May 31, 2019

American Conference of Governmental Industrial Hygienists
1330 Kemper Meadow Drive
Cincinnati, Ohio 45240

Submitted electronically to the ACGIH® Science Group at science@acgih.org

Re: 2019 Draft Notice of Intended Change Documentation for Antimony Trioxide

The Vinyl Institute[1] appreciates the opportunity to review and comment on ACGIH's proposed NIC draft Documentation for Antimony Trioxide.

Summary

In general, the VI supports the comments being submitted by the International Antimony Association (i2A) and provides these additional comments. VI opposes the proposed TLV-TWA of 0.02 mg/m^3 on the basis of a lack of evidence and transparency in accordance with best practices recommended by EPA, the National Institute for Occupational Safety and Health (NIOSH) and researchers from the Harvard H.T. Chan School of Public Health, Department of Biostatistics.[2] There are few references to statistical significance and probability values, no meaningful information about the derivation of the human equivalent concentration (HEC) of 4.8 to 5.8 mg/m^3 that would be needed to achieve the same daily deposited dose as the 3 mg/m^3 LOAEL derived from the NTP study or the specific uncertainty factors, including the numerical values of each uncertainty factor, used to determine the TLV and no tangible references to enable adequate peer review. The VI believes that the NIC should restate the assumptions and fully explain the analysis that drives the TLV recommendation, eliminate insufficient evidence from the supporting information, and discuss the human relevance of the animal study LOAEL in the context of the relevant data available from other animal studies, human occupational exposure data and other studies, especially mechanistic studies, which are important considerations deriving credible and scientifically defensible TLVs.

Dosimetry Assumptions are Overly Conservative

We understand that MPPD dosimetry modeling was used to estimate the concentrations of antimony trioxide human equivalent concentrations in the lungs from the concentrations to which the lungs of the rats were exposed in the NTP study. The MPPD model estimates deposition, clearance, and retention of inhaled particles in the respiratory tract of the human, rat, and mouse. It does not address the impact of

[1] VI is a U.S. trade association representing the leading manufacturers of PVC resins, vinyl chloride monomer, vinyl additives and modifiers, and vinyl compounds. The Vinyl Institute serves as the collective voice of the vinyl industry. More information can be found at www.vinylinfo.org.

[2] https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4643360/, and American Journal of Epidemiology, Volume 186, Issue 12, 15 December 2017, Pages 1303–1309, https://doi.org/10.1093/aje/kwx307

the particles on the tissue. The application of this model requires an estimate of the breathing patterns of potentially affected workers, which is determined primarily by (1) the breathing rate assumed and (2) the relative proportion of the time spent nose-breathing v. mouth-breathing while performing tasks during which exposures may occur, which is largely dependent on the breathing rate. The NIC assumed "conditions of light physical exertion." That appears to be overly conservative in that the NIOSH model assumes that an 8-hour workday consists of 2.5 hours of sedentary exposure and 5.5 hours of light exercise, as described by the International Commission on Radiological Protection (ICRP) human respiratory tract model [ICRP 1994]. [3]

Our understanding is that some dosimetry models only cover three breathing patterns: Nose breathing at rest (NB/R), mouth breathing at rest (MB/R) and mouth breathing under light exercise (MB/LE). This type of model would not provide the data required to model nose breathing under light exercise (NB/LE) although it would be the common breathing pattern for most workers. If that is the case with the MPPD model, all work that ACGIH has characterized as "light physical exertion" would have been treated as if it is performed with 100% mouth breathing. This would introduce another highly conservative factor to the analysis given that most workers do not mouth breathe during light exercise and those that do would augment nose breathing with mouth breathing rather than shifting to 100% mouth breathing. Again, in the absence of further detail, ACGIH is placing the reviewer in the position of accepting the results generated by a black box analysis.

A journal article written by prominent government scientists[4] describes a procedure for determining the HEC in sections titled "Calculating the DAF for Particles" and "Working Lifetime Lung Dose Estimation for Poorly Soluble Particles." In *Calculating the DAF for Parti*cles, the authors describe how the animal exposure associated with an adverse health effect (e.g., POD) can be extrapolated to a human-equivalent concentration (HEC) by applying a dosimetric adjustment factor (DAF) and explains the complex analysis required to develop that DAF, none of which is provided in the NIC.

In *Working Lifetime Lung Dose Estimation for Poorly Soluble Particles,* the authors explain their view that, when poorly soluble particles can cause adverse lung effects that are associated with

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[3] NIOSH Criteria Document for Occupational Exposure to Diacetyl and 2,3-Pentanedione, p151. https://www.cdc.gov/niosh/docs/2016-111/pdfs/2016-111-chap6.pdf?id=10.26616/NIOSHPUB2016111 ("For extrapolation purposes, an 8-hour work day was considered to consist of 2.5 hours of sedentary exposure and 5.5 hours of light exercise, as described by the International Commission on Radiological Protection (ICRP) human respiratory tract model [ICRP 1994]. The ICRP model assumes 20 breaths per minute and a tidal volume of 1,250 mL for light exercise and 12 breaths per minute and a tidal volume of 625 mL for sedentary sitting, for a total inhalation volume of 9.6 m3 in an 8-hour work day. Therefore, to extrapolate from rodents to humans, the BMC estimates described above were adjusted by a weighted average of the rat: human ratios of the predicted tissue concentrations for a particular anatomical region, under sedentary and light exercise conditions.")

[4] Kuempel et al., *Advances in Inhalation Dosimetry Models and Methods for Occupational Risk Assessment and Exposure Limit Derivation, Journal of Occupational and Environmental Hygiene, 12: S18–S40. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4685615/*

their biopersistence in lung tissue at sites of particle deposition, the relevant dose duration metric is the retained dose in the lungs over a full (45-year) working lifetime (rather than the average daily dose as described in *Calculating the DAF for Particles*). They further explain their view that the dose metric of total particle surface area of retained particles in the lungs appropriately describes the dose-response relationships for the category of low toxicity poorly soluble particles despite differences in particles size, chemical composition, and crystal structure. The NIC does not explain the approach followed or dose metric employed in its analysis.

Rationale for the UFc Should be Explained

Based on the TLV of 0.02 mg/m^3/day and the HEC_{LOAEL} of 4.8 mg/m^3/day in the NIC report, it appears the authors applied a composite uncertainty factor (UF_C) of 240:

$TLV = HEC_{LOAEL} \div UF_C$

$UF_C = (UF_H \times UF_A \times UF_S \times UF_L \times MF)$[5]

TLV = 0.02 mg/m^3/day and HEC = 4.8 mg/m^3/day

UF_C = 4.8 mg/m^3/day ÷ 0.02 mg/m^3/day

$UF_C = 240$

The composite uncertainty factor (UF_C) apparently was based on the uncertainties[6,7] referenced in the final paragraph on page 1 of the NIC. However, there is very little detail to justify the 240-fold uncertainty factor applied. Since a chronic animal study was used, $UF_S = 1$. With respect to the UF_A, according to NIOSH:

> The UF_A is often conceptualized as being composed of a sub-factor for toxicokinetic (TK) differences between species (i.e., differences in the internal dose to the target tissues for toxicity), and a sub-factor for toxicodynamic (TD) differences in the sensitivity (i.e., differences in the response of the target tissue to a given internal dose)…. The WHO applies a sub-factor of 4 for toxicokinetics and 2.5 for toxicodynamics.

The species-specific dosimetry modeling should have eliminated the toxicokinetics uncertainty. It is essential to identify the statistically significant adverse effect that occurred at the identified LOAEL and then quantify and provide a reasonable explanation of each of the individual uncertainty factors applied to permit an assessment of the merits of the suggested TLV. Specifically, two of the considerations

[5] The NIOSH paper describes the uncertainty factors used in setting OELs as follows:

[6] https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

[7] D. A. Dankovic et al.,The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits, J Occup Environ Hyg., 2015 Nov 25, 12.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4643360/

cited as justification for the application of uncertainty factors are not cited by either EPA or the NIH in their published papers. Those factors are:

- "The lack of a dose-response relationship"
- "The severity of the effect"

The NIOSH paper does identify a "Modifying Factor" (MF), explained as follows:

- "This factor adjusts for uncertainties not addressed by the UFs described above, and it allows for explicitly incorporating scientific judgment, especially when there are multiple reviewers. A modifying factor may also be considered if there is a need to address residual uncertainties not covered by the other factors. This factor also allows for scientific judgment to be applied to address the overall quality of the database and relevance of available studies to human risk assessment. Additional factors of <1 to 10 may be used in these cases."

Without further details, there is no way for a reviewer to know whether this factor was used and, if so, to critique what value was applied.

Weight of Evidence Technical References Should be Employed

Overall the NIC effort was very broad but shallow, citing papers that were never taken into consideration by the ATSDR work. Several of these unused citations were from a researcher named McCallum (1963, 1965, 1970, 2005). ATSDR defines a data gap broadly as any substance-specific information missing from the scientific literature, so it is likely that there are substantive reasons that the McCallum studies were discarded based on a lack of scientific evidence. Another was a study conducted by White and colleagues (1993) which states that "dermatitis occurred with fume exposure below 0.5 mg/m^3/day, concluding that this level of fume exposure was not protective." In the absence of substantive scientific evidence, this statement misleads readers into believing there is reason to support a study that should have been discarded.

In light of the White study reference, perhaps the most egregious flaw in the NIC recommendation to reduce the TLV is the fact that they base it on inhalation exposure but proceed to throw as much other data into the report as possible, without regard for applicability or quality of evidence. To improve the overall impact of the recommendation, the NIC should only present the facts that support their recommendation, and nothing more to attempt to sway an uninformed and non-critical reader toward a belief that is unfounded.

The VI believes that the NIC should restate the assumptions and fully explain the analysis that drives the TLV recommendation, eliminate insufficient evidence from the supporting information, and discuss the human relevance of the animal study LOAEL in the context of the relevant data available from other animal studies, human occupational exposure data and other studies, especially mechanistic studies, which are important considerations deriving credible and scientifically defensible TLVs.

Sincerely,

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