

*NIOSH Criteria Document Comments for Public Meeting – August 26, 2011*

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NIOSH Panel members and staff:

My colleagues and I believe that it is important for numerous stakeholders to be involved in the discussion regarding the possible health effects associated with diacetyl and 2,3-pentanedione and assure, to the extent possible, that all pertinent and reliable scientific information is used in the decision making process.

We have identified a few key issues within the Criteria Document that we believe deserve special attention. We have numerous comments which we believe NIOSH should give serious consideration and I will address a few of these today.

**First Comment:** In the Quantitative Human Health Risk Assessment section of the report, the risk assessment largely relied upon the findings from an updated analysis of the index facility that was recently published as Kanwal et al. 2011. There appear to be some limitations that should be further evaluated when reviewing data from the study of this group of workers.

- Duration and cumulative diacetyl exposure were negatively associated with the finding of an FEV1 below the lower limit of normal (i.e., pulmonary function decrements were observed in the lowest duration and lowest cumulative diacetyl exposure category). That is, an inverse or J-shaped dose response curve was observed.
- 66% of mixers, maintenance and QC workers that were hired after the first NIOSH survey (i.e., after the facility began implementing exposure controls) already reported respiratory symptoms. Thus, newer cohort members almost certainly had pre-existing respiratory conditions. If this finding is accurate, this subgroup may not reflect the typical person in the workforce.
- The mean length of employment for workers hired after the first NIOSH survey was 6 months. Prior to this, the mean length of employment was 6 years for similar workers. Thus, it is quite likely that heightened concerns about the potential health hazards may have changed behavior; making them possibly dissimilar cohorts.
- Workers hired after controls were implemented at the index facility were on average 10 years younger than those hired before controls were implemented. This difference in chronological age and other factors, make it difficult to reasonably compare these two groups.

**Second Comment:** The Quantitative Human Health Risk Assessment section of the report stated that "...the high-risk cases were not largely associated with specific job groups such as mixers or quality control; many came from the general production line." This observation is contradictory to the expectation that higher exposure tasks (i.e., such as those performed in mixing areas) would be associated with a higher risk of pulmonary function deficits.

As described in the Criteria Document, mean mixing room air concentrations were 2.36 ppm as opposed to lower concentrations of 0.49 ppm and 0.37 ppm measured in Production and Quality Control areas of the index facility (that is, the air concentrations were 5 times smaller). This also does not seem to support earlier statements in the Criteria Document where "NIOSH found evidence of a dose-response relationship (i.e., worse lung disease or more workers affected) with higher diacetyl exposure."

**Third Comment:** The Criteria Document stated that "the nominal standard for acceptable risk used was one per thousand excess risk, a choice often used in OSHA regulation." It is our understanding that this is OSHA's risk criterion for regulating carcinogens; however, we know of no such policy for non-carcinogens. To our knowledge, diacetyl is not considered a carcinogen and the endpoint modeled in the NIOSH human health benchmark dose analysis was changes in pulmonary function.

The EPA has conducted benchmark dose analyses for a variety of chemicals and this methodology has been cited by OSHA. Based on our review of the values posted on the USEPA Integrated Risk Information System website, the EPA has conducted benchmark dose analyses for approximately 33 chemicals, many of which are carcinogens. None of these analyses use an excess risk of less than 5% and those instances where an excess risk of 5% is used involve sensitive health endpoints such as neurological or reproductive effects. In addition, this data set may not be robust enough upon which to conduct a quantitative health risk assessment.

**Fourth Comment:** The Criteria Document stated that there is a potential "high-risk" group in the updated analysis of the Gilster-Mary Lee cohort, but such an occurrence would appear to be highly unusual, if not unprecedented. Further analysis and discussion as to why NIOSH believes this is a "high risk" subgroup, and the characteristics that make the members unique would seem appropriate. It is not clear that this cross-sectional data set is robust enough to fairly apply low dose extrapolation models designed to be applied to fairly homogenous data sets.

**Fifth Comment:** We reviewed other chemicals for which NIOSH has recommended comparably low TWAs (i.e., 1 to 16 ppb). We found that these chemicals are sometimes more acutely toxic than diacetyl by factors of 100 to 2,000 fold and the chronic toxicity involves much more serious effects. Further, to our knowledge, all known inducers of bronchiolitis obliterans in humans including phosgene gas, chlorine gas, and nitrogen oxide are highly reactive, caustic compounds and have been observed to cause severe deep lung destruction in animal studies at low concentrations. Diacetyl, on the other hand, does not cause even minimal deep lung effects in animals at concentrations high enough to cause severe necrosis of the upper respiratory pathway and death. In short, diacetyl does not fit the profile of a known inducer of BO and the animal data do not support that it is a risk factor for this health endpoint.

**Sixth Comment:** We request that NIOSH make publically available all corrected diacetyl air monitoring data collected by NIOSH researchers for which humidity, temperature and/or storage time duration data are available. We further request that these data be presented as individual samples, not as summary statistics. This is entirely appropriate and necessary for an occupational hazard of this magnitude.

**Final Comment:** In epidemiologic investigations, multiple comparison populations are often necessary to evaluate health effects in potentially exposed worker populations. The NHANES surveys are predominantly conducted in urban environments and may not be an appropriate comparison population for cohorts with more rural demographics. Thus, the NHANES cohort may not be the ideal comparison group, and we recommend these data be compared to other generally accepted populations that are regularly used by pulmonologists (i.e., the Knudson et al. and/or Crapo et al. cohorts).

I have received no outside funding of my travel expenses or time invested in preparing or presenting these comments. Our firm, who is engaged in consulting, believes we have a professional responsibility to share information with government bodies. We have in the past consulted and testified for flavorings manufacturers and as a result we have developed a body of knowledge about this issue. Scientists in our firm have studied this matter for the past 4 years and have published numerous papers or letters to the editor on the toxicological and medical aspects of this family of chemicals.

I hope that this panel will give these comments serious consideration and have brought copies of my comments for your review. Thank you.

## REFERENCES

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