngeal cancer) to develop a cancer-risk number. This value was further adjusted using assessment factors of 3 (interspecies extrapolation, non-systemic, local effect), and 2 (inter-individual variability), leading to a value of 0.21 mg/m³ as being protective against long-term exposure effects such as cancer. Since the short-term (30 minute) guideline of 0.1 mg/m³ is the lower of the two values, the WHO used that single guideline as being protective against both short-term (30 minute) and long-term (lifetime) formaldehyde exposures. Neilsen et al. (2016) recently re-evaluated the WHO (2010) formaldehyde indoor air quality guideline for formaldehyde exposures. They report (a) normal indoor air formaldehyde concentrations do not pass beyond the respiratory epithelium, and (b) naso-pharyngeal cancer and leukemia were observed inconsistently among studies. Incorporating new updates of the US National Cancer Institute (NCI) cohort, Neilsen et al. (2016) confirmed that relative risks in exposed individuals was not increased with mean formaldehyde exposures below 1 ppm and peak exposures below 4 ppm; authors concluded that overall, the credibility of the WHO guideline is supported by new studies.

4 ADDITIONAL COMMENTS ON THE LITERATURE REVIEW

4.1 Biological Plausibility Of Leukemia

ACGIH describes the Zhang et al. (2010) and the Lan et al. (2015) follow-up study, which examine chromosomal aneuploidy in Chinese workers exposed to formaldehyde while working in one of two factories (producing formaldehyde-melamine resins, and producing plastic utensils from formaldehyde-melamine resins) as compared to unexposed matched controls. Formaldehyde exposures in the all exposed workers (production and handling workers) were 1.28 ppm (median 8-hour TWA); for unexposed workers, median formaldehyde exposures were 0.026 ppm. Workers’ blood samples were obtained in 2006, and routine blood and biochemical tests of the samples were performed. In addition, investigators cultured peripheral blood cells. ACGIH states “Study outcomes found a relative decrease in peripheral blood cell counts in exposed workers and an increase in leukemia-specific chromosome changes in workers.” Zhang et al. (2010) described changes in a variety of hematological parameters, including statistically significant decreases in white blood cell, lymphocyte, platelet, and red blood cell (RBC) counts, and statistically significant increases in RBC mean corpuscular volume in formaldehyde exposed workers compared to controls. In addition, the authors reported a 20% decrease in mean colony formation frequency for Colony Forming Unit- Granulocyte/Macrophage (CFU-GM) colony-forming progenitor cells from exposed workers compared with those from controls, which the authors suggested as a possible toxic and/or inhibitory effect of formaldehyde on myeloid progenitor cells. The assay they used examines metaphases obtained from the CFU-GM colonies that developed after 14 days of culture in vitro, then examines these cells for cytogenetic changes using fluorescence in situ hybridization (FISH) techniques. The FISH analysis of the metaphases from the CFU-GM colonies was limited to samples from 10 highly exposed subjects as defined by the authors to be those with a median exposure of 2.14 ppm formaldehyde, as compared to 12 matched control (median exposure concentration of 0.026 ppm) samples (Gentry et al. 2013). Zhang et al (2010) reported an increased frequency of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFU-GM colony cells; they conclude these results demonstrate that formaldehyde exposure was associated with an increase in leukemia-specific chromosomal aneuploidy in vivo in the hematopoietic progenitor cells of the exposed workers. Importantly, no direct in vivo metaphases were examined in...
workers blood. A critical review and analysis of the available raw data from the Zhang et al. (2010) paper identified methodological limitations that raise questions regarding the strength of these findings (Gentry et al. 2013). An important finding was the reported aneuploidy of chromosomes 7 and 8 reported in the peripheral blood hematopoietic precursor cells (HPCs) in a subgroup of 10 heavily exposed workers -- referred to in the literature review of the Documentation as “leukemia-specific chromosome changes.” The frequencies of these aneuploid cells (i.e., monosomy [chromosome loss] for chromosome 7 and trisomy [chromosome gain] for chromosome 8) were reported to be significantly higher in exposed workers than in controls, with the monosomy 7 frequencies approximately 8-fold greater than the trisomy 8 frequencies (Zhang et al. 2010). However, the study did not follow the criteria described in the Methods section of the paper -- criteria that state that at least 150 metaphases per subject should be counted (Gentry et al. 2013). The differences reported by Zhang et al. (2010) were seen only in instances where fewer metaphases were counted; there would not have been any significant differences observed between exposed and controls for monosomy 7 or trisomy 8 had the authors’ own criteria been followed (Gentry et al. 2013).

Lan et al. (2015) report aneuploidy in peripheral blood HPCs derived from blood samples from a subgroup of the same cohort examined previously (Zhang et al., 2010). This subgroup included 29 formaldehyde-exposed workers with measured median formaldehyde concentrations of 1.38 ppm (8-hour TWA) and 21 controls, and was chosen as having a suitable number of metaphases for analyses. The protocol, identical to that used in the first study (Zhang et al., 2010), tested blood samples that had been stored since 2006. In this follow-up study (Lan et al., 2015), the analysis was extended to examining all chromosomes, both structural changes as well as numerical. Authors report that aneuploidy, including monosomy, trisomy and tetrasomy, were higher for all or almost all chromosomes in the exposed worker group compared to controls. For structural chromosome changes, statistically significant increases were only found for chromosome 5, not trisomy 8, in contrast to the findings of Zhang et al. (2010). Although the raw data from Lan et al. (2015) were not examined, the protocol used was identical to the original protocol (Zhang et al., 2010), and is thus subject to the same methodological concerns.

Both these reports (Zhang et al., 2010; Lan et al., 2015) imply that aneuploidy arose in vivo in bone marrow-derived HPCs in the peripheral blood. However, the protocol used to identify HPCs (described in Zhang et al., 2010) does not support an in vivo origin of cells with chromosome alterations. The methodology used to identify the rare HPCs in peripheral blood, the CFU-GM assay, requires 14 days of in vitro culturing of peripheral blood cells to allow individual HPCs to differentiate into granulocytes or macrophages and grow into identifiable colonies -- termed CFU-GM colonies. However, Zhang et al. (2010) (and presumably Lan et al. 2015) obtained metaphase spreads for FISH analysis by pooling all cells from the complete collection of colonies on Petri dishes with identifiable CFU-GM colonies before using FISH to analyze the metaphase spreads. Therefore, although these studies count aneuploid metaphases derived from the entire population of CFU-GM colonies present in a Petri dish, they do not characterize the individual colonies themselves. This is critical because if the aneuploidy cells arose in vivo, the resulting colonies would contain 100% aneuploid cells, with all of the progeny of that initial aneuploid cell also reflecting the chromosomal changes. However, it appears that the protocols these authors followed destroyed individual CFU-GM colonies by pooling cells to obtain metaphases for analysis. Analysis of the data from the Zhang et al. (2010) study indicates that, rather than arising in vivo, the cells with altered chromosomes likely occurred during in vitro culture (Albertini and Kaden, submitted). The literature summary within the ACGIH Documentation states: “The issue of biological plausibility is unresolved (Gentry et al. 2013; Pyatt et al. 2008; Goldstein 2011; Zhang et al., 2010; and Lan et al., 2015).” This simple summary glosses over the details of the controversy. It is important to understand the potential uncertainties in the conclusions from the Zhang et al. and Lan et al. studies and consider that in drawing conclusions regarding the biological plausibility of an association between formaldehyde exposure and leukemia. In this case, two papers from the same laboratory (Zhang et al. 2010; Lan et al. 2015) are used to support the statement, even though both studies examined the same worker population, used the same protocol, and had the same limitations. Goldstein (2011) concluded: “Replication of the findings of Zhang et al. remains central to the question of whether formaldehyde should be considered to be a known rather than a probable human leukemogen -- particularly without a clear understanding of the mechanism by which inhaled formaldehyde reaches bone marrow stem cells or without further independent replication of the epidemiological association of formaldehyde exposure with leukemia.” As noted, the Lan et al. (2015) study does not independently replicate the findings, and may in fact have used the same pooled cell population as the Zhang et al. (2010) study.
In addition to these noted concerns regarding the biological plausibility, new research also illustrates a lack of association. For example, in 2014 and 2015, NIEHS scientists presented research at the Society of Toxicology annual conferences exploring the hypothesis that formaldehyde may cause leukemia by causing genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. The results indicated that formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in the mice; Similarly, no cases of leukemia or lymphohematopoietic neoplasia were seen following formaldehyde inhalation in genetically predisposed C3B6.129F1-Trp53tm1Brd mice. Therefore, the newer toxicology studies continue to demonstrate the lack of a clear or convincing relationship between formaldehyde exposure and leukemia, or other lymphohematopoietic cancers.

ACGIH also states: “There is additional evidence from epidemiologic studies (Beane Freeman et al., 2009, Hauptmann et al., 2009, Meyers et al., 2013, Stayner et al., 1985) suggesting that formaldehyde exposure may be associated with increased risk of myeloid leukemia.” However, after further analysis of the NCI workers cohort, Checkoway et al. (2015) reported that acute myeloid leukemia, the type of leukemia mostly likely to be related to chemical exposure, was unrelated to cumulative formaldehyde exposure, or even exposures to peak exposure to formaldehyde (Checkoway et al. 2015). Moreover, Meyers et al. (2013) notes “We continue to see limited evidence of an association between formaldehyde and leukemia.” With respect to internal comparisons for myeloid leukemia, Meyers et al. (2013) reported “When we evaluated the effect of follow-up time on the risk of leukemia, RRs remained near unity for all time periods. For myeloid leukemia we observed an overall decline in risk towards unity through 1997. The RR for myeloid leukemia approached significance only in 1992. When we examined time windows, we observed little evidence of increased leukemia or myeloid leukemia risk with more recent exposure in the overall cohort.”

As noted in Section 2, these studies only provide limited evidence as reported by the authors of these studies (with the exception of Beane Freeman et al. 2009). No excess mortality from leukemia was seen when exposed populations were compared to external referent populations in the Beane Freeman et al. (2009) or Meyers et al. (2013) papers. (In addition, the Meyers et al. (2013) paper is an update of the Stayner et al. (1985) study, and they should not be considered independent studies.) Finally, there are a number of issues with the Hauptmann et al. (2003) study, including missing data in the exposure assessment, trend tests that were not reported for certain analyses – the validity of that study is therefore called into question. Importantly, Coggon et al. (2014) does not show any increased risk of leukemia, yet is not discussed in this context by ACGIH. All of these factors should be considered in an overall weight-of-evidence discussion of a potential association between formaldehyde exposure and myeloid leukemia.

4.2 Mechanistic Considerations (Threshold vs Non-Threshold)

There is ample evidence in animals that there is an observed threshold for many of the biological consequences of formaldehyde exposure (reviewed in Swenberg et al., 2013; WHO, 2010). For example, no histopathological changes were observed in rats exposed to up to 1.0 ppm for 2 years (Woutersen et al. 1989). Rhinitis, epithelial dysplasia and even papillomatous adenomas and squamous metaplasia of the respiratory epithelium of the nose were only found at formaldehyde concentrations of 2 ppm or more (Kerns et al. 1983; Swenberg et al. 1980). Similarly, squamous cell carcinomas were only observed at concentrations of 6 ppm or more (Kerns et al. 1983; Swenberg et al. 1980). At the 6 ppm concentration, transient increases were observed in nasal mucosa cell proliferation; cell proliferation rate increases were more long-lasting starting at 10 ppm exposures (Monticello et al. 1996). Molecular markers, such as DNA-protein crosslinks, also show this trend, with disproportionately greater amounts of DNA-protein cross-links per ppm formaldehyde at exposures of 6 ppm and greater, believed to reflect saturation of detoxification pathways (Casanova-Schmitz et al. 1984; Heck et al. 1990). Taken together, these studies suggest a threshold for both nasal squamous cell carcinoma and cell proliferation in rats exposed to formaldehyde, with no effects at concentrations of 6 ppm and below (Swenberg et al., 2013). Biologically-based models suggest that risks for developing nasal cancers significantly decrease at lower exposures—concentrations below 2 ppm (reviewed in Swenberg et al., 2013). Importantly, sensory irritation appears to occur at lower formaldehyde concentrations than cytotoxic irritation (Bruning et al. 2014). Thus, outcome measures such as eye irritation and nasal irritation may occur well below the threshold for adverse health outcomes.

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Based on the animal studies, it is clear that there is a threshold below which tumors do not occur, with an upward bend to the dose-response curve for tumors most evident at concentrations ≥2 ppm (Kerns et al., 1983; Monticello et al., 1996). There is a very similar dose-response profile for other effects such as cell proliferation (Monticello et al., 1996), formation of DNA-protein crosslinks (Casanova et al., 1991) and DNA adducts (Lu et al., 2011), suggesting that these endpoints are all limited by the same factors. For shorter, sub-chronic exposures (13 weeks) tumors were only observed in animals exposed to 20 ppm formaldehyde (Feron et al. 1988), which parallels the evidence for cell damage (hyperplasia, squamous metaplasia).

### 4.3 Endogenous Formaldehyde

Formaldehyde is an essential metabolic intermediate in all cells, and is produced endogenously in the body. It is an essential intermediate in the biosynthesis of purines, thymidine and certain amino acids. Owing to its high reactivity at the site of contact and rapid metabolism, inhalation exposure of humans, monkeys, or rats to formaldehyde does not alter the concentration of formaldehyde in the blood from that endogenously present. Modeling studies describing the absorption and removal of inhaled formaldehyde in the human nose predict that exposures in the range of 0.125–12.5 mg/m³ only cause extremely small increases in formaldehyde concentrations compared to the pre-exposure concentrations (reviewed in WHO 2010). Using radiolabeled and deuterated formaldehyde, Swenberg and others have shown that formaldehyde-related protein adducts, DNA adducts, and DNA-protein cross-links are present throughout the body, but only the adducts and cross-links at the site of exposure are related to exogenous formaldehyde exposures (reviewed in Swenberg et al. 2013).

### 5 CONCLUSION

#### 5.1 A1 Category “Confirmed Human Carcinogen” Is An Inappropriate Classification, Given The ACGIH Guidance

The current ACGIH TLV cancer classification recommendation (established in 1985) is A2 “Suspected Human Carcinogen.” The change of this to cancer classification, as proposed in the NIC to the A1 category “confirmed human carcinogen” therefore requires justification. The justification for this change to category A1 “confirmed human carcinogen” is not provided in the NIC. Furthermore, given ACGIH guidance for the A1 category “confirmed human carcinogen” (ACGIH 2012), the change to A1 category does not reflect weight-of-evidence based on epidemiology. The current ACGIH cancer classification category A2 “Suspected Human Carcinogen” is more appropriate, and in line with other worldwide regulatory bodies, given the current epidemiologic evidence that suggests no excess risk of upper respiratory tract cancer among populations of workers exposed at the level causing nasal irritation in humans. For these and other reasons outlined above, the change to a cancer classification category A1 “confirmed human carcinogen” is not justified.

#### 5.2 The Proposed Recommendations For A 0.1 ppm TLV-TWA Is Without Justification

The strongest basis for a TLV comes from the recent controlled human exposure studies (Lan et al. 2008; Mueller et al. 2013). Exposures in these studies were complex: some reflected a constant formaldehyde concentration and others reflected a baseline formaldehyde concentration and a series of short, high peak exposures. Eye irritation, as measured by blink frequency, was found to be the most sensitive parameter, with minimal irritation noted at the 0.5 ppm plus 1.0 ppm peak exposure regimen (the LOEL). From this, authors identified the 0.5 ppm alone (no 1.0 ppm peak exposure) and the 0.3 ppm plus 0.6 ppm peak exposure as the highest exposures without effects (the no-effect level). Although ACGIH notes the 0.5 ppm baseline, 1 ppm peak exposure group as the basis of the TLV recommendation, they appear to ignore the peak exposures and instead focuses on the 0.5 ppm baseline exposure. If this 0.5 ppm exposure is the basis of the TLV-TWA, it is not clear how this led the ACGIH to propose a 0.1 ppm TLV-TWA. If the 0.3 ppm/1.0 ppm mixed exposure is being examined in context of workday exposure, it is not clear how these exposures (3 hours at 0.3 ppm with a total of 1 hour – four 15 minute intervals – at 1 ppm) led the ACGIH to propose a 0.1 ppm TLV-TWA. If anything, the Andersen and Molhave (1983) study supports the concept of adaptation at continued exposures. Therefore, it is inappropriate to use these combination exposure scenarios to set a TLV-TWA. Furthermore, if the Lang et al. (2008) study is the basis of a TLV-TWA, the contrasting negative results of the Mueller et al. (2013) study must be discussed, and justification of picking one study over the other must be provided. ACGIH cites the Andersen and Molhave (1983) study as demonstrating a LOAEL of 0.3 mg/m³ for eye, nose, or throat irritation. However, this publication simply summarizes a previous study for these effects, and the summary should not be relied upon for analysis.
Combined, these studies support the concept that a TLV-STELE will be protective for longer-term exposures. If the TLV-TWA is being proposed as being protective of cancer, then evidence must be provided that the recommended concentration is relevant for the mechanism believed to be involved in cancer. There is evidence that the critical event is induction of cell proliferation, and that induction of cell proliferation has a threshold. The threshold concentration at which cell proliferation is induced is much higher than the concentration showing mild irritation, indicating that any short-term TLV-STELE will also be protective of effects from chronic exposures.

5.3 The Proposed Recommendation For A 0.3 ppm TLV-STELE Is In Line With The Current 0.3 ppm TLV-CEILING (Established In 1992). However, Even This Value Is Not Justified By Literature

Again, the best evidence for the TLV-STELE comes from the two recent controlled human exposure studies (Lang et al. 2008; Mueller et al. 2013). Eye irritation, as measured by blink frequency, was found to be the most sensitive parameter, with minimal irritation noted at the 0.5 ppm plus 1.0 ppm peak exposure regimen (the LOEL). From this, authors identified 0.5 ppm alone (no 1.0 ppm peak exposure) and 0.3 ppm plus 0.6 ppm peak exposure as the highest exposures without effects (the no-effect level). Since the stand-alone 0.5 ppm exposure did not result in measured effects, it is clearly the presence of the 1 ppm peaks that is associated with the increased blink frequency. It is not clear how this series of 15 minute, 1 ppm exposures supports a TLV-STELE of 0.3 ppm.
COMMENTS ON ACGIH NOTICE OF INTENDED CHANGE FOR FORMALDEHYDE

APPENDIX A: REFERENCES


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Feron, V J, P Bruynjtes, R A Woutersen, H R Immel, and L M Appelman. 1988. "Male Wistar Rats Were Exposed to 0, 10 or 20 Ppm Formaldehyde Vapour for 4, 8 or 13 Weeks (6 H / Day ; 5 Days / Week), and Were Then Observed for Periods up to 126 Weeks . Transient Growth Retardation Occurred in Both Test Groups . Death Rate Was Not." *Cancer Letters* 39 (39): 101–11.


RAC. 2012. *Committee for Risk Assessment RAC Opinion Proposing Harmonised Classification and Labelling at EU Level of Imazalil ( ISO ) EC Number : 252-615-0 CAS Number : 35554-44-0 CLH-O-000002720-08-03 / F Adopted*. Helsinki.


COMMENTS ON ACGIH NOTICE OF INTENDED CHANGE FOR FORMALDEHYDE


Scientific Committee on Occupational Exposure Limits (SCOEL). 2015. Formaldehyde Scientific Committee on Occupational Exposure Limits for Public Consultation at the Latest.


APPENDIX B: DETAILS OF STUDIES REVIEWED FOR PROPOSED TLVS

In addition to the discussion provided in Sections 1-6, above, this Appendix provides additional detail of the studies relied upon in the ACGIH Documentation, and additional comments on the presentation of studies. All references are provided in the Reference Section, Appendix A.

1 Basis of NRC 2011 Cancer Classification

In 2011, an NRC committee evaluated the Draft US Environmental Protection Agency (US EPA) Toxicological Summary in support of the Integrated Risk Information System (IRIS). The US EPA issued a draft toxicological summary that concluded that formaldehyde exposure caused cancers of the nasopharyngeal, leukemia and Hodgkin lymphoma in humans. Upon review, the NRC (2011) committee noted many problems with the US EPA assessment, including:

- Apparent inconsistency with respect to which upper respiratory cancer sites were causally related to formaldehyde exposure. The NRC (2011) reported that, on the basis of US EPA’s guidelines, sufficient evidence exists of a causal association between formaldehyde and cancers of the nose and nasal cavity (ICD8 160) and nasopharynx (ICD8 147), but not other sites of respiratory tract cancer.

- Inconsistency between the results for the 10 facilities included in the National Cancer Institute (NCI) cohort study (Hauptmann et al. 2004, updated by Beane Freeman et al. 2013) and weakness of the exposure-response relationship for NPC in connection with cumulative exposure.

- Lack of explicitly stated criteria used by the EPA to determine the causality for cancer, and lack of clarity regarding how the US EPA determined the weight and strength of evidence. (This applied to both upper respiratory cancer sites, as well as the lymphohematopoietic cancers.)

- Dose-response analysis for NPC was based on Hauptmann et al. (2004), which was recognized to have incomplete vital status ascertainment and was missing deaths from the analysis.

- For LHP cancers, the US EPA should focus on the most specific diagnoses available in the epidemiologic data. The category “all LHP cancers” combines diverse cancers that are not closely related in cells of origin and in other characteristics.

- Lack of concise descriptions of background for certain studies and evaluations of speculative hypotheses.

- Inadequate discussion of the specific strengths, weaknesses, and inconsistencies in several key epidemiology studies.

- Lack of support for plausible biological hypothesis supporting systemic delivery of formaldehyde to sites (e.g., leukemia) distant from the portal site of entry.

Separately, a NRC committee (2014) was charged with reviewing the formaldehyde assessment by the NIEHS NTP for the 12th RoC.

2 Human Exposure Studies

A number of studies are cited as supporting the TLV recommendations. Of these studies, the controlled human exposure studies (chamber studies) provide the most interpretable results. We summarize these studies and their interpretation below. The occupational studies carry many confounding issues (uncontrolled exposure concentrations, co-exposures, improper controls), but are discussed here for completeness.

The Lang et al. (2008) study is a well conducted study of 21 volunteers exposed to formaldehyde under controlled conditions, and was highlighted by ACGIH as one of the studies the TLV recommendation is based on. This study involves 21 volunteers (11 men, 10 women) who were exposed to formaldehyde in a double-blind and random order in a 30 m³ exposure chamber over a 10 week period using a repeated measure design. Each person was exposed for a 4 hour duration, and exposures included both a constant exposures to 0, 0.15, 0.3, or 0.5 ppm (corresponding to approximately 0, 0.19, 0.38, or 0.63 mg/m³) as well as, in some exposure scenarios, a peak exposure of up to 1
COMMENTS ON ACGIH NOTICE OF INTENDED CHANGE FOR FORMALDEHYDE

ppm. In these exposure scenarios with peaks, people were also exposed to a series of four transient exposures of 0.6 (approximately 7.6 mg/m³) or 1.0 ppm (approximately 1.24 mg/m³). In addition, some of the exposures included exposure to a masking agent, ethyl acetate. Measures of health effects included assessment of conjunctivitis redness, blinking frequency, nasal resistance and flow, various pulmonary function measures, reaction times, and subjective ratings of physical and mental state. Eye irritation, as measured by blink frequency, was found to be the most sensitive parameter, with minimal irritation noted at the 0.5 ppm plus 1.0 ppm peak exposure regimen (the lowest observed effect level). From this, authors identified the 0.5 ppm alone (no 1.0 ppm peak exposure) and the 0.3 ppm plus 0.6 ppm peak exposure as the highest exposures without effects (the no-effect level). The Lang et al. (2008) study was also selected by WHO (2010) as a key studies to base the formaldehyde indoor air quality guideline upon.

The more recent Mueller et al. (2013) study examined the chemosensory effects of formaldehyde on hyposensitive and hypersensitive men exposed to formaldehyde in a 30 m³ exposure chamber for 5 consecutive days, 4 hours per day. Hypo- and hypersensitivity were determined based on nasal sensitivity to CO₂. Exposure concentrations in the chamber were either a single exposure to 0, 0.5, or 0.7 ppm formaldehyde, or at a baseline exposure of 0.3 ppm or 0.4 ppm with a set of 4 intermittent 15 minute peak exposures of 0.6 or 0.8 ppm, respectively. Subjective measures of symptoms, as well as conjunctival redness, eye-blink frequency, self-reported tear film break-up, and nasal flow rates were assessed. None of the formaldehyde exposure concentrations, including the 0.7 ppm constant or 0.4 ppm with peak exposures to 0.8 ppm resulted in any changes in these measured parameters. The only significant difference noted was for olfactory perception of “impure air,” particularly in the hypersensitive group.

This study, which was published in 2013, was not included in the ACGIH assessment. Like the Lang et al. (2008) chamber study, this study was a carefully controlled set of exposures with a series of objective measures of sensitive effects. The Mueller et al. (2013) study established a NOAEL of 0.7 ppm (constant) as well as 0.4 ppm with 0.8 ppm peak exposures.

Anderson and Molhave (1983) reported on a series of 5 previously published controlled human exposure studies involving formaldehyde, with additional data reported for one of these studies. Some studies examined transient eye or airway irritation, and others examined detection of odor. In one study, male volunteers were exposed either continuously to formaldehyde, or an alternating exposure to formaldehyde and clean air. Those continuously exposed subjectively reported better air quality than those exposed on-and-off, even if the formaldehyde concentrations were identical. Providing additional results from a previously reported study by the authors, Anderson and Molhave (1983) reported decreases in nasal flow rates in the anterior portion of the nose (but not the posterior regions) in volunteers exposed for 4-5 hours duration to formaldehyde concentrations of 0, 0.3, 0.5, 1, and 2 mg/m³. The authors reported more of an effect following exposure to 0.5 mg/m³ compared to 0.3 mg/m³, but no further effects following exposure to 1 or 2 mg/m³. Similarly, while effects were seen after 1-3 hours of exposure, further effects were not seen when exposures were increased to 4-5 hours of exposure. They also discussed the study examining eye and airway discomfort, reporting that during the first 2 hours of exposure, no discomfort was reported following exposure to 0.3 or 0.5 mg/m³, but that longer exposures produced discomfort, with less of an effect following exposure to 0.5 mg/m³ than 0.3 mg/m³. Discomfort was reported in the first hour of the 1 and 2 mg/m³ exposure groups, but stabilized or decreased with longer durations. Overall, subjects reported plateaueing or lessening symptoms at higher concentrations or durations of exposure, which the authors suggest implies adaptation to the irritating effects.

ACGIH cites Anderson and Molhave (1983) as demonstrating a LOEL for decreased mucocilliary flow rate in the anterior region of the nose (although in the basis for the TLV section they refer to this as an adverse effect) of 0.3 mg/m³. While true, this statement skips much of the detail showing that effects did not persist or worsen with prolonged or higher (1 or 2 mg/m³) exposures. Similarly, ACGIH cites this study as demonstrating a LOAEL of 0.3 mg/m³ for eye, nose, or throat irritation. One important limitation to this study is the lack of a control group with a sham exposure, something that the ACGIH evaluation does not acknowledge.

Alexandersson and Hedenstierna (1988) reported on a group of workers in the wood industry who use acid-hardening lacquers to finish the wood. These lacquers involve formaldehyde-containing amino resins, which can
release free formaldehyde. In this study, exposures and endpoint including pulmonary function measures, immunology measures, and work-related symptoms such as eye, nose, and throat irritation. The measured formaldehyde exposures in exposed workers ranged between 0.12-1.32 mg/m³, with a mean 8-hour TWA of 0.4 mg/m³. Peak exposures averaged 0.7 mg/m³, with a range of peaks between 0.14-2.60 mg/m³. Results in these workers were compared to an unexposed local control population from the same factory (exposures not reported). Although the percentage of non-smokers in the control group was greater than in the exposed workers, the authors concluded that the formaldehyde -exposed non-smokers had a relatively larger decrease in lung function than formaldehyde -exposed smokers, so discounted that difference in the two populations. The authors reported eye, nose, and throat irritation to be more commonly reported by exposed workers than controls. Lung function measures were decreased in formaldehyde -exposed workers following 2 days outside the workplace (weekends), but no differences in lung function measures were observed across a work shift. Further, changes in pulmonary function only correlated across groups, and did not correlate with exposure measures (peak, mean, or duration).

Subjective respiratory symptoms and spirometry measures were used to evaluate effects of formaldehyde on mucus membranes and the lungs in 109 workers employed at particle board or molded products operations (Horvath et al. 1988). Comparisons were made to a control population of 254 individuals employed at nearby food-processing facilities. Formaldehyde concentrations were assessed using active and passive monitors, with eight-hour, TWA concentrations ranging from 0.17 to 2.93 ppm (0.26 to 4.4 mg/m³), a mean formaldehyde concentration of 0.69 ppm (1.04 mg/m³), and a median concentration of 0.62 ppm (0.93 mg/m³) in the particle-board and molded products workers, and concentrations of 0.05 ppm (0.08 mg/m³) in the food-processing workers. Authors reported a dose-dependent excess of irritant symptoms and a decline in certain lung function parameters in formaldehyde-exposed workers. No group-related differences in spirometry measures or respiratory symptoms were observed, but authors reported a correlation between formaldehyde exposure and pulmonary changes.

Irritation, histopathological changes and cell toxicity in the nasal mucosa were examined in 75 men with occupational exposures to formaldehyde or to a combination of formaldehyde and wood dust (Edling et al., 1988). Exposed individuals worked in one of three plants: two processing particle boards and one processing laminate. Findings in these workers were compared to an age- and smoking habit-matched control group of 25 men without industrial exposure to formaldehyde. Formaldehyde concentrations in the plants were measured during the 1975-1983 time period in the range of 0.1 – 1.1 mg/m³, with peak exposures up to 5 mg/m³. The exposed group self-reported a history of nasal and respiratory symptoms, relating to irritation of the eyes, nose, and upper airways. Tissues samples from nasal biopsies revealed loss of cilia and hyperplasia or dysplasia in most of the workers in the particle board and laminate factories, with no difference between the group exposed to formaldehyde and wood dust (Particle Board factory) and those exposed only to formaldehyde (laminate). No relationship with estimated dose was observed.

The three occupational studies cited by ACGIH (Horvath et al. 1988; Edling, Hellquist, and Odkvist 1988; Alexandersson and Hedenstierna 1988) involved occupational exposures in industries where other irritants were present and where formaldehyde concentrations were high (generally above 1 mg/m³). These studies are therefore less desirable for basing LOAELs (and TLVs) upon, as they have both poorer exposure characterization and more possible confounding as compared to the controlled human exposure studies.

### 2.1 Upper Respiratory Tract Cancers

ACGIH cites one occupational cohort study and 5 population-based case-control studies in support of the A1 Confirmed Human Carcinogen Classification (p. 2 of Documentation, list item (1)). These studies appear to have been cited because they were considered to be of strong quality or moderately strong quality by the NRC (2014) committee. It appears, however, that these studies were selected primarily based on strength of a reported (positive) association; other strong or moderately strong quality studies that reported no increased risk of NPC and/or sinonasal cancers were not discussed in this section. Specifically, two large occupational cohort studies (Meyers, Pinkerton, and Hein 2013; David Coggon et al. 2014) reported no increased risk of NPC and sinonasal cancers after additional follow-up of mortality. One census-based cohort study of Finnish men employed during 1970 (Siew et al. 2012) suggested no increase in risk of NPC or nasal cancers, after adjusting for wood dust exposures. In addition, studies by Marsh et al. (2014, 2016) provide results of sensitivity analyses and subcohort
analysis (one of the 10 facilities included in the NCI cohort study). Most of the evidence supporting the NPC association is from population based-case control studies; however, only two of the population based case-controls studies evaluated previous infection with Epstein Barr virus. Epstein Barr virus is a recognized risk factor for NPC, although its role in the etiology of NPC is not yet understood (American Cancer Society, 2016).

2.1.1 Epidemiology Studies With Limitations Reporting a Positive Association With Formaldehyde Exposure

Beane Freeman and colleagues (2013) studied solid tumors in an update through 2004 of the NCI cohort of 25,619 workers in formaldehyde industry. These workers were exposed to formaldehyde at any of 10 facilities before 1966 and as early as 1934. The median duration of follow-up was 42 years. Risk of NPC was increased for workers with ≥4.0 ppm peak exposure (RR 7.66, 95% CI: 0.94-62.34, 7 deaths), workers with average intensity ≥1.0 ppm, (RR 11.54, 95% CI 1.38 - 96.81, 6 deaths) and cumulative exposure ≥ 5.5 ppm-years (RR 2.94, 95% CI 0.65-13.28, 3 deaths), when compared to the referent categories. Two of the 10 NPCs occurred among those not exposed to formaldehyde resulting in also resulting in increased risks when compared to the lowest exposure groups (RR 4.39, 95% CI 0.36-54.05 when compared to the group with peaks exposure 0 - < 2.0 ppm workers; RR 6.79, 95% CI 0.55-83.64 when compared to the group with average intensity 0.1 - 0.4 ppm; and RR 1.87, 95% CI 0.30-11.67 when compared to the group with cumulative exposure > 0 -<1.5 ppm-years).

Five of the 8 NPCs that had formaldehyde exposure worked in Plant 1 and these 5 were all peak exposures ≥ 4.0 ppm. In a sensitivity analysis in which the 5 workers from Plant 1 were excluded, 2 NPC deaths remained in the highest peak category (RR 3.36, 95% CI 0.3 - 37.27) (Beane Freeman et al. 2013). The apparent cluster of NPC seen at Plant 1 contrasts with deficits in NPC at the remaining facilities and this finding has been discussed by others (most recently by Marsh et al. 2016; 2014). Marsh et al. (2016) performed re-analyses of the NCI cohort and reported 6 of 11 NPC deaths occurred in Plant 1, while two deaths occurred in Plant 3 among workers in the lowest exposure category of highest peak, average intensity, and cumulative exposure. Marsh et al. (2016) reported a SMR of 7.34 (95% CI = 2.69-15.97) among workers exposed to formaldehyde in Plant 1 compared with a SMR of 0.82 (95% CI 0.17-2.41) among workers exposed to formaldehyde in Plants 2-10. Marsh et al. (2016) also reported a statistically significant interaction between formaldehyde exposure and plant group (Plant 1 vs. Plants 2-10), demonstrating plant heterogeneity.

Beane Freeman et al. (2013) reported no increased risk of nose and nasal sinuses in relation to average, cumulative, or peak formaldehyde exposure. Five deaths were observed, and two occurred among those who were not exposed to formaldehyde. Also, death certificate data did not allow Beane-Freeman et al. to identify histologic type of nose and nasal cancers, so it is unknown if these were squamous cells carcinomas.

Below are specific comments on the description of the study in the Draft Documentation, p. 26:

“The cohort consisted of workers in 10 industrial plants in the U.S., followed from January 1, 1966 through December 31, 2004,...”

Comment: Workers had to be employed before January 1966 in be included in the cohort. Follow up for mortality began earlier than 1966 for most of the cohort, as early as soon as employment records were complete for each of the 10 facilities (as early as 1934, as late as 1958).

“There were a total of 10 deaths from nasopharyngeal cancer. The overall SMR for NPC in workers exposed to formaldehyde was 1.84 (95% CI 0.84 - 3.49)."

Comment: Although there were a total of 10 deaths from nasopharyngeal cancer, the overall SMR for NPC in workers exposed to formaldehyde was based on 9 exposed deaths, instead of 8 exposed deaths. Beane Freeman et al. (2013) included one death that was reported as NPC on the death certificate, but for which information from secondary sources showed that it was actually due to oropharyngeal cancer (Beane Freeman et al. 2013). If the death had been correctly classified, the SMR for NPC in workers exposed to formaldehyde would be lower (SMR 1.64, 95% CI 0.71-3.23) and consistent with the overall SMR for NPC in workers not exposed to formaldehyde was 1.45 (95% CI 0.17-5.25) based on 2 deaths.
“Five of the 10 deaths from NPC occurred in one plant that had relatively high peak and average exposure compared to the other plants.”

Comment: In addition, the RR was elevated for NPC among the group that was not exposed to formaldehyde (RR=4.39, 95% CI 0.36-54.05, based on 2 deaths) as well as the group exposed to the highest average intensity (> 1 ppm). Excluding NPC deaths from one plant resulted in no increased risk for the remaining 9 facilities (Marsh et al. 2016). In addition, Marsh et al. (2016) reported that the risk estimates were sensitive to the choice of the referent group (using workers not exposed to formaldehyde as the referent group versus using low exposure categories of peak, average exposure, and cumulative exposure as the referent categories) (as chosen by Beane Freeman et al. 2013).

“The trend analysis suggested that peak exposure may be more important in determining the risk of NPC (p-trend = 0.005)”

Comment: This is an incorrect interpretation of the trend test. The size of the effect and the precision of the confidence interval provides more important information for evaluating an exposure-response relationship than the p-value for the trend (see figures reported by Marsh et al. 2016). The p-value for the trend test merely provides information regarding differences in the risk estimate in categories relative to the referent category and does not provide information on the shape of the dose-response curve. Also, the RR for NPC in the highest peak category was non-statistically significant (RR 7.66, 95% CI 0.94 - 62.34) while the RR for the highest average intensity was significantly increased (RR 11.54, 95% CI 1.38 - 96.81). In combination, this suggests that peak exposure is not the exposure metric that determines the risk of NPC.

In addition, the ACGIH Documentation cites population case-control studies (Hildesheim et al. 2001; Vaughan et al. 1986a; 1986b; 2000; West et al. 1993).

Vaughan et al. conducted a population-based case-control study of NPC and sinonasal cancers to evaluate occupational formaldehyde exposure (Vaughan et al. 1986a) and residential formaldehyde exposure (Vaughan et al. 1986b). A total of 27 NPCs and 53 sinonasal cancers diagnosed during 1979-1983 and reported to a population-based cancer registry in Washington State. A total of 552 controls were selected by random digit dialing. Formaldehyde exposure was assigned using a job-exposure matrix which classified jobs based on expert judgement of likelihood (unlikely, possible, or probable) and intensity (high levels / low levels) of formaldehyde exposure. The authors reported no statistically significant associations between occupational formaldehyde exposure and NPC or sinonasal cancers; however risks were increased for the highest exposure score categories for NPC (OR=2.1, 95% CI 0.40 - 10.0) after excluding jobs that occurred approximately 15 years before diagnosis for cases and date of interview for controls. The results of residential exposures reported that those living in mobile homes for 1 to 9 years and 10 or more years had increased risks of NPC (OR 2.1, 95% CI 0.7 to 6.6 based on 4 cases and 64 controls OR 5.5, 95% CI 1.6 1 - 19.4 based on 4 cases and 18 controls); however, no associations were seen with living in residences with inside construction of particle board or plywood.

Vaughan et al. (2000) conducted a population-based case-control study of 196 incident cases of NPC diagnosed 1987-1993 from 5 cancer population-based cancer registries (Washington, Detroit, Connecticut, Iowa, and Utah) that participated in the Surveillance Epidemiology and End Results program (Vaughan et al. 2000). A total of 244 controls were identified by random-digit dialing. Occupational history and chemical exposures were collected using a structured telephone questionnaire. (Approximately 19% of the interviewed cases were conducted with proxies, typically spouses; only 1.2% of control interviews were with proxies). A total of 79 cases reported working previously in a job with exposure to formaldehyde compared to 70 controls (OR=1.3, 0.8 - 2.1 for all epithelial carcinomas). Of those with differential squamous cell carcinomas, the OR was 1.5 (95% CI 0.8 -2.7). No association was seen between NPC and maximum exposure received. No association was seen with increasing cumulative exposure (ppm-years) for 27 cases of squamous cell epithelial not otherwise specified with probable or definite formaldehyde exposure, compared to 30 controls with probable or definite exposure. In contrast, only 17 cases reported wood dust exposure (compared to 24 controls). No association with maximum exposure, duration of exposure, or cumulative exposure was seen with wood dust exposure, and the risk estimates were decreased after
adjusting for formaldehyde exposure. Authors concluded that the “results supported the hypothesis that occupational exposure to formaldehyde, but not wood dust, increases the risk of NPC.”

Hildesheim et al. (2001) conducted a population-based case-control study of 375 incident NPC cases and 325 community controls in Taipei, Taiwan. The authors reported no statistically significant increased risks of NPC in relation to formaldehyde exposure based on 74 cases and 41 controls exposed to formaldehyde (RR=1.4, 95% CI 0.93 - 2.2), after controlling for age, sex, education, and ethnicity. Risks of NPC did not appear to increase with duration of exposure or cumulative exposure after excluding exposures that occurred in the 10 years preceding diagnosis or interview. However, the authors reported consistent associations between wood dust exposure and risk of NPC (RR=1.7, 95% CI 1.0 - 3.0) based on 52 exposed cases and 26 exposed controls, after adjusting for age, sex, education, and ethnicity. With respect to the study as reported in the Documentation, the paragraph on Hildesheim et al. (2001) reports “After stratification by EBV status, there was a statistically significant association between NPC and formaldehyde exposure (RR=2.7, 95% CI 1.2 - 6.2).”

For clarification, the RR of 2.7 (95% CI 1.2 - 6.2) was among EBV-positive subjects after adjusting for age, sex, education, and ethnicity. Risk estimates were not provided for EBV-negative subjects (of which there were only 15 of 375 cases and 231 controls in the entire study). More than 95% of cases were positive for EBV, and it is difficult to disentangle the effect of EBV in the analysis. At the very least, the results suggest that Epstein Barr virus possibly modifies the association seen with formaldehyde exposure.

No dose response patterns were seen with increased duration of exposure or cumulative exposure. In contrast, relative risks for wood dust exposure increased with duration, and cumulative exposure, and were greatest in the highest categories of wood dust exposure (RR=2.4, 95% CI 1.2 - 5.1) for cumulative exposure ≥ 25 unit-years (intensity x duration) and RR=2.4 (95% CI 1.1 - 5.0) for duration of exposure > 10 years. The authors noted that the risk estimates for wood dust exposure did not change materially after adjustment for formaldehyde exposure and likewise, the risk estimates for formaldehyde did not change materially after adjustment for wood dust exposure.

Several limitations are noted. No direct exposure measurements were available. This study used job history information obtained from study subjects. The degree of misclassification for formaldehyde exposure and wood dust exposure was unknown. The NRC (2014) stated in its critique of this study “considerable overlap in wood dust, formaldehyde exposure; authors were concerned about greater misclassification for formaldehyde than wood-dust assignments.” In fact, Hildesheim et al. only speculated that “the potential for misclassification remains. In particular, if the degree of mis-classification is higher for formaldehyde and solvent exposure compared with wood dust exposure, this could explain our inability to demonstrate a clear association between formaldehyde and solvent use and NPC. Also, given that classification of exposure to hardwood versus softwood was made based on job histories alone, it is likely that this assessment is prone to misclassification, and our findings regarding hardwood versus softwood should therefore be viewed with caution.” (p. 1151).

West et al (1993) conducted a population-based case-control study of 104 NPC cases recruited from a hospital in the Philippines and 205 hospital and community controls. Among all cases and controls, the RR was 4.0 (95% CI 1.3 - 12.3) for subjects exposed to formaldehyde with at least 25 years or more since first exposure (14 cases, 10 controls) when compared to those never exposed to formaldehyde, after adjusting for education, occupational dust/exhaust exposures, consumption of processed meats and fresh fish, smoking, herbal medicines, and use of anti-mosquito coils. This analysis, however, did not lag exposures; as a result, the referent group (never exposed) excluded 8 cases and 3 controls exposed only in the 10 years immediately preceding diagnosis/interview (these exposures would be unlikely related to development of NPC, considering a disease induction period of 10 years or more). Curiously, the results were not adjusted for EBV status, however, despite an earlier study reporting a RR of 21.8 (95% CI 8.4 - 51.8) among study subjects from the same group of cases and controls who tested strongly positive for anti-EBV antibodies (based on 88 cases and 30 controls) (Hildesheim et al. 1992).

These studies (and other population-based case-controls studies) were limited by the exposure assessment. No formaldehyde measures were available. Exposure was estimated using expert judgment. Industrial hygienists estimated exposure to formaldehyde and wood dust for each self-reported job by assigning a probability of exposure to formaldehyde and an estimated 8 hour time-weighted average concentration. Of 21 jobs that were
reported to have definite exposure to formaldehyde, the 8 hr TWA was estimated to be <0.1 ppm for 17 while 4 jobs had estimated exposure of 0.10-0.50 ppm. In contrast, 9 jobs with possible formaldehyde exposure were estimated to have exposure >0.5 ppm (8hr TWA). Misclassification of exposure was likely, and it is not clear that the bias from misclassification of exposure was non-differential (toward the null).

2.1.2 Epidemiology Studies of High Quality Or Moderately High Quality That Show No Association With Formaldehyde Exposure

Industrial cohorts had measurably high concentrations of formaldehyde exposure. One limitation noted about results from industrial cohort studies is that NPC (as well as sinonasal cancers) are rare (NTP, 2014; IARC 2012). If an association is absent, inadequate statistical power to detect an association is frequently cited (Meyers, 2013; IARC 2012). If these occupational cohort studies had experienced mortality rates similar to those of the general population, only one or two NPCs or sinonasal cancers would be expected in the study population. Nevertheless, if formaldehyde exposure were strongly associated with these cancers, the association should be seen in these cohorts that experienced historically high formaldehyde exposures (Coggon et al. 2014; Meyers et al. 2013; Hauptmann et al. 2009). For example, angiosarcoma of the liver and mesothelioma are rare diseases; nevertheless, excess cancers were easily observed in cohorts that had high historical exposures to vinyl chloride and asbestos, respectively. In addition to the NCI cohort studied by Beane-Freeman et al. (2013), other cohorts (Meyers et al. 2013; Coggon et al. 2014) had known exposure to relatively high concentrations of formaldehyde in the past; however, no association between these tumors and formaldehyde exposure were reported.

Meyers et al. (2013) studied 11,098 garment workers at three manufacturing facilities employed for at least 3 months since 1955, when formaldehyde was first introduced to processes treat fabric. The investigators reported 0 deaths from nasopharyngeal cancers (1.33 expected) and 0 deaths from sinonasal cancers (0.95 expected). All workers had been exposed before 1980. Although exposures were not measured before 1980, an industrial hygiene survey performed in the early 1980s reported GM TWA exposures of 0.15 ppm (geometric standard deviation 1.90) (Meyers, Pinkerton, and Hein 2013). The range of arithmetic means across factories was 0.09 to 0.22 ppm (Elliott et al. 1987). The NIOSH investigators reported that the workforce was likely exposed to formaldehyde at higher levels during the years 1955 to 1978 than it was in 1988, and that exposure was reduced gradually to current levels (Elliott et al. 1987).

Coggon et al. (2014) studied 14,008 workers at 6 facilities in England and Wales. Workers began follow up as early as 1941. Coggon et al. reported only death occurred in a worker with low/moderate exposure (1.7 deaths expected for exposures above background exposure of 0.1 ppm (TWA). No deaths from cancers of the nose and nasal sinuses were observed (0 vs. 0.9 expected). Although the cohort was smaller than the US cohort of formaldehyde workers and producers, proportionally more workers (35%) were exposed to average intensity > 2 ppm (Coggon et al., 2003) than in the US formaldehyde workers cohort (4.7%, reported by Hauptmann et al. 2004). As a result, the absolute number of workers exposed to higher TWA formaldehyde levels was greater in the UK cohort (3,991 workers reported by Coggon et al. 2003) compared to the US cohort (1,204 workers). Coggon et al. (2014) concluded “Our results provide no support for an increased hazard of myeloid leukemia, nasopharyngeal carcinoma, or other upper airway tumors from formaldehyde exposure. These results indicate that any excess risk of these cancers, even from relatively high exposures, is at most small.” “The results did not indicate any excess risk for nasopharyngeal cancer.”

Siew et al. (2012) studied the cohort of all Finnish men born between 1906 and 1946 who were employed during 1970. A total of 292 nasal cancers and 149 NPCs were diagnosed and reported to the Finnish Cancer Registry during 1971-1995. After adjusting for wood dust exposure, socioeconomic status, age, period of follow-up, and smoking, no increased risk of nasal cancer (RR=1.11, 95% CI 0.66 - 1.87, based on 17 cases among formaldehyde-exposed workers) or of nasopharyngeal cancer (RR=0.87, 95% CI 0.34 – 2.20, based on 5 cases among formaldehyde-exposed workers) were observed when compared to those who were not exposed to formaldehyde. In contrast, the risk ratios for nasal cancer, nasal squamous cell carcinoma (a subset of nasal cancer) were increased for wood dust exposure after adjusting for formaldehyde exposure. Nasopharyngeal cancer
was not increased among Finnish men who had any exposure to wood dust (RR=0.66, 95% CI 0.30 - 1.45), after adjusting for formaldehyde exposure, socioeconomic status, age, period of follow-up, and smoking.

Based on the body of epidemiological literature, studies of increased NPC among industrial and professional workers with formaldehyde exposures are inconsistent and provide limited epidemiological evidence of a causal association.

2.2 Recommendations For Presenting Epidemiology Studies

Below we list comments and recommendations regarding the carcinogenicity section (pp. 26-30).

2.2.1 Include Brief Discussions Of Study Limitations

Epidemiology studies are observational studies and as such, they are subject to confounding and systematic bias. How these factors influence results is not discussed. For example, it is widely accepted in the industrial hygiene community that well characterized exposure data are necessary to estimate risks validly. Yet, many of the epidemiology studies had limitations with respect to exposure assessment. For example, the exposure reconstruction for Hauptmann et al. (2009) relied extensively on next-of-kin reports and more than 30% of the data were missing.

Separately, Hauptmann et al (2009) reported the same p-values for trend tests (p=0.04 for trend and p=0.02 for trend) in tables 3 and 4, calling into question some of the authors’ interpretations of the data (see Letter to the Editor by Cole et al. 2010; no response from authors).

Furthermore, exposure-response associations between peak formaldehyde exposures and diseases reported in updates of the NCI cohort (Beane Freeman et al. 2013; Beane Freeman et al. 2009) suggest that exposure data were stronger than a semi-quantitative approach. In earlier publications, authors stated clearly that measurements of peak exposure were not available (see Stewart et al. 1986). Hauptmann et al. (2003) in an earlier update was explicit: “No measurements of peak exposure were available…peak exposures were therefore estimated…from knowledge of the job tasks and a comparison with the 8-h time-weighted average.”

2.2.2 Improve Consistency Of Results Reported For Cancer Sites

If risks are reported for cancer sites (for example, brain, leukemia, and lung) other than NPC and/or sinonasal cancers, these risks should be consistently reported in all studies, and not only when statistically significant results are reported. For example, if some studies report brain cancer results because of increased risks, studies that report non-elevated brain cancer risks should also be reported so that a comprehensive picture of the consistency of findings is available for the reader.

Three studies reported in the documentation primarily address cancer outcomes other than NPC or sinonasal cancers (e.g., brain cancer, leukemia, Hodgkin Disease/NHL) (Beane Freeman et al. 2009; Michael Hauptmann et al. 2009; Partanen et al. 1993). These studies should be reported in a separate section from the studies that discuss NPC and sinonasal cancers.

In addition, NPC results were omitted from the Hauptmann et al. (2009) paragraph (p.29). Hauptmann et al. (2009) reported 4 deaths from NPC, including 2 deaths among study subjects who worked in jobs with embalming (OR = 0.1, 95% CI 0.01 - 1.2).

2.2.3 Provide Rationale For Relying Upon The NRC (2014) Review Of Formaldehyde And Discuss Limitations Of NRC (2014) Review

On p. 26, the Documentation says: “The following discussion will focus primarily on key studies of formaldehyde and nasopharyngeal cancers, which were considered to be strong or moderately strong in study quality in the U.S. National Academy of Sciences review (US NAS, 2014).”

No clear rationale is specified for using the NAS (NRC 2014) as an authoritative source. If the NRC (2014) review is cited, please note that the NRC review was undertaken to address the National Toxicological Program (NTP) Report on Carcinogens (RoC) assessment of formaldehyde. In the absence of explicit guidance, the NRC (2014) committee interpreted the RoC listing criteria for sufficient evidence of carcinogenicity as indicated by at least two
studies of moderately strong or strong quality that showed an association between formaldehyde exposure for a specific cancer site in two different study designs or populations. In addition, the study results could not be explained by chance, bias, and confounding. The NRC committee identified criteria for strong quality: studies of large populations that had gradients of well characterized exposure and sufficiently long follow-up to detect cancers. The NRC (2014) review did not consider limitations of the studies it identified as strong quality, nor did it consider studies reporting negative results when considering the consistency of findings.

In addition, the carcinogenicity section also cites literature that was considered to be weak (Roush et al. 1987; Armstrong et al. 2000) or was not cited (Olsen et al. 1984; Brinton et al. 1984; Brinton, Blot, and Fraumeni 1985; Hernberg et al. 1983) by the NRC (2014) committee.

2.2.4 Discount Results From Weaker Study Designs And Studies That Were Used To Generate Hypotheses (PMR Studies) And Do Not Represent Independent Study Populations

The NRC (2014) committee considered several proportionate Mortality Ratio (PMR) studies to be of strong or moderately strong quality. PMR studies are a weaker study design than case-control studies or cohort studies. Only deceased subjects are included in PMR studies, and the pattern of proportional deaths that occur among the decedents may or may not be representative of all deaths in the population that gave rise to them (i.e., assuming comprehensive follow-up of a cohort). PMR studies are frequently conducted when the only information that is available is information on decedents and PMRs are computed for a large number of diseases. By design, the number of observed deaths from all causes combined will equal the number of expected deaths; as a consequence, when some diseases show increased PMRs, other diseases will show deficits (and vice versa), making PMRs difficult to interpret. Certain causes of death reported in PMR studies are also be subject to differential selection bias (i.e., the “healthy worker effect”) (Checkoway et al. 2004). PMR studies can be used for preliminary analyses and to generate hypotheses, but the study design is not useful to test hypotheses. When only information on deaths are available, a more appropriate analysis is a case-control design (see Hauptmann et al. 2009). Descriptions of these studies belong under “Other Epidemiology Studies.”

Walrath and Fraumeni (1983; 1984) were exploratory analyses (hypothesis generating) of causes of death among deceased funeral directors and embalmers. Further, the Walrath and Fraumeni cohorts (1983, 1984) overlap significantly with Hayes et al. (1990) (listed under Other Epidemiology Studies) and Hauptmann et al. (2009). These studies should not be considered independent study populations. In addition, the section “Other Epidemiology Studies” also lists PMR or proportionate cancer incident (PCIR) studies.

The results from Hayes et al. (1990) supersedes Walrath and Fraumeni (1983, 1984) because there is significant overlap, and the population of deceased subjects is larger. In turn, this study is superseded by the case-control study conducted by Hauptmann et al. (2009).

Stayner et al. (1985) is a proportionate mortality study of garment workers exposed to formaldehyde. This study is not an independent population, but overlaps with the NIOSH garment workers cohort (Meyers, Pinkerton, and Hein 2013).

2.2.5 Review Results And Correct Data Omissions Or Errors In Reporting Study Results

The paragraph describing results from Andjelkovich et al. (1995) states “Smoking status was ascertained on 65% of the cohort.” For clarification, smoking status was ascertained for 65% of the exposed and 55% of the referent cohort.

“The SMR for lung cancer was 1.20 (95% CI 0.89 - 1.58) but this may be attributable to smoking and exposure to silica.” The SMR was 1.20 among exposed and 1.19 among not exposed.

The paragraph describing results from Stroup et al. (1986) states “There was one observed death (compared with 6.8 expected deaths) from the category “buccal cavity and pharyngeal cancers”.”
More specifically, Stroup et al. (1986) reported “No deaths from cancers of the nasal cavity or sinuses were found, and the SMR of 0.2 for cancers of the buccal cavity and pharynx was based on one death from salivary gland cancer.” This paper reported that estimates of formaldehyde exposure in anatomy or embalming at the time of the study were in the 1 to 3 ppm range, with higher concentrations encountered intermittently. Also, results for leukemia were elevated, but not statistically significant. The SMR for chronic myeloid leukemia was 8.8 and the confidence interval (95% CI 1.8-25.5) was provided on p. 1219 of Stroup et al. (1986). The results for leukemia could be described in a section on LHP results and results for brain cancer are only of interest, should a section on other cancers be deemed necessary.

The paragraph describing results from Bertazzi et al. (1989) includes results for cancer sites that showed statistically significant increased risks; however, the relationship with formaldehyde exposure is not clear (and may not be relevant). As noted in the last sentence in the paragraph “There were no statistically significant excess risks when the analysis was limited to the subcohort of workers exposed to formaldehyde.” Any results presented in this paragraph should be restricted to the subcohort of workers exposed to formaldehyde.

The paragraph describing Olsen et al. (1984) requires a correction and some further description: “In a study based on the Danish Cancer Registry, Olsen et al. (1984) observed a statistically significant excess risk among 839 cases of cancer of the nasal cavity and sinuses among adult males (relative risk = 2.8).” 839 is the number of cases among males and females. Among 560 males, the RR=2.8 (95% CI 1.8 - 4.3) for carcinoma of the sinonasal cavities. Among 279 females, the RR=2.8 (0.5 - 14.3) for carcinoma of the sinonasal cavities. After adjusting for wood dust exposure, the RR=1.6 (95% CI 0.7 - 3.6 based on 23 cases and 125 controls) for *males with 10 years or more since first exposure. Olsen and Asnaes (1986) used the same study subjects and restricted the analysis to 287 histologically verified cancers of the nasal cavity, 179 cancers of the paranasal sinuses and 293 cancers of the NPC. For squamous cell carcinoma of the nasal cavity and paranasal sinuses specifically, the authors reported a risk of 2.4 (95% CI 0.8 - 7.4) based on 8 cases and 81 controls), after adjusting for wood dust exposure for males with 10 years or more since last exposure.

### 2.3 Animal Studies

An early carcinogenicity study in F344 rats and C57BL/6 x C3H F1 mice examined large groups (approximately 120 male and 120 females each) of animals exposed by inhalation to formaldehyde at concentrations of 0, 2.0, 5.6, and 14.3 ppm, 6 hr/day, 5 days/week, for 24 months (Kerns et al. 1983). The exposure period was followed by an observation period of up to 6 months of without further formaldehyde exposures. Animals were sacrificed at intervals during the study, as well as at the end (30 months). Concentration-related lesions were observed in the nasal cavity and proximal trachea. Rhinitis, epithelial dysplasia, and squamous metaplasia occurred in all exposure groups of rats and in the intermediate and high exposure groups of mice. The rhinitis, dysplasia, and metaplasia improved 3 months post-exposure in the highest exposure groups of mice, and in the lower exposure groups of (2.0- and 5.6-ppm) of rats. Nasal cell squamous cell carcinomas were observed in the majority (103/120) rats and in 2 male mice exposed to the highest concentration (14.3 ppm) of formaldehyde; and in 2 rats exposed to 5.6 ppm formaldehyde.

In a shorter-term exposure study, Male Wistar rats were exposed to 0, 10 or 20 ppm formaldehyde for 4, 8 or 13 weeks (6 h/day; 5 days/week), and were then observed for 156 weeks (Feron et al. 1988). Although death rates were not different among groups, some initial growth retardation was observed in the formaldehyde-exposed animals. Histopathological changes (hyperplasia, squamous metaplasia) were observed in the nasal respiratory and olfactory epithelium of animals exposed to 20 ppm, with less severe changes of the respiratory epithelium (but not the olfactory epithelium) seen in a few animals exposed to 10 ppm. Formaldehyde-induced nasal tumors originating from the respiratory epithelium (squamous cell carcinomas, carcinoma in situ and polypoid adenomas) were only seen in the 20 ppm group (but not the 10 ppm group), primarily in those animals exposed for the full 13 weeks.

Examining the role of cell proliferation in nasal squamous cell carcinomas, as well as lower formaldehyde exposure concentrations, Monticello et al. (1996) exposed rats to lower concentrations of formaldehyde (0, 0.7, 2, 6, 10, or 15 ppm) under a similar protocol as the Kerns et al. (1983) study. They reported that formaldehyde induces nonlinear, concentration-related increases in nasal epithelial cell proliferation and squamous cell carcinomas. Formaldehyde
induced squamous cell carcinomas in a highly nonlinear fashion, with no observed effects at the level of 2 ppm or below, a minimal response at 6 ppm, and a sharp increase at 10 and 15 ppm. Increased cell proliferation, measured through uptake of [methyl-^3^H]-labelled thymidine into cells, was seen at formaldehyde concentrations of 6 ppm or more. Authors concluded that sustained increases of cell proliferation in nasal cells, coupled with previously demonstrated nonlinear kinetics of formaldehyde binding to DNA, account for the nonlinearity of formaldehyde-induced nasal cancer in rats.

For the animal studies, it is clear that there is a threshold below which tumors do not occur, with an upward bend to the dose-response curve for tumors in animals most pronounced at concentrations ≥2 ppm (Kerns et al., 1983; Monticello et al., 1996). There is a very similar dose-response profile for other effects such as cell proliferation (Monticello et al., 1996), formation of DNA-protein crosslinks (Casanova et al., 1991) and DNA adducts (Lu et al., 2011). For shorter, sub-chronic exposures (13 weeks) at tumors were only observed for the 20 ppm exposure group (Feron et al. 1988), which parallels the evidence for cell damage (hyperplasia, squamous metaplasia). Although the ACGIH document acknowledges the evidence for a non-linear dose-response relationship for nasal squamous cell carcinoma in animal and epidemiology studies, the animal studies provide clear evidence that this effect is not linear, only occurring at high exposures.