

## **Review of 2016 ACGIH Formaldehyde: TLV(R) Chemical Substances Draft Documentation, Notice of Intended Change**

### **Introduction**

The 2016 formaldehyde: TLV(R) Chemical Substances Draft Documentation, Notice of Intended Change recommends a Threshold Limit Value (TLV)-Time Weighted Average (TWA) of 0.1 ppm with a TLV-Short Term Exposure Level (STEL) of 0.3 ppm. This represents a significant reduction (i.e., 66%) from the existing TLV-CEILING of 0.3 ppm (2001). TLVs are intended to be protective for potential adverse effects from occupational exposure to a specific chemical. In the case of potential irritant effects of formaldehyde from such exposures, the key endpoint of concern, the data relied upon should be derived from inhalation studies in which formaldehyde was the only substance in the air available for inhalation. Consequently, while the present 2016 DRAFT ACGIH Formaldehyde: TLV(R) Chemical Substances Draft Documentation, Notice of Intended Change (hereafter DRAFT) reviews a variety of occupational exposure data, an evidence-based conclusion should be based upon data from studies conducted in a controlled environment. Indeed, much of the controlled human exposure data in the present DRAFT are identical to those in the Documentation for the 2001 TLV (e.g., Weber-Tschopp et al., 1977, Kulle et al. 1987, 1993, NRC 1980, 1981, IARC 1982, Bender et al. 1983, and Schuck et al. 1966). Essentially the same data have been used by ATSDR (1999, 2007), NAS (2007), WHO (2010), MAK (2006), OECD/SIDS (2002), NICNAS (2006), SCOEL 2015, Neilsen et al (2016) and most notably ACGIH (2001) to conclude that 0.3 ppm was an appropriate TLV. As discussed below, the empirical evidence from extensive human studies demonstrates that reported irritant effects below 0.3 ppm are no different from effects reported following exposures to clean air (i.e., 0 ppm) (i.e., false positives).

According to the ACGIH guidelines “*The purpose of the TLV® Documentation is to clearly describe, present and **interpret the appropriate scientific information** supporting the derivation of the TLV® and its associated notations for a given chemical.*” [emphasis added] While this process involves scientific judgement, given the above mandate it is unknown, and unexplained, how the available data summarized in Table 1 were “interpreted” to yield the DRAFT TLV of 0.1 ppm. This suggests that the criteria in the ACGIH Operations Manual (p. 4, i.e., scientifically credible, leading edge, well-supported, scientifically valid, reliable, understandable and clear, produced with a balanced, unbiased and clearly-defined process) may not have been adequately followed.

The DRAFT documentation does not provide the scientific reasoning for reducing by 66% the existing TLV to derive the proposed value of 0.1 ppm. It is assumed that the first two paragraphs of the DRAFT put forth the most compelling data supporting this change. The DRAFT cites two studies in support of the proposed TLV of 0.1 ppm. The first study (Lang et al. 2008) reports an effect threshold of 0.5 ppm. This study is entirely appropriate and supports the existing TLV of 0.3 ppm. However, the second study cited (Andersen and Molhave 1983), is a thirty-three year old, non-peer reviewed book chapter, which reported a LOAEL of 0.24 ppm for eye irritation, did not include a 0 ppm control, and, therefore, was incapable of determining if the reported 19% response rate at 0.24 ppm was real or a false positive. This conclusion is well-supported by at least four controlled studies (i.e., Kulle 1993, Sauder et al. 1987, Witek et al. 1987 and Bender et al. 1983) which report positive response rates between 5-39% at 0 ppm formaldehyde exposure. Consequently, the results from the Anderson and Molhave study with design flaws which have been shown to be incorrect by more carefully conducted studies, should not be afforded any weight in establishing an evidence-based TLV.

Furthermore, the practical consequences of re-interpreting the large body of controlled human data in order to change the TLV from 0.3 ppm to 0.1 ppm are substantial. Because 0.1 ppm is the upper range of formaldehyde found in normal indoor air (EPA 2011) it is unwarranted that the appropriate data (not to mention authoritative bodies around the world) supporting 0.3 ppm as an occupational TLV would be essentially ignored and seemingly arbitrarily reduced by 66% to set an occupational exposure limit equivalent to formaldehyde concentrations found in indoor air.

SCOEL (2008) proposed a TWA value of 0.2 ppm based on “...*possible interindividual differences in susceptibility to irritation by formaldehyde, which may be expected based on the entire body of data.*” However, based on additional data the most recent SCOEL (2015) **raised** the TLV from 0.2 ppm to 0.3 ppm noting, “...*a Limit Value of 0.3 ppm (8 h TWA) with a STEL of 0.6 ppm. As sensory irritation is a concentration rather than a cumulative dose-driven effect, a STEL value is appropriate.*”

## Discussion

Lowering the existing ceiling value of 0.3 ppm to a TLV of 0.1 is scientifically unwarranted. As discussed below, this is particularly the case since, based on Haber's law (which is not mentioned in the DRAFT) once symptoms are produced at a certain concentration, they are not exacerbated by continued exposure at that concentration.

Another key document which should have been included in the DRAFT is a qualitative analysis of controlled human exposure data to derive human health effects criteria (i.e., sensory irritation) for formaldehyde (US EPA/NCEA 2005).

In this rigorous analysis, response data from six human volunteer studies comprising 250 observations and reported symptoms were categorized into the four numerical descriptors and symptoms: (0) no effect noted or reported; (1) mild signs and symptoms: irritation noticed, but not considered annoying; (2) moderate signs and symptoms: irritation annoying; and (3) severe signs and symptoms: incapacitating. From these data, a number of mathematical models were used to assess responses arriving at a conclusion that *“An important advantage of this approach is that all relevant data can be used in the derivation as opposed to a NOAEL for the critical effect. The benefit of doing so allows health risks to be estimated across various exposure levels.”* As noted in this document, this approach was also endorsed by the US EPA Science Advisory Board, which observed that the process *“...makes use of every bit of data available...The underlying premise of the approach is that the severity of the effect, not the specific measurement or outcome incidence, is the information needed for assessing exposure-response relationships for non-cancer endpoints...”* This detailed modeling process showed a clear threshold at 0.5 ppm for any symptoms of sensory irritation and an effective concentration at 1.5 ppm for moderate effects.

Another deficiency of the DRAFT is that it neither mentions nor discusses Haber's law in the context of establishing a TLV. For formaldehyde-induced sensory irritation, there are essentially no meaningful differences between short-term and longer-term exposure (US EPA, 2004; NAS, 2007; Shusterman et al., 2006). As concluded by NAS (2007), *“Formaldehyde irritation does not appear to follow Haber's law (concentration [c] × exposure time [t] = response [k] for extrapolating between short-term and long-term toxicity levels. Generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure.”* Also noted by NAS (2007) was that *“The degree of sensory and irritant effects at lower exposure levels depends on concentration rather than duration.”* This conclusion is based on test results derived from human chamber studies which clearly demonstrate that once symptoms are produced at a certain concentration, they are not enhanced with additional exposure time. As shown in Table 1, abundant empirical data demonstrates that 0.3 ppm is an unequivocal threshold for formaldehyde-induced sensory irritation.

The existing TLV of 0.3 ppm, which by definition is a No Observed Adverse Effect Level (NOAEL) for occupational exposure (i.e., 8 hr/day, 5 days/wk), has now been determined to be the STEL. Other than the results of Andersen and Molhave (1983), which are addressed above, no data are cited, or rationale provided, justifying decreasing the existing TLV of 0.3 ppm to derive the new TLV of 0.1 ppm. Based on numerous controlled human chamber studies there is no functional difference between the proposed TLV of 0.1 ppm and the STEL of 0.3

ppm as both are identical in not producing sensory irritation at either concentration.

**Table 1. Summary of results from controlled human studies of formaldehyde-induced sensory irritation including authoritative reviews**

| <b>Controlled human studies in 2001 ACGIH Documentation</b>   | <b>Reported sensory irritation threshold for HCHO (ppm)</b> | <b>Comments</b>                                                                                                                                                                                                                      |
|---------------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Weber-Tschopp et al. 1977                                     | 1.2                                                         | Threshold for sensory irritation                                                                                                                                                                                                     |
| Kulle et al. 1987                                             | 1.0                                                         | 0.5 ppm no irritation; 1 ppm 15.8% slight irritation                                                                                                                                                                                 |
| Kulle 1983                                                    | 1.0                                                         | Eye irritation @ $\geq 1$ ppm                                                                                                                                                                                                        |
| Bender et al. 1983                                            | 1.0                                                         | <i>"slight to moderate irritation"</i>                                                                                                                                                                                               |
| Schuck et al. 1966                                            | 0.01                                                        | Eye irritation; results at odds with every other study                                                                                                                                                                               |
| Andersen and Molhave 1983                                     | 0.24                                                        | 0.24 ppm indistinguishable from 0 ppm based on other controlled studies                                                                                                                                                              |
| <b>Additional controlled human studies in 2016 DRAFT</b>      |                                                             |                                                                                                                                                                                                                                      |
| Arts et al. 2006                                              | 1.0                                                         | <9.5% experience moderate eye irritation at 1 ppm (benchmark dose)                                                                                                                                                                   |
| Lang et al. 2008                                              | 0.5                                                         | Discrepancy between DRAFT, i.e., reported <b>LOAEL</b> for objective eye irritation of 0.3 ppm & 0.5 ppm for subjective irritation and Lang et al., i.e., reported <b>NOEL</b> for both objective & subjective irritation of 0.5 ppm |
| <b>Additional controlled study not included in 2016 DRAFT</b> |                                                             |                                                                                                                                                                                                                                      |
| Muller et al. 2013                                            | 0.7                                                         | No eye irritation in hypo- or hypersensitive individuals                                                                                                                                                                             |
| <b>Authoritative reviews included in 2016 DRAFT</b>           |                                                             |                                                                                                                                                                                                                                      |

|                                                         |           |                                                                                                                                                            |
|---------------------------------------------------------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NRC 1980, 1981                                          | 0.1 – 2.0 | Reported lower range for irritation (i.e., 0.1 ppm) likely influenced by studies lacking 0 ppm control                                                     |
| Paustenbach et al. 1997                                 | 1.0       | <i>“Based on weight of evidence ... persons exposed to 0.3 ppm... generally reported eye irritation...no different than.. when...exposed to clean air”</i> |
| <b>Authoritative reviews not included in 2016 DRAFT</b> |           |                                                                                                                                                            |
| ATSDR 1999, 2007                                        | 0.3       | Threshold for sensory irritation                                                                                                                           |
| NAS 2007                                                | 0.3       | Threshold for sensory irritation                                                                                                                           |
| WHO 2010                                                | 0.3       | Threshold for sensory irritation                                                                                                                           |
| ACGIH 2001                                              | 0.3       | Threshold for sensory irritation                                                                                                                           |
| MAK 2006                                                | 0.3       | Threshold for sensory irritation                                                                                                                           |
| OECD/SIDS                                               | 0.3       | Threshold for sensory irritation                                                                                                                           |
| NICNAS 2005                                             | 0.5       | <i>“ the LOEL is considered to be 0.5 ppm”<sup>1</sup></i>                                                                                                 |
| SCOEL 2015 Draft                                        | 0.3       | Threshold for sensory irritation                                                                                                                           |
| Nielsen et al 2016                                      | 0.3       | Threshold for sensory irritation                                                                                                                           |

## Conclusion

The proposal to change the existing TLV “ceiling” value of 0.3 ppm to a Time Weighted Average (TWA) of 0.1 ppm is unsupported by empirical data and is inconsistent with a majority of authoritative and/or regulatory bodies world-wide. Furthermore, the seemingly arbitrary decision to decrease by 66% the existing TLV of 0.3 ppm to the proposed value of 0.1 ppm appears inconsistent with the data evaluation criteria in the ACGIH Operations Manual.

## References

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<sup>1</sup> NICNAS (2005) did not report threshold concentrations (i.e., NOAEL) for sensory irritation.

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