Rec 11/17/11 SAD

November 15, 2011

NIOSH Docket Office
Robert A. Taft Laboratories
MS-C34
4676 Columbia Parkway
Cincinnati, OH 45226

RE: Comments on the draft NIOSH Document "Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione." 76 *Fed. Reg.* 44338. 25 July 2011. Docket Number NIOSH 245.

Dear Sir/Madam:

Over the past decade, diacetyl – a naturally occurring chemical used for flavoring – has attracted much attention and scientific inquiry. Given the gravity of the more critical health effects reported in some microwave popcorn workers and the limited clinical findings that are reported to be consistent with a rare obstructive lung disease called bronchiolitis obliterans (BO), the attention paid by the scientific and regulatory communities is expected. NIOSH's concerns and interest in protecting workers from this potential workplace hazard is laudable and certainly consistent with the agency's mission. However, scientific inquiry and regulatory action, to be properly grounded, must be based on recognized and well-accepted epidemiological, toxicological, exposure, and risk assessment methods using properly collected and representative data.

Overview

It is our belief that the NIOSH Draft Criteria Document for a Recommended Standard – Occupational Exposure to Diacetyl and 2,3-Pentanedione (hereafter "Criteria Document") misapplies assessment methods and extrapolates beyond the verifiable scientific evidence in a number of areas. The Criteria Document asserts that causation has been established between diacetyl and occupational lung disease, when the available exposure, epidemiological, and toxicological data only provides definitive support for diacetyl as a marker chemical "associated" with adverse effects within a complex mix of workplace chemicals. The Criteria Document proposes a Recommended Exposure Limit (REL) based on data limited to a single microwave popcorn production plant, while the final REL will apply to a much broader population of workers in numerous different industries, in many different and potentially unique occupational settings, at hundreds of thousands of locations. The document also claims support from a risk assessment using animal data that offers little evidence for the anticipated dose-response in humans. The Criteria Document also avoids presentation of significant contradictory data regarding potency: the proposed REL of 5 ppb for diacetyl is 10-fold lower than the dose that a relatively light smoker would receive on a daily basis from smoking just a half-pack of cigarettes per day.[1] In short, the current draft of the Criteria Document, although well intended, contains many over-reaching interpretations and unsupportable conclusions with regard to causation, exposure characterization, risk assessment and control technology.

General Comments

Scope – As currently presented, the proposed scope of the Criteria Document is too broadly defined. Although the effort identifies the agency's concerns regarding diacetyl and 2,3-

pentanedione, the document makes vague and inconsistent references to broad and poorly defined groups of other substances. The terms chosen to describe these groups range in vagueness from categorical to non-specific (e.g., alpha-diketones, alpha-dicarbonyl compounds, chemicals with structural similarities, moieties that are biologically active, capable of producing similar toxic effects, other flavoring chemicals, agents of concern, other compounds). Besides being confusing to the reader, this presents a misleading picture, since the scientific information available to assess diacetyl (or 2,3-pentanedione) does not extend to the other groups of substances equally, and in many cases not at all. Furthermore, the terms used to describe the groups are vague enough to allow for multiple interpretations and disagreement among experts (e.g., when is a structure dissimilar, when can a compound with multiple carbonyl groups be excluded, do we allow a "biologically active" chemical or compound "producing similar toxic effects" to be included regardless of potency?). Because the Criteria Document does not adequately define the scope of the recommended standard, NIOSH cannot expect the general public, labor, industry, or health and safety practitioners will be able to make proper determinations in a consistent and meaningful manner.

Applicability – Recognizing the extensive use of diacetyl and other flavorings, the number of facilities with flavoring operations, and the diversity of food products involved, stakeholders can appreciate the challenge facing NIOSH. However, limiting the quantitative risk assessment to data from a single operation (NIOSH, Company G) in one small portion (microwave popcorn manufacturing) of the affected industries, limits the value and applicability of the risk assessment. Extrapolating from such limited information to other plants is difficult, extrapolating from microwave popcorn manufacturing to other industries is questionable, and extrapolating to all affected industries cannot be scientifically supported. The practice of using severely limited data also extends to the agency's assessment of engineering controls where a validation of efficacy was performed at only one plant (ERG, 2009c) in another minor portion (pre-popped buttered popcorn) of the affected industries, and in a work environment substantially different from the plant used to conduct the quantitative risk assessment. As presented, the document reflects a process of conducting assessments using limited data of questionable relevance, while attempting to support the results with anecdotal information. It should also be noted that where clearly confounding or contradictory evidence exists that evidence is not included as part of the agency's assessment.

Definition of "Reasonably Achievable" – It complicates our ability to respond, when NIOSH has yet to establish a definition or described an objective protocol for assessing when a control should be demeaned as "reasonably achievable" and when it should not:

- What is the definition of achievable? – Is being achievable a statement of currently available and proven control technology, or does it apply to unproven technologies as well (i.e., what OSHA has identified as "forceable" control technologies)?
- What is the definition of reasonable? – Is a control reasonable when it is only shown to be partially effective, or should it meet a certain criteria (e.g., efficacy in 90, 95, or 99 percent of the processes studied)? Is an engineering control reasonable when it cannot achieve compliance with the REL and the workers are forced to rely on respiratory protection?

The lack of a definition and an objective assessment protocol allows for the inclusion within the Criteria Document of poorly documented and subjective decisions regarding both the efficacy and utility of control measures:

- NIOSH has stated [p. 217] that engineering controls are available to reduce personal breathing zone measurements to diacetyl in a range from 83.9 to 99.4 percent. However, even when one uses the higher level of efficacy, the engineering controls cited would not achieve compliance with the REL (measured as a TWA) when initial exposures are above 1 ppm.[2] Given that many uncontrolled operations can exceed levels above 1 ppm (as documented by NIOSH and ERG), how can the agency claim that this is a "reasonably achievable" control measure?
- The control measures at the facility (NIOSH, Company G) that were the subject of the quantitative risk assessment – even with NIOSH's assistance and encouragement during repeated visits over approximately three years – did not result in the facility achieving mean exposure levels below the REL at 9 of the 14 job categories that were the subject of the assessment [Table A3.4]. We do not believe that a 60 percent failure rate should be used as evidence of a "reasonably achievable" control measure.

Even if NIOSH's estimates of mean exposure levels and control efficacies are indeed accurate and transferable to the wider industrial community:

- Compliance with the REL will only be achieved through an extensive reliance on respirators.
- Unlike the NIOSH recommended standard that was developed to "...ensure that worker exposures are ***routinely*** [emphasis added] below the REL..." [p. 214], should OSHA promulgate a similar level, it will require ***all*** exposures to be below the permissible exposure limit (PEL).

Both the aforementioned implications are contrary to NIOSH's statements in the Criteria Document that engineering controls are a "reasonably achievable" measure. Compliance with this REL or a similar OSHA PEL can be argued to be both unreasonable and unachievable.

Chapter 3: Effects of Exposure In Workers

Table 3-1 – In the summary of Kreiss, et al. (2002) the Criteria Document states, "Quartile of cumulative exposure to diacetyl was ***related*** [emphasis added] to the frequency and extent of airways obstruction." There was a statistical "association" but the use of the term "related" implies a causation that has not been proven. Since the presence and effect of other agents in the microwave popcorn plant were not scientifically evaluated or considered, the claimed association is also unsupportable.

Table 3-1 – In the summary of Lockey, et al. (2009) the Criteria Document states, "Cumulative diacetyl exposure of 0.8 ppm-year or more ***conferred*** [emphasis added] an odds ratio of 9.2 for obstruction." There was a statistical "association" but the use of the term "conferred" implies a causation that has not been proven.

The table includes reference to a NIOSH (2009d) cross-sectional survey of observed health effects in bacterial product workers as compared to flavoring workers. This study has limited relevance to the issue(s) at hand and any reliance on it should be reconsidered.

The table includes a reference to VanRooy, et al. (2007) and states that four workers were identified as having BO. The VanRooy article actually states they had bronchiolitis obliterans syndrome (BOS), which indicates the presence of symptoms consistent with BO but without obligate pathological confirmation. Use of this reference and NIOSH's subsequent conclusions

should be reconsidered since the association between BO and diacetyl exposure is still largely unproven.

Page 55, Lines 12-15 – The agency's inclusion of area samples in the body of data used to calculate the estimates of worker exposures is problematic:

- It is contrary to good industrial hygiene practice [A Strategy for Assessing and Managing Occupational Exposures, AIHA (2006)].
- Ignores NIOSH's own research [Occupational Exposure Sampling Strategy Manual, Leidel, et al. (1977)].
- Violates the very recommendations it is providing to industry when attempting to comply with the proposed REL [p. 24 and p. 285].

It is a long establish tenet of industrial hygiene and exposure assessments that area samples are not reliable representations of personal breathing zone exposures. Depending on the processes involved, the jobs being performed, and the movement of workers, area samples may grossly over or under estimate an individual's actual exposure. This misplaced reliance on area sampling is a serious flaw in the data compilation and calls into question the validity of the underlying exposure and subsequent quantitative risk assessments.

Page 68, Lines 14-17 – The Criteria Document discusses Lockey, et al. (2002) and cites "findings consistent with bronchiolitis obliterans" for four workers in addition to an index case of BO at a flavor manufacturing facility. The report then states, "All five workers with bronchiolitis obliterans had normal spirometry tests at the start of employment." In actuality, the four workers had clinical findings "consistent with" BO, but were not pathologically confirmed cases. Also, the Criteria Document concedes that these workers had no further decline in lung function following cessation of exposure to flavoring chemicals. Thus, since classic BO is an irreversible and progressive condition that results in increasing disability and need for a lung transplant, and since the 2002 report was written there is no indication that any lung transplants have occurred in these workers, it is appropriate to question if the workers had the medical condition known as BO. Finally, Dr. Lockey attributes the cause of the workers' findings to acetaldehyde, not diacetyl – NIOSH should reconsider the use of this article and their subsequent conclusions.

Page 71, Lines 10-13 – The report states, "Available information on TWA and peak exposures to diacetyl in flavoring and diacetyl manufacturing plants where workers ***have developed bronchiolitis obliterans*** [emphasis added] indicates that workers' exposures in these plants may have been similar to workers' exposures at microwave popcorn plants." A more correct statement would be "...have displayed clinical findings consistent with bronchiolitis obliterans." There is not sufficient medical or scientific support for an actual diagnosis of BO in these workers. In addition, the clinical findings may be explained by other lung conditions and/or etiologies.

Page 72, Lines 2-4 – The report states, "At the three other microwave popcorn plants where mixers ***developed bronchiolitis obliterans*** [emphasis added], TWA diacetyl exposures from personal samples were 0.31 ppm, 0.69 ppm, and 1.33 ppm." A more correct statement would be "...displayed clinical findings consistent with bronchiolitis obliterans." Again, there is not sufficient medical or scientific support for an actual diagnosis of BO in these workers.

Page 79, Line 14 – The report too simplistically equates BO with fixed airways obstruction. The use of a medical diagnosis of BO or BOS has been misapplied, because the diagnostic criteria for

BO has not been met (i.e. the workers improve or stabilize, no reports of transplants, or the pathology has not been confirmed).[3] There are medical reports that describe the microwave popcorn workers as having "restrictive lung disease, as well as airways obstruction."[4] That same report also notes that there were two subjects with "bronchodilator response", thus negating the presence of a "fixed" obstruction. Accordingly, the use of NIOSH's existing terminology and reliance on "fixed obstruction" as the symptom associated with the lung disease in microwave popcorn workers is not correct as it is not based on recognized medical or scientific data, or criteria.

Page 85, Lines 12-14 – The report states, "Biologic plausibility is supported by the evidence of diacetyl toxicity identified in several animal exposure studies and other nonhuman research." This statement is flawed in that a parallel manifestation of BO-type symptoms has not been observed in mammalian toxicity studies of diacetyl and butter flavorings. Furthermore, there is no animal model for BO. This is taking a leap of "plausibility" in the face of contrary evidence (i.e., no rodent has been shown to developed BO).

Page 87, Lines 27-30 – The report states, "Investigations of severe lung disease consistent with constrictive bronchiolitis obliterans among diacetyl-exposed workers have provided substantial evidence of a causal relationship between diacetyl exposure and development of this disease. Exposure preceded disease development and lung disease risk decreased with control of exposures." This assertion is seriously flawed in that the literature supports the identification of diacetyl as a marker for exposure to one or more causal agents, but no definitive causal relationship with diacetyl has ever been demonstrated. Reduction in exposure to diacetyl in the plant setting also likely results in decreased co-exposure to one or more other flavoring chemicals and other agents such as glues, inks, salts, oils, and other volatile chemicals known to be present in the popcorn plants, any one or combination of which could be the cause(s) of observed health effects. Furthermore, NIOSH relies on the Jasper studies for much of the data in the Criteria Document but – importantly – none of the 122 volatiles detected in the workplace (many of which were unrelated to either flavorings or diacetyl) have been tested in animals to determine if they could cause BO, were not considered in the exposure characterization, and were not included as part of the quantitative risk assessment.[5]

General Comment on Chapter 3 – In many, if not most, cases where the report includes a statement that one or more individuals "developed bronchiolitis obliterans," a more correct statement would be "...displayed clinical findings consistent with bronchiolitis obliterans." In very few cases have the workers had pathologically confirmed cases of BO. Furthermore, even in these limited cases with pathological evidence, there have not been follow up studies of any of the workers reported. Accordingly, there is no basis on which to conclude that any particular agent caused the actual disorder known as BO. Since no agent, or group of agents, has been identified as a definitive causative factor, and since no associated recognized disease state has been identified with a reasonable degree of scientific or medical certainty, there is simply insufficient evidence upon which to draw the conclusions set forth in this Chapter.

Chapter 4: Toxicology of Diacetyl and 2,3-Pentanedione

Page 104, Lines 1-8 – The report discusses Morgan, et al. (2008) and Palmer, et al. (2011) that used oropharyngeal aspiration and intratracheal installation of a bolus of diacetyl to generate BO or BO-like responses in rats. The report rightly points out that these results may have limited applicability to risk assessment due to their nature as large bolus doses. This report has no

significant applicability to the determination of whether diacetyl is related to BO caused by inhalation in humans or animals. Indeed, aspiration itself is a known cause of BO.[6]

Chapter 5: Quantitative Risk Assessment Based on Worker Data

Page 114, Lines 16-17 – The report states, "Although ***diacetyl causes bronchiolitis obliterans*** [emphasis added], a debilitating and potentially fatal condition, it may be associated with a spectrum of disorders." This statement that causation has been established between diacetyl and BO is erroneous. Again causation has not been established.

The R-squared values associated with the multiple regression models for percent predicted FEV_1 and other dependent variables versus various diacetyl exposure metrics for Company G were all relatively low, explaining little of the variance (with most in the mid-teens and a select few in the 30s or low 40s). This provides little confidence in the predictive ability of the models for explaining FEV_1 in the studied population, regardless of the statistical significance achieved.

Page 116, Lines 2-8 – NIOSH recognized that the sampling and analytical method (i.e., NIOSH Method 2557) used to characterize personal breathing zone and area samples at Company G and other workplaces were affected by the humidity at the time of the sampling and holding time. Specifically, that the combined effect is to "progressively underestimate diacetyl" with increases in humidity (absolute humidity) of the workplace and length of sample storage (time to extraction). NIOSH researched the problem, proposed a correction procedure,[7] and applied it to samples from the affected studies that detected diacetyl, because "...underestimation of worker exposure may lead to overestimation of respiratory health risk in quantitative exposure-effect analyses." NIOSH choose not to apply the same correction to samples initially reported as being below the limit of detection (LOD) noting that: "It is not possible to know if the workplace diacetyl concentration was indeed below the LOD or if the losses due to humidity and days from sampling to extraction in the laboratory caused the sample value to be below the LOD."

Accepting the limitations associated with the aforementioned correction scheme, failing to address the non-detect samples with some type of corrective measure introduces a significant amount of uncertainty and affects the confidence to be placed on any resulting exposure statistics.

- Forty percent (104/262) of the personal samples and 42 percent (146/346) of the areas samples collected at Company G were initially reported to be below the LOD.
- Two hundred and fifty-one (251) results, used by NIOSH in the exposure assessment, were reported to be below the LOD – using the biased method.

Since "less than detectable" results are reported as the LOD/2 during the determination of exposure statistics, the confirmation of even the smallest amount of diacetyl in a portion of these samples has the potential to double the lowest value used to calculated mean exposures.[8] Since it would be extremely unusual for all but a minority of the 251 samples to report a lack of diacetyl in air near operations where it is known to be present and handled, it must be assumed that the NIOSH exposures have been underestimated.

Chapter 6: Quantitative Risk Assessment Based on Animal Data

The assumption of no tissue site concordance between humans and test organisms is questionable and adds substantial uncertainty to the risk assessment.

Page 180, Lines 20-21 – One (1) ppm diacetyl = 0.00352 µg/mL on the basis of diacetyl's molecular weight of 86.09, the proposed REL of 5 ppb translates into 0.0176 mg/m^3. If converted

to a daily dose the REL may be expressed as 0.005 mg/kg/day. Interestingly, considering the mean diacetyl content in cigarette smoke [0.336 mg/cigarette (Fujioka & Shibamoto 2006)] smoking just a half pack of cigarettes per day for 15 years (a light smoker by definition) results in a daily dose of 0.048 mg/kg/day. Light smokers receive a 10-fold higher diacetyl dose than the proposed REL on a daily basis. Also, since the early seventies the U.S. Government has required health warnings on cigarette packs and physicians/health scientists have closely researched the effects of smoking and lung disease since that time. Despite this intense research and lengthy observation, no cases of BO have been reported in the over 200 million smokers since 1973 in the United States. This constitutes the largest epidemiological disease data set known- yet no significant findings related to BO are associated with smoking. This is remarkable evidence that diacetyl is not causative of BO in humans and explains to a large degree why no significant dose response could be established for diacetyl exposure and BO by NIOSH.

Page 194, Lines 18-23 – The Criteria Document states, "Uncertainties also exist in relation to species differences in toxicodynamics and the related issue of exposure-response behavior at low doses (i.e., whether or not a threshold may exist for the diacetyl-induced respiratory tract effects observed in humans). Because of these uncertainties, ***it is not possible to definitively state that one effective dose measure is to be preferred over the other nor to determine toxicologically what dose response relationship should be expected*** [emphasis added]." This excerpt suggests a low level of confidence in the understanding of the diacetyl dose-response relationship expected in humans, yet NIOSH uses these highly uncertain risk assessment results in support of the REL development.

Chapter 7: Basis of the Recommended Standards for Diacetyl and 2,3-Pentanedione

Page 210, Lines 26-28 – NIOSH states in the Criteria Document that the epidemiological data meet the Hill criteria (Hill 1965) for causation with relation to diacetyl exposure and severe occupational lung disease. This statement is incorrect. The current epidemiological data only suggests support for diacetyl as a marker for one or more agents found in the complex chemical mixtures reported in flavoring plants associated with occupational lung disease.

Page 213, Lines 17-18 – NIOSH cites a single non-peer reviewed study [Eastern Research Group, 2009c] as demonstrating that the REL is achievable with engineering controls when diacetyl is used or handled. NIOSH neglects to point out that this study is not for all affected industries, is only representative of "pre-popped buttered popcorn" operations. The use of the engineering controls did achieve reductions in some airborne concentrations (as would be expected). However, even in the study that NIOSH choose to cite, one STEL sample (98.9 ppb) still exceeded the STEL of 25 ppb and an area sample found airborne concentrations (5.4 ppb) above the TWA of 5 ppb. Importantly, the subject pre-popped buttered popcorn operation started with relatively low initial concentrations (i.e., below 1 ppm for most TWA samples and only a few ppm for STEL samples). Such low initial concentrations do not represent a significant challenge for engineering control technologies. Of the twelve Eastern Research Group studies performed [ERG A through L], no other industry group appears to have been subjected to a similar evaluation of controls,[9] even thought several of the ERG studies presented initial exposures that were orders of magnitude higher than those found in the operation selected. The higher conditions would have been a truer test of the engineering controls. To base a broad claim of achievability from the partial success at one plant in a single small sector of the economy cannot be construed as a representative or a reasonable basis for a recommended standard (also see Definition of Reasonably Achievable under the General Comments).

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Chapter 8: Hazard Prevention and Control of Exposures to Diacetyl and 2,3-Pentanedione

Page 222, Lines 1-2. The pronouncement that the control recommendations are applicable "to not only diacetyl and 2,3-pentanedione and other flavorings and flavoring chemicals" may be theoretically possible, but will not likely be "reasonably achievable" or technically feasible in many operations.

- Flavoring ingredients consists of volatile, semi-volatile, and non-volatile chemicals that, depending on formulations and quantities of the ingredients, can behave in ways not addressed by NIOSH (e.g., heavier than air vs. lighter than air vapors).
- Formulations for many flavorings involve the use of micro-scales that are sensitive to even minor air velocities (less than 50 linear feet per minute) and are not amenable to control by local exhaust ventilation.
- NIOSH's own estimates of control efficacy would not achieve the REL for many industrial operations (see Definition of Reasonably Achievable under the General Comments).

The section on hazard prevention is a general presentation on common engineering control solutions available from numerous standard reference documents, but it does not present a validation of the control measures during the production of flavoring chemicals, the formulation of flavors, or their use in food production or preparation operations. There is insufficient evidence to advance a claim of "reasonably achievable" to the OSHA docket.

Closing:

We believe the current scientific evidence indicates that diacetyl may be a possible marker for workplace conditions causative of occupational lung disease. However, we find it difficult to accept the agency's claim it is sufficient to establish causation between diacetyl, 2,3-pentanedione, or other specific flavorings and BO. We also believe that additional work is needed in the areas of exposure characterization, risk quantification, and control assessment. We fully understand the magnitude of the effort confronting NIOSH and hope that the information and criticisms we have provided will assist the agency with its efforts. We further believe that addressing our concerns will help to ensure scientifically sound assessments, better decisions, and a more appropriate work product.

Should the agency have any questions or wish to discuss these issues further, please do not hesitate to contact the authors of this letter. Issues regarding toxicology and the quantitative risk assessment should be addressed to Dr. Frank L. Mink, while issues regarding methods, exposure assessments, and control technology should be addressed to Mr. Leslie J. Ungers.

Sincerely,
Ungers & Associates, Inc.

Leslie J. Ungers, MS, CIH

MAI

Frank L. Mink, PhD, Toxicologist

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Footnotes:

[1]Based on known diacetyl concentrations in cigarette smoke [Fujioka, K. and Shibamoto, T. Determination of Toxic Carbonyl Compounds in Cigarette Smoke. Environmental Toxicology (2006)].

[2]Calculated as the REL/[1-0.994 or 833 ppb] (i.e. 0.833 ppm).

[3]Bronchiolitis Obliterans Syndrome in Popcorn Production Plant Workers. Akpinar-Elci, M., Travis, W.D., Lynch, D.A., Kreiss, K.

[4]Id.

[5]NIOSH GC-MS Thermal Desorption Tubes – Peak Identification, SEQ 9661-AA,AC. Freedom of Information Response FOI-A-HUBBS000340-341 (attached).

[6]Elliott, C.G. et al. Charcoal lung: bronchiolitis obliterans after aspiration of activated charcoal. *Chest* 96(3). 672-674 (1989) and Rinaldi, M., et al. Gastro-esophageal reflux as cause of obliterative bronchiolitis: a case report, *Transplant. Proc.* 27(3), 2006-2007 (1995).

[7]Cox-Ganser, et al. Correcting Diacetyl Concentrations from Air Samples Collected with NIOSH Method 2557 (2011).

[8]The estimated LOD for the analytical portion of NIOSH Method 2557 is 0.6 ug/sample and the resulting lower limit of the working range for the method is 57 ppb [Diacetyl, Method 2557, NIOSH Manual of Analytical Methods, Fourth Edition].

[9]In addition to the pre-popped buttered popcorn operation, Eastern Research Group investigated a coffee roaster, bakery, snack food producer, sauce producer, low-cal cracker maker, retail baker, flavor producer, and several dairy product producers, including sour cream and cottage cheese.