Dragon, Karen E. (CDC/NIOSH/EID)

From: Bob Hawk <Bob.Hawk@popweaver.com>
Sent: Friday, November 18, 2011 10:49 AM
To: NIOSH Docket Office (CDC)
Subject: NIOSH Diacetyl and 2,3-Pentanedione Criteria Document - E Copy Filing by Weaver Popcorn Company, Inc.
Attachments: Weaver Popcorn Company, Inc. - Letter To - Dr. Lauralynn Taylor McKernan - Dated 11.17.11.pdf

Attn: NIOSH

Please note this is our electronic filing of the Weaver Popcorn Company, Inc. comments to the NIOSH Diacetyl and 2.3 Pentanedione Criteria Document.

Thank you.

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November 17, 2011

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Robert A. Taft Lab.
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Re: NIOSH Docket Number 245
NIOSH Diacetyl and 2,3-Pentanedione - Draft Criteria Document

Dear Dr. McKernan:

As you know, Weaver Popcorn Company, Inc. ("Weaver") is deeply concerned regarding NIOSH's draft criteria document for diacetyl and 2,3-pentanedione. The proposed recommended exposure limits ("RELs") and the data and analysis upon which the proposed levels are based do not stand up under objective scientific scrutiny. Regretfully, the publication of the draft alone has placed this flawed conclusion in the public domain where it may be seized upon as evidence for the demonstrably false assessment that low levels of diacetyl and 2,3-pentanedione that have never caused harm to anyone in the past are in fact dangerous. That injury would only be compounded were the proposed RELs to be adopted.

A brief introduction of Weaver may be appropriate. Weaver is an eight-decade-old, family-owned business headquartered in Indiana. Weaver produces only popcorn products, including unpopped popcorn, microwave popcorn and pre-popped popcorn. Weaver is committed to providing all of its employees with a healthy and safe workplace. Safety and health are core values of Weaver.

In providing these comments, we are guided in part by our own ten-year experience in addressing the emerging data on health implications of using butter flavorings in food manufacturing. We have invested heavily, including the extensive use of outside scientists, to provide a safe environment for our employees. Partly as a result of our investment, we have a strong sense both of what works, and what does not, in providing a safe workplace. Our experience and the scientific data demonstrate that the proposed levels are so far below the threshold of human health effects as to be unnecessarily burdensome to business.

NIOSH has worked with us before and knows our commitment to safety and health. We met with NIOSH and showed them our microwave popcorn manufacturing facility and the measures we take to protect our workers and ensure their safety and health. We are disappointed that NIOSH would not have included us and others in the private sector with relevant experience and

knowledge in its process before now. Had NIOSH done so, we could have avoided both the publication of such a deeply flawed document and the negative consequences of having such a document in the public domain.

While we appreciate that NIOSH gave us an additional 30 days to respond to the draft criteria document, the complexity of the issues and the flaws in the analysis reflected in this letter demonstrate that far more time and study is needed if the goal is really to set the right exposure level necessary to protect workers.

To provide a thorough scientific review of the draft criteria document, we engaged the services of Dr. Candace Doepker and her colleagues from ToxStrategies, Inc. and Dr. Kendall Wallace and Gilman Veith from StrataTox, LLC to assist us with preparing the following comments.

Our major concerns with the NIOSH draft criteria document are:

A. The proposed RELs were based on flawed risk assessment assumptions.

   1. The risk assessment is based on an uncertain exposure assessment due to the adoption of too many assumptions.

   2. It is not clear from the document, but it appears that the risk assessment emphasizes Case Definition 1 (Forced Expiratory Volume in one second ("FEV_1") below normal) as the critical health effect metric. This definition is not specific for diacetyl exposure, and thus creates false positives.

B. The animal risk assessment is based on limited data from a single risk characterization study: Thus the model has a high degree of uncertainty and adopts extremely conservative assumptions about the appropriate benchmark dose.

C. The risk assessment model NIOSH chose to utilize is most often used for cancer-causing chemicals, rather, than a non-cancer health effect, in this case lung disease, which is typically modeled assuming that there is a threshold below which no adverse effects would occur.

D. The proposed RELs and short-term exposure limits ("STELs") are inconsistent with the levels set to minimize risks from exposure to other chemicals of comparable reactivity.

E. The industrial hygiene recommendations are counter to prior NIOSH recommendations, for instance with respect to the requirement for full-face respirators.

F. The proposed REL is so low that naturally occurring diacetyl in many foods will likely result in exceedances of the proposed standard.

The consequences of setting incorrect limits would go well beyond Weaver. Many restaurants, wineries, breweries and other food businesses could be forced to stop production if the limits are set too low for effective counter measures.

We will now look at each of these points in more detail.

A. The Proposed RELs Were Based On Flawed Risk Assessment Assumptions

1. Uncertainties In The Exposure Assessment

Critical to a successful quantitative risk assessment (QRA) is the ability of the assessor to have confidence relating exposure to the risk of an adverse event. The exposure reconstruction used in the risk assessment model relies almost entirely on industrial hygiene measurements from the Gilster-Mary Lee Corporation facility in Jasper, MO ("GMLC facility"). Despite the fact that nine surveys were conducted during which nearly 400 personal and area samples were collected, there is sufficient uncertainty (or lack of documentation addressing uncertainty) in the data to render the exposure reconstruction inadequate for purposes of deriving a REL. Specifically, we believe that NIOSH made several assumptions that are likely to underestimate historical exposures, which would impact the dose response relationship upon which the recommended RELs are based and thus, we request that NIOSH address our concerns. The primary uncertainties with the exposure data/exposure reconstruction are as follows:

a. **NIOSH relied on area samples** collected during the first survey in November 2000 **to estimate personal breathing zone concentrations** for as far back as July 1986, when it was assumed diacetyl was first used at the GMLC facility.

   i. No personal breathing zone samples were collected during the November 2000 survey. This may be understandable for an initial survey; however, reliance on these data for up to a 14-year period introduces considerable uncertainty to the estimated cumulative exposures for workers who were at the facility during this period.

   ii. Depending on where the area samples were collected, NIOSH applied different assumptions for converting the area samples to personal breathing zone samples. While these differing assumptions may be valid, NIOSH provides no rationale as to their basis. Consistent with NIOSH's publicly stated desire to be transparent in this process, we request that NIOSH provide a detailed rationale and/or formulas for how it extrapolated area to personal breathing zone samples.

b. In applying the November 2000 data to previous years, **NIOSH assumed that no engineering controls or process changes were made** during that time period (i.e., July 1986 through November 2000), but a closer look at the Health Hazard Evaluation ("HHE") reports indicates some changes

were indeed made and these could have lowered exposure compared to those which would have occurred in prior years.

c. NIOSH acknowledges in the HHE report for this facility that local exhaust ventilation was added to the mixing room to control salt dumping operations and roof air intake systems were added in the microwave area in the summer of 1999. NIOSH also acknowledges that many of the workers believed that conditions in these areas of the plant **improved** following installation of these control measures.

d. NIOSH should provide evidence or a rationale for assuming that these engineering changes would not have reduced diacetyl exposures in these and other areas of the GMLC facility.

e. The consequence of applying lower level exposure estimates (whether or not they are recognized as resulting from the implementation of these engineering controls changes) is that lower and thus likely incorrect estimates were applied when assessing risk. This is a potentially critical mistake further compounded when uncertainty factors are applied.

f. NIOSH **had to make assumptions when adjusting the air sampling results** to account for the effects of humidity and time to extraction on the reported diacetyl concentrations. It is our opinion that not only is more transparency needed in the adjustments applied, but we question whether the correction factor could be appropriately applied to exposure values that exceeded 25 ppm.

   i. Air samples collected during the nine surveys at the GMCL facility were analyzed by NIOSH Method 2557, which was the predominant analytical method used at the time. Subsequent studies demonstrated that this method is affected by humidity and time to extraction, **resulting in underestimates of the actual diacetyl concentrations.** We are aware that NIOSH developed a method to adjust the measured concentrations to account for these effects, and the method to adjust was published in the peer-reviewed literature.[1]

   ii. NIOSH states in the draft criteria document that it adjusted the air sampling results from the GMLC facility using the published method to account for these effects; however, **NIOSH does not provide any discussion as to the adequacy of the sample-specific humidity data** to make these adjustments.

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[1] Cox-Ganser J., Ganser G., Saito R., Hobbs G., Boylstein R., Hendricks W., Simmons M., Eide M., Kullman G., Piacitelli C. (2011), *Correcting diacetyl concentrations from air samples collected with NIOSH Method 2557*, J. Occup. Environ. Hyg. 8(2):59-70.

iii. Although the HHE report states that relative humidity data were collected during the surveys, only the first interim report, dated August 2001, documents that such samples were collected. Furthermore, there is no discussion of the relative humidity data in the interim report or elsewhere in the HHE report. This is not necessarily surprising given that the importance of the humidity data was not recognized until after the HHE report was issued.

iv. NIOSH acknowledges in its publication that the upper end of reliable data from the correction method is 25 ppm. Importantly, concentrations above 25 ppm were measured during the first survey of mixers, which adds further uncertainty to (and likely **underestimates**) the historical exposures to these workers. Additionally, a review of transcripts from the California OSHA advisory meetings where the GMLC data was discussed, indicates that some of the reported exposure values for GMLC were as high as 1200 ppm. NIOSH needs to clearly disclose how they took into account the problem of correcting for values higher than 25 ppm.

Other scientists who have reviewed the available exposure and epidemiological data have concluded that because the animal toxicology studies have much better documented exposure levels they are more accurate for purposes of preparing a human health risk assessment, despite the interspecies issues that always occur with animal toxicology studies. The intent of the Maier et al., 2010[2] paper was to determine whether the data for diacetyl were sufficient to develop a health-based occupational exposure limit ("OEL"). The authors first reviewed the available worker exposure data from several epidemiology studies. Maier et al. evaluated the quality of the studies by considering: general design, exposure measurements and methods used to evaluate health effects. They expressed many concerns and in the end concluded the animal data were the better choice for developing an OEL because there were too many uncertainties in the epidemiology studies that were available. Based on the amount of uncertainty that remains in the exposure reconstruction NIOSH utilized, we tend to agree with Maier et al.

2. Decrease In FEV_1 Is Not Specific To Diacetyl Exposure

For the QRA to be robust, it is critical for the assessor to accurately select the health effect or end point of concern. Health impairment associated with diacetyl exposure was defined in the QRA as pulmonary function falling below the lower limit of normal ("LLON"). Although not entirely clear from the document, it appears that NIOSH emphasized decrement in FEV_1 (Case Definition 1) as a measure of diacetyl impact, as opposed to case definition 2... The selection of decrease in FEV_1 as the health effect end point for the risk assessment has enormous consequences because that decision then drives the selection of the proposed REL. The risk assessment is weakened through the use of FEV_1 as the end point **since reduction in FEV_1 is**

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[2] Maier A., Kohrman-Vincent M., Parker A., Haber T., (2010) *Evaluation of concentration-response options for diacetyl in support of occupational risk assessment*, Reg. Tox. and Pharm., 58:285-296.

not a specific surrogate measure for bronchiolitis obliterans[3], which is the only disease NIOSH has associated with exposure to diacetyl and butter flavorings.

Based on NIOSH documented historical testing, the critical health effect in popcorn production workers is bronchiolitis obliterans ("BO"). BO is characterized as an irreversible fixed (not resolved by administering bronchodilator drugs) obstructive disease. By spirometry, this is measured as an irreversible [fixed] decrease in FEV_1 < LLON and FEV_1/FVC < LLON(case definition 2). Nevertheless, it appears in the draft criteria document that NIOSH chose instead decrement in FEV_1 without considering decrements in vital capacity, as the critical health effect metric for conducting the risk assessment.

The use of FEV_1 as the critical event is not uncommon. It is often used, for example, to set exposure guidelines for various irritant and reactive VOCs encountered in the paints and plastics industries, to mention examples. The basis for this broader use demonstrates why it is not appropriate here:

a. Decreases in FEV_1 are observed with exposures to many agents that do not cause BO.

b. The decreases in FEV_1 observed in response to inhalation of reactive VOCs is thought to occur as the result of an immediate and direct effect of airway irritation. This is not the case for BO.

c. Many cases of decrease in FEV_1 are reversible. BO is not considered to be reversible.

d. Decreases in FEV_1 are indicative of large airway obstruction, not total lung capacity (FVC) as is the case for BO.

e. There is no data to suggest that a large percentage of those persons with reduced FEV_1 will ultimately develop bronchiolitis obliterans. For example, in Chaisson et al., 2010,[4] the authors conclude, "*It is known that diacetyl exposure causes bronchiolitis obliterans and fixed obstructive lung disease. But, correlation between actual disease and incidence of abnormal longitudinal FEV_1 decline remains unknown.*"

An additional concern with the choice of FEV_1 decline is the potential for collecting poor quality data associated with this endpoint. Although spirometry is a useful screening tool, it is usually combined with other medical tests and physical examination before a diagnosis can be made.

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[3] The extremely low incidence of bronchiolitis obliterans in industry itself bears some note.

[4] Chaisson NF, Kreiss K., Hnizdo E., Hakobyan A., Enright PL, (2010) *Evaluation of methods to determine excessive decline of forced expiratory volume in one second in workers exposed to diacetyl-containing flavorings*, J. Occup. Environ. Med. 52(11):1119-1123.

NIOSH found that the quality of the spirometry data was questionable. In the HHE report 2000-0401-2991 (page 11) NIOSH points out that "most tests could not be assessed with regard to quality because a sufficient number of forced expiratory maneuvers were not recorded during the test." If NIOSH did not have confidence in the quality of the data used to assess the manifestation of the health effect, how can NIOSH be certain the correct data are being modeled in the QRA?

The quality of the spirometry is important as noted by Kay Kreiss in her article (Chaisson et al., 2010). "The fixed annual limits of decline such as the ATS or ACOEM criteria, or the 8% FEV_1 cutoff may work in some situations, but they allow for significant over or underestimation of the 95^{th} percentile depending on the quality of the spirometry in the workplace." Such over or underestimation weakens the association between assessing risk of exposure and health effect endpoint.

The NIOSH document correctly notes: "Bronchiolitis obliterans is thought of as largely irreversible obstruction; reversibility of obstructive changes was assessed in these HHEs using bronchodilator medication for individuals with FEV_1/FVC and FEV_1 less than their respective LLofNs." (p. 119 of draft criteria document). However, 57% percent of the cases defined using FEV_1 were not tested for reversibility. Therefore, all cases were defined as being irreversible without testing the majority of them.

NIOSH also notes: "The classification of cases was not based on clinical diagnoses because the systematic medical data collected in the HHEs were limited to the questionnaire and spirometry tests. A complete diagnostic work-up of probable cases is not routinely performed in NIOSH HHEs though full disclosure of individual test results and recommendations for referral are provided to participating workers." (p. 119 of draft criteria document). Classifying cases in the absence of clinical diagnoses adds further uncertainty to the QRA.

These uncertainties in the data call into question the scientific justification of choosing the decrease in FEV1 as a biologically relevant endpoint.

B. The Animal Based Risk Assessment Is Based On Very Little Data And The Benchmark Dose Selected Is Inappropriate

We have reviewed the animal-based risk assessment for diacetyl (and 2,3-pentanedione) and while in general support how NIOSH utilized the 2009 work of Allen, we have identified some concerns inherent to the assessment.

1. The Available Animal Data For Diacetyl Is Limited, Which Leads To Large Degrees Of Uncertainty In The Results

a. NIOSH's benchmark dose modeling is based on a 12-week subchronic study in mice, with five mice per treatment group (10 mice per dose when 6- and 12-week exposures are combined).

b. In the analysis by Allen, the limited data were subjected to seven different dichotomous dose-response models, and the range of results for the

benchmark dose spanned 3,700–fold differences. A more robust dataset would be expected to yield more concordant results amongst the mathematical models employed.

c. The critical effect was peribronchial lymphocytic inflammation, which was not observed in any of the control animals; however, nasal inflammation was observed in 3 of 10 control animals and peribronchiolar inflammation was observed in 2 of 10 control animals. The apparent absence of inflammation in the peribronchial region of the lungs in the control group, which is in between the nasal and peribronchiolar regions, is curious and results in a lower benchmark dose estimate for this endpoint.

2. NIOSH Exacerbates This Uncertainty By Choosing To Estimate The Lower Confidence Level Of The Benchmark Dose Assuming An Acceptable Risk Of 1 In 1000 ($BMDL_{0.1}$)

a. The acceptable risk level of 1 in 1000 is more routinely applied to carcinogens. Neither diacetyl or 2,3-pentanedione is carcinogenic.

b. EPA typically estimates the benchmark dose assuming an acceptable risk level of 10% (1 in 10; $BMDL_{10}$) for dichotomous data; however, lower values have been used based on the limit of sensitivity (statistical power to detect a response). Because there were 10 mice in each dose group, a response of 3/10 (30%) would be required to be statistically significant. Thus the default $BMDL_{10}$ is more appropriate than the $BMDL_{0.1}$ (1 in 1000).

c. Moreover, if the first positive dose has a response rate that exceeds the benchmark dose, there is considerable uncertainty due to extrapolation below the range of observation. Considering that there was a 50% response rate at the lowest diacetyl exposure dose (25 ppm) in the index animal study, a $BMDL_{10}$ is already out of the range of observation and thus a $BMDL_{0.1}$ is highly uncertain. This is the primary difference between the NIOSH analysis and the analysis conducted by Maier, et al. (i.e., if the acceptable risk level is set at 10%, both analyses result in $BMDL_{10}$ within a factor of 3 of one another).

d. Further, applying the 1 in 1000 acceptable risk level NIOSH assumes a linear dose-response relationship even at these low exposure concentrations. This not only presumes a non-threshold response but it contradicts toxicological plausibility as well as the published epidemiology data for diacetyl.

e. Without the extreme assumption of a 1 in 1000 acceptable risk, NIOSH's QRA based on the animal data does not support the proposed REL of

5 ppb for diacetyl, but instead would be in line with that recommended by Maier, et al. and with the levels set for other chemicals of comparable reactivity (see below).

The lack of toxicity data for 2,3-pentanedione makes it even more difficult to establish a REL for 2,3-pentanedione based on sound scientific evidence. However, that does not mean that setting the REL at the lowest level theoretically measurable is appropriate. Given the high degree of uncertainty in the analysis of risk, any proposed REL should be subject to revision once more robust and definitive animal studies have been completed.

3. Concerns With Use Of 1/1000 Risk Level

NIOSH's proposed REL for diacetyl is based on a risk level of one in one thousand, which is stated to be "a choice often used in OSHA regulation." Although there is precedent for using this stringent precautionary standard for carcinogens, there is significantly less precedent for applying this risk level to non-carcinogenic effects (e.g., cadmium, bloodborne pathogens). OSHA has used other methods for establishing permissible exposure limits ("PELs") for non-carcinogens (e.g., glycol ethers). Further, NIOSH recently took a different approach when deriving an REL for carbon nanotubes. In that case, NIOSH used the more common method of benchmark dose modeling, with a target effects level of 10%. This approach is consistent with that used recently by EPA to derive inhalation toxicity criteria for non-carcinogens.[5]

C. Use Of A Model Better Suited For Cancer-Causing Chemicals

One major concern with NIOSH's risk assessment process is with the use of extrapolation methods typically reserved for risk assessments of cancer-causing chemicals or substances. As correctly observed on page 137 of the draft criteria document, "all of the risk assessments developed here assume some degree of low-dose linearity." However, non-cancer effects are generally not treated as having a low-dose linear mechanism. For example, on page 131 of the draft criteria document it is stated that 13 cases, where case definition was FEV_1<LLON, out of a total of 314 workers were observed in the low duration/low exposure levels, 8.2 of which were estimated to be excess cases, a rate of 26 cases per 1000 workers. The average exposure in the 13 cases was 0.79 ppm. NIOSH then extrapolated 26/1000 at 0.79 ppm to derive 1/1000 at 0.03 ppm. There is no basis to conclude — or even assume — that the risks would scale in this fashion, which assumes both that effect varies linearly with exposure level, and that there is no zero-effect threshold. Indeed the lack of evidence of actual BO resulting from these low exposures suggests that the dose/response relationship is non-linear and/or that there is a non-trivial zero-effect threshold.

The current proposal appears to assume that there is not a "threshold" or level below which worker exposure to diacetyl presents no discernible health risk. We believe that any limit should take this into account.

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[5] EPA (Environmental Protection Agency) [2011]. Benchmark Dose Software (BMDS). [http//www.epa.gov/ncea/bmds/index.html]. Date accessed: March 2011.

1. An understanding of the lung toxicology and chemical reactivity suggests that low exposures (inhaled doses) of diacetyl cause only minor injury to the respiratory epithelium. That is rapidly repaired leaving no residual damage or risk to respiratory health.

2. The Lockey, 2009[6] study had robust enough data to demonstrate a no observed adverse effect level ("NOAEL") of 0.074 ppm (74 ppb) and lowest observed effect level ("LOEL") of 0.348 ppm (348 ppb) based on pulmonary function deficits. Maier, et al, 2010 pointed out that the Lockey values provide an approximate range for an effect level threshold in the microwave popcorn worker population.

3. The original Allen, 2009[7] modeling of animal data suggested a representative best fitting model would appear threshold like at low doses.

NIOSH should also explain the peer review process used to approve the modeling approach utilized in this risk assessment since this does not appear to be based on any published methodology (e.g., U.S. EPA's BMD modeling software).

D. The Proposed RELs Are Inconsistent With Similar Exposure Guidance For Other Similar Compounds

Regardless of the robustness of the data in conducting a risk assessment, one test of accuracy is to compare the ultimate estimate with that published previously for chemicals of comparable reactivity or perceived risk. Toward this end, we conducted a posthoc read-across exercise for the proposed REL for diacetyl with the published RELs, PELs, and RD50s (exposure concentration producing a 50% decrease in respiratory rate) for chemicals we suspect to share similar reactivity as well as those that assuredly present a greater or a lesser risk for inhalation toxicity.

These comparisons, or read-across, also serve to examine the consistency of the risk assessment models used to derive limits for exposure. Table 1 presents examples of common chemicals for which there is a rich toxicology database. Some of these may be irritating to airways, but none of the chemicals in Table 1 are known to react with proteins. All of the established PELs are 10,000 ppb or above for these classes of nonreactive chemicals.

Table 1. Chemicals that do not bind to proteins airways

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[6] Lockey JE, Hilbert TJ, Levin LP, Ryan PH, White KL, Borton EK, Rice CH, McKay RT, LeMaster GK [2009]. *Airway obstruction related to diacetyl exposure at microwave popcorn production facilities.* Eur Respir J 34(1):63-71.

[7] Allen BD [2009a]. *A quantitative risk assessment for diacetyl based on respiratory tract lesions in mice.* Chapel Hill, NC: Prepared for the Occupational Safety and Health Administration, Prime Contract Number DOLQ05622303.

Non-Reactive Chemicals	NIOSH REL-ppb	OSHA PEL-ppb	ACGIH TLV-ppb	RD50 ppb
Acetic acid	10,000	10,000	10,000	227,000
2-Hexanone	1,000	100,000	5,000	
2-Propanone	150,000	200,000	250,00	
Styrene		100,000	50,000	980,000
Dipropylketone	50,000		50,000	
Dichloroethylene		200,000		

Table 2 presents common chemicals found in the workspace air in the paint and plastics industries. These chemicals are well studied and have greater potential to cause adverse effects than diacetyl. The PELs for these chemicals vary from 2,000 to 200,000 ppb. Diacetyl and 2,3-pentanedione both have reactivity most similar to these chemicals although the reactivity is more narrowly restricted to fewer molecular targets. A read-across from these chemicals alone would suggest a derived PEL for diacetyl to be greater than 2,000 ppb.

The RD50 for diacetyl in humans was estimated to be 29,000 ppb,[8] which is intermediate between the nonreactive chemicals in Table 1 and the reactive chemicals in Table 2.

Table 2. Chemicals which can react more strongly with proteins in airways

Common Reactive Chemicals	NIOSH REL-ppb	OSHA PEL-ppb	ACGIH TLV-ppb	RD50 ppb
Methyl acrylate		10,000		
Methyl methacrylate		100,000		
Acetaldehyde		200,000	100,000	3,900
Ethyl acrylate		25,000	5,000	
Crotonaldehyde		2,000		
Furfural		5,000		

Table 3 presents three notorious chemicals that are highly reactive in the airways and blood, with risk of potent and rapid death and/or severe lung injury. The PELs for phosgene and acrolein are 100 ppb, driven in part by rapid and potentially lethal effects. Diacetyl and 2,3-pentanedione are clearly not comparable to these chemicals in their toxicological behavior. It would be hard to justify on a scientific basis that diacetyl or 2,3-pentanedione cause a greater concern, and thus should have lower limits of exposure, than these three compounds.

[8] Larsen ST, Alarie Y, Hammer M, Nielsen GD [2009]. *Acute airway effects of diacetyl in mice.* Inhal Toxicol 21(13):1123-1128.

Table 3. Highly Reactive Chemicals

Highly Reactive Lung and Nervous System Toxins	NIOSH REL-ppb	OSHA PEL-ppb	ACGIH TLV-ppb	RD50 ppb
Acrolein	100	100	100	2,900
Hydrogen Cyanide		10,000		
Phosgene	100	100		

Table 4 presents three reactive chemicals that bind to DNA; all of which are mutagenic and carcinogenic. The PELs for these chemicals are derived from the long-term non-threshold risk of cancer. Although the PELs range from 20 to 2,000 ppb, NIOSH has recommended levels which are as low as possible based on current technology. The evidence available to date suggests that the naturally occurring diacetyl and 2,3-pentanedione do not fall into this class of chemicals.

Table 4. Highly Reactive Chemicals with DNA and are Carcinogens

Industrial Carcinogens	NIOSH REL-ppb	OSHA PEL-ppb	ACGIH TLV-ppb	RD50 ppb
Toluene-2,4-diisocyanate*	5	20	20	390
1,3-Butadiene*	Low as Possible	2,000	10,000	
Diazomethane*		200		

This comparison based on the general toxicological behavior of chemicals suggests that, unless there is substantial risk of carcinogenicity or cumulative toxicity, the results of the risk assessment for diacetyl and 2,3-pentanedione lead to much higher proposed exposure limits, even after applying a reasonable safety factor.

In summary, based on the similarity of toxicological behavior of diacetyl and 2,3-pentanedione with other chemicals assessed by OSHA and NIOSH, the proposed limit of 5 ppb for diacetyl suggests that the risk assessment is premature, highly uncertain, and that overly conservative assumptions have been applied to produce an overly protective limit.

E. The Proposed Industrial Hygiene Recommendations Run Counter To Prior Recommendations

The proposed REL is a factor of 100 lower than the lowest proposed PEL for diacetyl resulting from OSHA's regulatory process in 2009. The draft criteria document states that the REL is achievable based on OSHA-sponsored site visits (Line 17, page 213). However, this statement is not correct with respect to 2,3 pentanedione. If there is any evidence that the REL for 2,3-pentanedione is achievable, that evidence should be cited.

When NIOSH publishes a criteria document, OSHA can rely on that document to cite employers under the General Duty Clause Section (5) (a) (1) of the Occupational Safety and Health Act. This is extremely troubling where there has been no scientifically-based finding of technological feasibility. Congress specifically intended that this outcome be avoided when it passed Section 6(b)(5) of the Occupational Health and Safety Act which requires OSHA to make findings of technological feasibility when promulgating standards:

> The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which **most adequately** assures, **to the extent feasible**, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life. Development of standards under this subsection shall be based upon research, demonstrations, experiments, and such other information as may be appropriate. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest available scientific data in the field, the feasibility of the standards, and experience gained under this and other health and safety laws. Whenever practicable, the standard promulgated shall be expressed in terms of objective criteria and of the performance desired.

Thus, Weaver respectfully asks that NIOSH carefully consider the practical effect on employers before publishing a criteria document. Employers should not be subjected to meeting an REL which otherwise would not pass scrutiny under the protections provided under the Administrative Procedure Act if it had been passed as a regulation. The criteria document can become a *de facto* regulation.

The report cites Eastern Research Group, Inc.'s ("ERG") study (draft criteria document line 4, page 217) as the basis for the decision that engineering controls can reduce diacetyl levels in a popcorn production facility. The report cites ERG data indicating reductions in personal breathing zone measurements on a time-weighted average ("TWA") and a short-term basis from 83.8% to 99.4%. TWA measurements were reduced to below the level of detection ("LOD") (generally about 3 ppb). We understand NIOSH is basing this statement on a 500 minute total (eight hours 20 minutes) personal exposure and lab results reported as <LOQ. The values we are referring to are 2.7 ppb, 2.9 ppb, and 3.5 ppb. These values are reported as "none detected (ND)." ERG explicitly states in this report that ND is interpreted as 0 ppm.] Then after ERG visited this facility in 2010 they reported the values in Table A2 as less than the LOQ values. This is contrary to the actual values which were in fact higher than the Action Level of 2.6 ppb that NIOSH is proposing.

The last bullet on page 220 of the draft criteria document states the following: "*Data gathered on diacetyl exposure demonstrated that engineering controls and work practices currently available can control diacetyl exposures below the REL. A validated analytical method can be*

used to effectively measure worker exposure at these levels." However, the only data referred to in this Chapter discussing that the REL is achievable using currently available engineering controls and work practices is the ERG Report 2009c. (Eastern Research Group, Inc [2009c]: Site visits related to diacetyl and flavorings that contain diacetyl: food production facility G—buttered popcorn production (pre-popped). OSHA Docket No. 2008-0046-0081).

We are concerned that one plant alone does not prove that diacetyl exposures can be reduced below the REL for all workplaces in all food industry environments. Further, the ability to achieve the RELs is also suspect because very few laboratories have been able to measure to the very low levels reported in the OSHA validated method for diacetyl. While these levels may be achievable in research laboratories, they are not routinely achieved in a reliable and reproducible manner by the majority of laboratories. Since many employers have been conducting their industrial hygiene monitoring to measure for much higher limits of detection, the data to support the widespread use of such very low levels of detection is very limited in our experience. This issue is even more pronounced for 2,3-pentanedione.

Finally, as several commentators at the public hearing in August, 2011, noted, it is unclear on what basis the document recommended the use of full-face respirators rather than half-face respirators. Since the NIOSH diacetyl or butter flavorings HHE was published, NIOSH's recommendation has been that employers can use half-face respirators and that is what is currently used throughout the industry.

The draft criteria document states that a Full Face Air Provided Respirator ("FFAPR") should be worn when exposures may exceed the proposed NIOSH RELs. The concept for this recommendation comes from the NIOSH Respirator Selection Logic [2004c]. Step 6 in the NIOSH Respirator Selection Logic specifically asks: "*Is the contaminant an eye irritant or can the contaminant cause eye damage at the workplace concentration*"? (Diacetyl and 2,3-pentanedione are eye irritants). If you choose "yes" then NIOSH recommends the use of a FFAPR.

This logic circumvents the employer's ability to conduct a workplace hazard assessment and apply ANSI Z87.1-2003 (as required by 29 CFR 1910.132, 133 and 134). OSHA defers to ANSI Z87.1-2003 regarding compliance for eye/face protection. The way Annex I (eye/face protection selection chart) in ANSI Z87.1-2003 reads, it would allow for cover goggles (no ventilation), cover goggles (indirect ventilation), and cup goggles (indirect ventilation). The ANSI standard further recommends that for "severe exposures" a face shield should be added for extra protection.

During the NIOSH stakeholder meeting an attendee asked whether the employees would be sufficiently protected by wearing indirect ventilated or no ventilation goggles with a HFAPR. NIOSH agreed that this would be acceptable practice and stated that it would revisit this issue and consider revising the draft criteria document accordingly.

F. Naturally Occurring Diacetyl May Result In Ambient Levels Higher Than The Proposed REL During Food Production

As set forth above, the available science demonstrates that the proposed RELs are too low and the QRA is unreliable because of the lack of reliable data on exposures in the index plant, and the animal analysis is too conservative by objective measures. We are very concerned that these overly conservative RELs could call into question what appears to be decades of safe experience with naturally occurring diacetyl in a wide variety of foods. The lack of prevalence of BO in the food production industry where low levels of naturally occurring diacetyl have occurred for decades reinforces the scientific conclusion that the proposed RELs are several orders of magnitude too low.

NIOSH needs to take into account naturally occurring levels as they are relevant to the proposed REL in two ways. First they demonstrate that lifetime exposures well in excess to the proposed RELs do not result in any significant incidence of BO or airway injury in the general population. Second, they mean that the proposed RELs are not achieved even if diacetyl and 2,3-pentanedione were completely eliminated from flavorings and all other aspects of the manufacturing process.

Since at least 2006 the presence of diacetyl in many food products has been discussed, notably in the advisory meeting minutes prior to the adoption of California OSHA's diacetyl rule (California Code of Regulations, Title 8, Section 5197). During that rulemaking process the following foods were identified as having naturally occurring diacetyl:[9]

- strawberries
- margarine
- wine
- beer
- baked goods
- dairy products
- roast chicken
- tomatoes
- coffee

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[9] Flavor Advisory Meeting on Diacetyl and Chemicals in the Flavoring Manufacturing Industry in California, California Div. of Occupational Safety and Health, Cal/OSHA, (Sept. 28, 2006), http://www.dir.ca.gov/dosh/doshreg/Flavor092806Minutes.pdf.

In many cases, naturally occurring diacetyl concentrations can exceed the amounts of synthetic diacetyl added during manufacturing. The industries that process the products listed above have been in operation for many decades — some approaching 100 years — without any evidence of the unusual clusters of BO. This fact begs the question whether it is prudent to impose the proposed REL and thereby cause public concern for products which have naturally occurring diacetyl and which have been safely manufactured and consumed for long periods of time.

The publicly available scientific literature provides additional insight into naturally occurring levels of diacetyl. As an example, according to an article entitled "Emissions from Cooking Microwave Popcorn" (Rosati, et al, *47 Critical Review in Food Science and Nutrition* 701-709 (2007)), EPA conducted testing of hot air popped corn. At page 706 of the article, EPA reported "chemicals emitted during hot air popping were extremely low with all chemical concentrations well below 0.1 nanograms per cc ...." Although no further detail was provided in the paper on the individual chemical or the specific diacetyl concentration from this hot air popped corn, it does demonstrate that EPA found some level of chemicals that, if this were all diacetyl, would convert to a diacetyl air concentration of approximately 28 ppb at room temperature and pressure.[10] Even if this was only one-quarter diacetyl, it would still exceed the proposed REL.

Other industries and occupations likely unable to achieve the extremely low REL would include bakers, both at traditional bakeries and those employees involved in baking food products containing natural butter, snack food manufacturers, candy manufacturers, short order cooks preparing foods cooked in butter, and potentially winery and brewery workers, as well. We believe it is bad public policy to set an exposure level that cannot be met even in workplaces in which no chemicals are added whatsoever, but in which naturally-occurring products and dairy products are used as ingredients in the final food product. This is particularly true here where these industries have existed for decades without any evidence of increased risk of BO.

Finally, although less is known about the levels of naturally occurring 2,3-pentanedione, and therefore further study is necessary, we do know that laboratories are having a difficult time attaining the detection levels NIOSH has adopted as the REL for 2,3-pentanedione. Please see the attached letter from Concentra.

CONCLUSION

The proposed criteria document proposes RELs and STELs for diacetyl and 2,3-pentanedione that are not warranted by the available scientific data and are not achievable with existing engineering and analytical technologies. Issuance of the proposed RELs based on deeply flawed science will needlessly threaten significant portions of the American economy and could mistakenly lead consumers to believe that products they have used safely for decades pose a risk where none exists. Before moving forward, the following specific issues need to be addressed before any fair and meaningful recommendation can be made:

- The human risk assessment relies on exposure reconstruction data that is wrought with uncertainty and appears to emphasize a health effect end point (decreased

[10] Based on several assumptions regarding room size, vapor dispersion, and other factors.

FEV_1) that is not specific for diacetyl exposure. It should be revised based on exposure data that can withstand public scrutiny and an appropriate choice of health effect end point.

- The issue of a susceptible population is an important public health concern and NIOSH should try to identify the reason why some individuals may be particularly susceptible to diacetyl exposure so that appropriate respiratory protection can be provided to those workers.

- The risk assessment model utilized should be one that is appropriate to a non-cancer endpoint by including the concept of a threshold below which no adverse health effects would occur.

- The animal risk assessment is based on limited risk characterization data and should be re-examined as additional studies are published. The conservative assumptions about the appropriate $BMDL_{0.1}$ should be re-examined and a $BMDL_{0.1}$ that is consistent with current understanding of diacetyl toxicology selected.

- The acceptable level of risk selected is inappropriate for a non-carcinogen and an appropriate risk factor should be incorporated into the risk assessment.

- The proposed RELs and STELs are inconsistent with the levels set to minimize risk of exposure to other chemicals of comparable as well as far greater risk potential than diacetyl and 2,3-pentanedione and should be re-examined in light of the current approach to regulating other similar chemicals.

- The industrial hygiene recommendations should be changed to allow the use of half face respirators and goggles.

- Naturally Occurring Diacetyl — further study is needed to identify the levels of naturally occurring diacetyl (and possibly 2,3-pentanedione) released during food production processes and to determine the proposed RELs taking these naturally occurring levels along with the historical absence of airway disease in these industries into account.

Weaver has been vigilant in responding to the emerging evidence regarding the use of butter flavorings in food manufacturing and has made significant investments to address these issues so we can continue to ensure a safe workplace. Weaver supports RELs based on sound science. But we do oppose levels set on faulty science that are far below that necessary to protect workers and would needlessly cause serious harm to many food businesses. We look forward to working with NIOSH to develop the necessary data to support an appropriate REL for both diacetyl and 2,3-pentanedione.

To that end, we ask for the opportunity to meet with NIOSH about the issues contained in this letter. We would be glad to meet with NIOSH at the time and place of its choosing, with any

other participants you believe would be helpful. We believe that with an open dialog, we can reach a prudent REL that protects workers based on good science.

Sincerely,

WEAVER POPCORN COMPANY, INC.