Criteria for a Recommended Standard:
Occupational Exposure to Diacetyl and 2,3-Pentanedione

Response to Public and Stakeholder Comments

The National Institute for Occupational Safety and Health (NIOSH) Response to Diacetyl and 2,3-Pentanedione Public and Stakeholder Comments document contains the NIOSH responses to the public and stakeholder comment submissions received by the NIOSH Docket Office during the public comment periods. Information from the public meeting, external review draft document for public comment, and public and peer review comment submissions from the 2011 public comment period are available on the NIOSH Diacetyl and 2,3-Pentanedione Criteria Document Docket page: http://www.cdc.gov/niosh/docket/archive/docket245.html. Information from the re-review of Chapter 6 and new section of Chapter 8, including the external review draft chapters and the public comment submissions are available on the Regulations.gov website at https://www.regulations.gov/document?D=CDC-2013-0021-0001. The NIOSH Response to Diacetyl and 2,3-Pentanedione Peer Review Comments is available as a separate document at http://www.cdc.gov/niosh/docket/archive/docket245.html.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATS	American Thoracic Society
BMD	Benchmark dose
BMR	Benchmark response rate
Cal/OSHA	Division of Occupational Safety and Health, aka Cal/OSHA
EPA	Environmental Protection Agency
ERG	Eastern Research Group
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association
FEV_1	Forced expiratory volume in one second
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
HHE	Health hazard evaluation
hr	Hour
L/min	Liter per minute
LOD	Limit of detection
LOQ	Limit of quantitation
LUMO	Lowest unoccupied molecular orbital
min	Minute
ND	Not detected
NHANES III	National Health and Nutrition Examination Survey III
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
OEL	Occupational exposure limit
OSHA	Occupational Health and Safety Administration
PEL	Permissible exposure limit
ppb	Parts per billion
PPE	Personal protective equipment
ppm	Parts per million
QRA	Quantitative risk assessment
REL	Recommended exposure limit

RQL	Reliable quantitation limit
SDS	Safety data sheet
SPIROLA	Spirometry Longitudinal Data Analysis software
STEL	Short-term exposure limit
TDI	Toluene diisocyanate
TERA	Toxicology Excellence for Risk Assessment
TWA	Time-weighted average
yr	Year

Track No.	Commenter	Full comment (copied verbatim)	Response
EC - 1	Eastern Research Group, Inc.	Page 44_Line 9:_Move "ND*" to the MEAUREMENT RANGE column. In the CONTROLS IN PLACE column, add "Dilution ventilation; heat extraction for adjacent process".	The document was revised as suggested.
EC - 2	Eastern Research Group, Inc.	Lines 25-26: Modify capitalization and punctuation in CONTROLS IN PLACE column to read: "Heat extraction hoods, dilution ventilation".	The document was revised as suggested.
EC - 3	Eastern Research Group, Inc.	Lines 29-31: Revise CONTROLS IN PLACE column to read: "Dilution ventilation, slot hood at tumbler, modified tank cover, work practice changes".	The document was revised as suggested.
EC - 4	Eastern Research Group, Inc.	Lines 37-39: Revise CONTROLS IN PLACE column to read: "Dilution ventilation; controls for other purposes: immediate rinsing, cool temperature".	The document was revised as suggested.
EC - 5	Eastern Research Group, Inc.	PAGE 45 Line 5: Revise CONTROLS IN PLACE column to read: "Dilution ventilation, hose from tank to floor drain".	The document was revised as suggested.
EC - 6	Eastern Research Group, Inc.	Line 9: Revise CONTROLS IN PLACE column to read: "Dilution ventilation, oven room heat extraction".	The document was revised as suggested.
EC - 7	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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	See response to EC-11.

		"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?	
EC - 8	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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	See response to EC-32.

		as evidence of a "reasonably achievable" control measure.	
EC - 9	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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.	While respirators may need to be used for some tasks, engineering controls exist that have been shown to reduce worker exposures to levels below the recommended exposure limit (REL). A 3-year study of a large microwave popcorn production facility showed that the use of exposure controls can dramatically reduce diacetyl exposures to all production workers. As a result of the implementation of exposure controls from January 2001 through May 2003, average diacetyl air concentrations declined two orders of magnitude in the mixing room (from 38 parts per million [ppm] to 0.46 ppm) and the quality control laboratory (from 0.54 to 0.002 ppm), and three orders of magnitude in the packaging area (from 1.69 ppm to 0.002 ppm for machine operators). These interventions included enclosing the mixing room and providing general room exhaust ventilation and local exhaust ventilation for the mixing tanks. Closed transfer processes were implemented through the installation of a pump for transfer of flavor/oil mixtures from mixing room to holding tank and the use of flavoring transfer pump for 5-gallon containers. The building of an enclosure for all oil/flavoring holding tanks and installing local exhaust ventilation on all tanks further reduced exposures to employees in the packaging area of this plant. The installation of a replacement air system for all production

			areas was completed to provide make-up air for the facility. In addition, the temperature of the flavor and oil tanks was decreased to reduce evaporation of volatiles. In the final survey conducted following the implementation of all engineering and process controls, personal diacetyl exposures for all workers/job categories in the plant were less than the limit of detection (LOD) of 0.002 ppm with the exception of mixers, which ranged from below the LOD to 2.92 ppm.
EC - 10	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	*]* **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 I 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; even thought several of the ERG studies presented initial exposures that were orders of magnitude higher than those found in the operation	See response to EC-11.

		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).	
EC-11	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**Chapter 8: Hazard Prevention and Control of Exposures to Diacetyland 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).	NIOSH RELs are based currently on the technical feasibility and not "reasonably achievable." The current NIOSH [1995] REL policy specifies that "NIOSH RELs will be based upon risk evaluations using human or animal health effect data, and on an assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques." To this end, technical feasibility has been addressed by providing data from a microwave popcorn plant that reduced the exposures to most workers below the REL using engineering controls. The operations conducted by this facility including weighing, mixing, and transfer of diacetyl-containing flavorings are common processes in many flavoring and food production facilities. It can be concluded that the ability of this facility to reduce the exposures of most production workers below the REL would indicate feasibility for other diacetyl substitutes.
EC-12	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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	See response to EC-11.

		insufficient evidence to advance a claim of "reasonably achievable" to the OSHA docket.	
EC-13	David Egilman, MD, MPH, Brown University and Hank Schilling- Never Again Consulting	**Choice of cover picture** The cover depicts a worker openly pouring diacetyl from a bucket to a smaller container with a respirator as his only apparent respiratory protection. This picture is a poor representation of how diacetyl should be handled. As NIOSH is aware diacetyl is toxic at relatively "low" concentrations and should be handled in a closed system whenever possible. Respirator protection is not enough on its own. For example, Lockey et al. (2009) found that workers who were only exposed after the use of powered air-purifying respirators was mandated were nevertheless at a 5.7-fold increased risk for obstructive lung disease. We believe a picture of a worker openly handling diacetyl gives the wrong impression in terms of the degree of risk and level of protection required to protect worker health.	The cover of this document has been revised in response to comments.
EC-14	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	The Criteria Document states that engineering controls are available to control worker exposures down to the RELs, but also acknowledges (in a different section) that there may be situations where extended respirator use may be necessary. Should these apparently contradictory statements be reconciled or given fuller explanation?	These statements are not contradictory because it is an established principle of industrial hygiene that the use of respirators is allowed when effective engineering controls are not feasible or while they are being implemented.
EC-15	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In Section 7.7 concerning controlling vapor exposures, the statement that engineering controls can reduce exposures to less than the limit of detection (LOD) appears to be based on only one study involving popcorn flavor manufacturing. That there is but a single example backing this statement may cause some to question the plausibility of the assertion.	NIOSH RELs are based currently on the technical feasibility and not “reasonably achievable.” The current NIOSH [1995] REL policy specifies that “NIOSH RELs will be based upon risk evaluations using human or animal health effect data, and on an assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques.” To this end, technical feasibility has been addressed

			by providing data from a microwave popcorn plant that reduced the exposures to most workers below the REL using engineering controls. Section 7.7 has been revised to include a 3-year study of a large microwave popcorn production facility showed that the use of exposure controls can dramatically reduce diacetyl exposures to all production workers. As a result of the implementation of exposure controls from January 2001 through May 2003, average diacetyl air concentrations declined two orders of magnitude in the mixing room (from 38 ppm to 0.46 ppm) and the quality control laboratory (from 0.54 to 0.002 ppm), and three orders of magnitude in the packaging area (from 1.69 ppm to 0.002 ppm for machine operators). These interventions included enclosing the mixing room and providing general room exhaust ventilation and local exhaust ventilation for the mixing tanks. Closed transfer processes were implemented through the installation of a pump for transfer of flavor/oil mixtures from mixing room to holding tank and the use of flavoring transfer pump for 5-gallon containers. The building of an enclosure for all oil/flavoring holding tanks and installing local exhaust ventilation on all tanks further reduced exposures to employees in the packaging area of this plant. The installation of a replacement air system for all production areas was completed to provide make-up air for the facility. In addition, the temperature of the flavor and oil tanks was decreased to reduce evaporation of volatiles. In the final

			survey conducted following the implementation of all engineering and process controls, personal diacetyl exposures for all workers/job categories in the plant were less than the LOD of 0.002 ppm with the exception of mixers, which ranged from below the LOD to 2.92 ppm.
EC-16	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Consider recommending additional protections (e.g., higher level of respiratory protection) where both dust and vapor exposures are present and/or stating that in these situations process-based controls are especially important. Since there is no current method to quantify additional exposure coming from the particulate phase, basing protections on vapor measurements alone will not address the true level of risk.	Diacetyl can also be contained in a powder, either by encapsulation or adherence to a substrate. Measurement of airborne dust particles according to their size (e.g., inhalable, thoracic, and respirable) can help to explain where they may deposit in the respiratory tract. Several types of sampling devices are available (e.g., inhalable dust samplers, impactors, cyclones, and sampling cassettes) to provide measurements of different size fractions of airborne dust, or total airborne dust. In most cases, dust is collected onto a filter and the filter can be analyzed via gravimetric means to provide the mass of the dust including any adsorbed or encapsulated substances such as diacetyl and 2,3-pentanedione. Filters should be hydrophobic in nature (e.g., polyvinyl chloride) to minimize collection of moisture. After being measured gravimetrically, filters can be chemically analyzed for diacetyl and other content. Validated methods such as NIOSH Method 0500 for total dust and NIOSH Method 0600 for respirable dust [NIOSH 1994] are available for the collection and gravimetric analysis of airborne dust. The airborne exposure concentration level measured needs to reflect the concentration levels of both the diacetyl vapor and any

			particulates that may be present, and then the proper type of respiratory protection will still be selected. The air-purifying respirators recommended have the necessary particulate and gas/vapor removing elements. In summary, if particulate and vapor exposures are present, the airborne exposure concentration level measured needs to reflect the concentration levels of both the diacetyl vapor and any particulate present, and then the proper type of respiratory protection will still be selected.
EC-17	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Consider recommending additional protections for workers exposed to 2,3-pentanedione levels in the 5 ppb - 9.3 ppb range, which has been identified as a range with potential health risk but cannot be measured with current analytical methods.	Exposure levels of 2,3-pentanedione below 9.3 parts per billion (ppb) are below the proposed NIOSH REL; therefore, respiratory protection at that level is not required but still can be used if so desired.
EC-18	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In the Hazard Communication section, since flavor manufacturers will be preparing Material Safety Data Sheets (MSDSs) for their downstream customers, NIOSH should encourage them to list the presence of diacetyl and its substitutes at any level as well as listing the known health effects and necessary protective measures. Non-informative MSDSs for flavoring mixtures seriously limit employers' efforts to protect workers in food production. NIOSH could also state that inadequate MSDSs may result in OSHA action against the preparing company.	NIOSH has updated the diacetyl/2,3-pentanedione criteria document to provide additional information on hazard communication. This includes providing Globally Harmonized System of Classification and Labeling of Chemicals (GHS) classifications for diacetyl, 2,3-pentanedione, and mixtures containing these substances, based on the toxicological and physical-chemical data that are presented in the criteria document. This has resulted in classification of these compounds under several GHS human health endpoints and one physical hazard endpoint. NIOSH has also updated this document with recommendations with guidance on how these chemicals should be labeled as part of product labels and safety data sheets (SDSs)

			so that workers are informed of the potential hazards associated with exposure to these chemicals in both neat form and in mixtures.
EC-19	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In regard to the respirator selection table, explain what is meant by Maximum Use Concentrations. Are these 8-hr TWAs? Are there any circumstances where half-mask respirators may be appropriate (if not, that should be stated)? Since NIOSH believes the risk assessment supports the same REL for both diacetyl and 2,3-pentanedione. and they are only different because of the analytical constraints, would it be appropriate for the Maximum Use Concentrations in this table to be the same?	Maximum use concentration is the maximum atmospheric concentration of a hazardous substance from which an employee can be expected to be protected when wearing a respirator. It is determined by the assigned protection factor of the respirator or class of respirators and the exposure limit of the hazardous substance. The NIOSH RELs for diacetyl and 2,3-pentanedione are based on time-weighted exposure (TWA) exposures for up to a 8-hour workday during a 40-hour workweek. Maximum use concentrations are calculated in this case by multiplying the NIOSH REL by the assigned protection factor for that class of respirators. NIOSH maximum use concentrations are therefore based on up to an 8-hour TWA exposure. Only self-contained breathing apparatus can be used for entry into any atmosphere that is immediately dangerous to life or health. Diacetyl and 2,3-pentanedione should not have the same maximum use concentrations because these are based on the NIOSH REL of the compound in question. NIOSH does not recommend half mask respirators for respiratory protection against diacetyl or 2,3-pentanedione because NIOSH is not aware of any standards for gas-tight goggles that would permit NIOSH to recommend such goggles as providing adequate eye protection. This policy is stated in the NIOSH Respirator Selection Logic [2004b] page 21.

EC-20	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	NIOSH should recommend that employers adopt policies on the duration of use for hand protection, i.e., policies on when it is necessary to dispose of gloves so as to prevent exposure via breakthrough.	Based on this comment, the following language was added to section 8.5, in Chapter 8 after the first sentence: "It is important to select the most appropriate chemical resistant glove for the application and to determine how long it can be worn, and whether it can be reused. Procedures should be implemented to ensure that the gloves are replaced before breakthrough occurs. NIOSH recommends that before purchasing gloves or other protective clothing, the employer should refer to the SDS from the manufacturer of the diacetyl and 2,3-pentanedione being used, and /or request documentation from the glove or protective clothing manufacturer that the gloves meet the appropriate test standard(s) for the hazard(s) anticipated, and to request any glove and protective clothing breakthrough time data against diacetyl and 2,3-pentanedione that may be available from these sources."
EC-21	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In Section 8.2 on Engineering Controls, the statement that PPE is more expensive than engineering controls may not be true for all circumstances. There are stakeholders that may contest this statement given typical costs of $150,000 to $300,000 for installation of local exhaust systems in some flavoring manufacturing facilities with additional costs for ongoing operating of the controls. In addition, respiratory protection is often still warranted in addition to engineering controls.	Modified sentence to read: "The use of respirators and other personal protective equipment (PPE), as mentioned above, is a less desirable and less effective technique to reduce exposures that is normally considered as the last line of defense to reduce exposures."
EC-22	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH,	With regard to Section 8.2.1: a) Emphasize the need to prevent paper, gloves, etc., from being pulled into local exhaust systems, something that has been demonstrated to substantially impact exhaust efficiencies. Screens or other barriers have proven	This section was reworked to address the issues discussed by the reviewer. See section 8.2.1 General Considerations, specifically the revised and new bulleted points, which have been changed based on this comment.

	California Department of Public Health	effective for this purpose. b) Consider recommending continuous negative room pressure indicators for isolation rooms. C) Address the advisability and limitations on the use of contact/proximity switches that activate local exhaust systems on an as-needed basis, something employers will consider for energy conservation purposes. D) In this section, NIOSH proposes that manufacturers "install hood static pressure gauges (manometers) near hoods to provide a way to verify proper hood performance." By listing manometers in parentheses, NIOSH leaves the impression that these are the only acceptable device. In fact, there are other types of qualitative airflow monitors that are commonly utilized and, increasingly, quantitative airflow monitors with digital readouts are being used for exactly this purpose.	
EC-23	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In section 8.2.2, add quality control, research and development, and maintenance to the listing of job categories that may incur significant exposures to flavoring chemicals.	Quality control and research and development have been added to the listing of job categories (Table 8.1) that may incur significant exposures to flavoring chemicals. A sentence on maintenance personnel was added to the document. Because maintenance personnel tasks are intermittent, we felt the job category should not be listed in the table. Also, a section on laboratory chemical hoods has been added. This section describes the fume hood requirements along with general guidelines. See Table 8.1 and new subsection 8.2.2.1.1 Laboratory Chemical Hoods.
EC-24	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In Section 8.3.2, point out that some closed transfer processes can also produce significant exposure for personnel required to dismantle and clean/sanitize the equipment after a production run. These activities can be required frequently for certain flavoring manufacturing processes.	A statement has been added to the section to state that using PPE should be considered when cleaning diacetyl containing vessels. The potential for exposure during cleaning of flavoring production is present for closed and open processes and should be addressed by

			employee monitoring and the implementation of appropriate engineering controls and/or personal protective equipment.
EC-25	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In Section 8.4, Table 8.2, also list the half-face air-purifying respirator (APR) as a minimal option for short, transitory exposures - e.g., supervisors or QC personnel that are only momentarily in an isolation room where powder forms of diacetyl are not being processed. Powder forms of diacetyl and 2,3-pentanedione also need to be included in the respirator decision logic, although their selection cannot be based on measured concentrations at this time.	The draft criteria document did not list any half mask respirators in Table 8.2. NIOSH policy is to recommend only full facepiece respirators when there is the potential for eye irritation. Half mask respirators with goggles are not being recommended because NIOSH is not aware of any standards for gas-tight goggles that would permit NIOSH to recommend such goggles as providing adequate eye protection. This policy is from the NIOSH Respirator Selection Logic [2004b], page 21. Diacetyl can also be contained in a powder, either by encapsulation or adherence to a substrate. The air-purifying respirators recommended have the necessary particulate and gas/vapor removing elements. Measurement of airborne dust particles according to their size (e.g., inhalable, thoracic, and respirable) can help to explain where they may deposit in the respiratory tract. Several types of sampling devices are available (e.g., inhalable dust samplers, impactors, cyclones, and sampling cassettes) to provide measurements of different size fractions of airborne dust, or total airborne dust. In most cases, dust is collected onto a filter, and the filter can be analyzed via gravimetric means to provide the mass of the dust including any adsorbed or encapsulated substances such as diacetyl and 2,3-pentanedione. Filters should be hydrophobic in nature (e.g., polyvinyl

			chloride) to minimize collection of moisture. After being measured gravimetrically, filters can be chemically analyzed for diacetyl and other content. Validated methods such as NIOSH Method 0500 for total dust and NIOSH Method 0600 for respirable dust [NIOSH 1994] are available for the collection and gravimetric analysis of airborne dust.
EC-26	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	The industrial hygiene recommendations are counter to prior NIOSH recommendations, for instance with respect to the requirement for full-face respirators.	The respirator recommendations for diacetyl and 2,3-pentanedione are not counter to earlier NIOSH policy recommendations. No examples are given of such a conflict are provided by the reviewer.
EC-27	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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. 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.	This facility did indeed achieve significant reductions in diacetyl exposure among all production workers. This study has been highlighted for an example of technical feasibility of controlling exposures to below the REL at a microwave popcorn facility. See also response to EC-32.
EC-28	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**The Proposed Industrial H ygiene 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	See response to EC-32.

EC-29	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	When NIOSH publishes a criteria document, OSHA can rely on that document to cite employers under the General Duty Clause Section (S) (a) (I) 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)(S) 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	The diacetyl criteria document is a highly influential scientific assessment and is considered a significant guidance document. It was developed in accordance with the Office of Management and Budget Guidance Practices Bulletin. NIOSH has an established criteria to create RELs, which includes a quantitative risk assessment, analytical feasibility, and engineering achievability [NIOSH 1995]. NIOSH cannot comment on how another agency may use or may not use the information provided in our documents.

		regulation. The criteria document can become a *de facto* regulation.	
EC-30	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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 5OO 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	Eastern Research Group (ERG) mistakenly interpreted not detected (ND) values as zero ppm. When the issue was revisited and the analytical results reviewed, that issue was clarified.
EC-31	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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	See response to EC-32.

		production facility G -- buttered popcorn production (pre-popped). OSHA Docket No. 2008-0046-0081).	
EC-32	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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.	Section 7.7 has been revised to include a 3-year study of a large microwave popcorn production facility showed that the use of exposure controls can dramatically reduce diacetyl exposures to all production workers. As a result of the implementation of exposure controls from January 2001 through May 2003, average diacetyl air concentrations declined two orders of magnitude in the mixing room (from 38 ppm to 0.46 ppm) and the quality control laboratory (from 0.54 to 0.002 ppm), and three orders of magnitude in the packaging area (from 1.69 ppm to 0.002 ppm for machine operators). These interventions included enclosing the mixing room and providing general room exhaust ventilation and local exhaust ventilation for the mixing tanks. Closed transfer processes were implemented through the installation of a pump for transfer of flavor/oil mixtures from mixing room to holding tank and the use of flavoring transfer pump for 5-gallon containers. The building of an enclosure for all oil/flavoring holding tanks and installing local exhaust ventilation on all tanks further reduced exposures to employees in the packaging area of this plant. The installation of a replacement air system for all production areas was completed to provide make-up air for the facility. In addition, the temperature of the flavor and oil tanks was decreased to reduce evaporation of volatiles. In the final

			survey conducted following the implementation of all engineering and process controls, personal diacetyl exposures for all workers/job categories in the plant were less than the LOD of 0.002 ppm with the exception of mixers, which ranged from below the LOD to 2.92 ppm.
EC-33	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	*33* 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.I 32, 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	NIOSH policy is to recommend only full facepiece respirators when there is the potential for eye irritation. Half mask respirators with goggles are not being recommended because NIOSH is not aware of any standards for gas-tight goggles that would permit NIOSH to recommend such goggles as providing adequate eye protection. This policy is from the NIOSH Respirator Selection Logic [2004b] page 21.

		ventilation). The ANSI standard further recommends that for "severe exposures" a face shield should be added for extra protection.	
EC-34	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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.	This was considered, but NIOSH policy is to recommend only full facepiece respirators when there is the potential for eye irritation. Half mask respirators with goggles are not being recommended because NIOSH is not aware of any standards for gas-tight goggles that would permit NIOSH to recommend such goggles as providing adequate eye protection. This policy is from the NIOSH Respirator Selection Logic [2004b] page 21.
EC-35	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	The industrial hygiene recommendations should be changed to allow the use of half face respirators and goggles.	NIOSH policy is to recommend only full facepiece respirators when there is the potential for eye irritation. Half mask respirators with goggles are not being recommended because NIOSH is not aware of any standards for gas-tight goggles that would permit NIOSH to recommend such goggles as providing adequate eye protection. This policy is from the 2004 NIOSH Respirator Selection Logic [NIOSH 2004b] page 21.
EC-46	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	In Section 8.3.2, point out that some closed transfer processes can also produce significant exposure for personnel required to dismantle and clean/sanitize the equipment after a production run. These activities can be required frequently for certain flavoring manufacturing processes	Duplicate of EC-24
EC-48	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**The action Level of 2.6 ppb for diacetyl is burdensome and not feasibile.** NIOSH acknowledges that "…*Employers in the food manufacturing sector are generally small business owners with 89% in establishments employing fewer than 100 workers and n*	Little information exists on airborne diacetyl concentrations in the wide range of food industries mentioned by the commenter. However, the circumstances of diacetyl exposure do not change its toxicity. With

		early 53% in establishments employing fewer than 10 workers .... " (NIOSH 2011b, p. 214). Diacetyl is used as an additive in a range of prepared food products, and is served in many places where fresh foods are prepared due to its natural occurrence in wine, beer, butter, cheese, coffee, fruit and other foods (NIOSH 2011b, p. 21). In fact, diacetyl is formed endogenously in small amounts in humans (Kawano 1959; Ziatkis and Sivetz 1960; Gabriel et al. 1972). With an action level that is barely twice the quantitation limit, it is difficult to imagine a food or beverage processing or preparation area that would not exceed this proposed action level. The requirements that are triggered by the proposed action level for diacetyl, therefore, render the requirement to measure down to 2.6 ppb unreasonable and not technologically feasible. A comprehensive health and safety program that includes exposure monitoring (i.e., industrial hygiene sampling) is required if there is a possibility that an employer might be at the action level. Given the near ubiquity of diacetyl in our society, there would not be enough industrial hygienists to meet this demand. Measurements of airborne concentrations of diacetyl at the action level would also trigger a requirement for medical surveillance, including spirometry. NIOSH acknowledged the paucity of spirometric services that can deliver quality spirometry for reliably pinpointing subtle changes that would be required. For example, NIOSH diacetyl researchers found that: " ...*In California public health surveillance, only one of 13 commercial providers of surveillance spirometry for flavoring workers who reported results to the California Department of Public Health met a minimum quality criterion of 80% of test sessions with FEV1 of good quality* .... " (Cai et a. 2006) Thus, NIOSH's requirement for spirometry and medical surveillance for the large	respect to the inadequate number of industrial hygienists and high quality occupational medicine providers, companies specifying high quality services will drive a market response to their needs. Without such requirements, the preventive occupational health community is unlikely to change to meet preventive needs. No change in the document was made in response to this comment, although a justification for occupational medicine preventive services has been added to Chapter 9.

		population group that would be "captured" by this proposed rule is simply not feasible.	
EC-49	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	Consider explaining in-depth to the public what NIOSH means by "engineering control achievability". As a past OSHA official, I interpret this as "capable of being done **once**". Please clarify and consider explaining to the public the difference between technological feasibility as it relates engineering and work practice controls and engineering control achievability in the criteria document. Clarifying this difference will help employers understand what NIOSH means with regard to trying or implementing "feasible" options in their workplaces. This will also assist OSHA as they move forward in promulgating a health standard on food flavorings containing diacetyl and diacetyl substitutes.	The 1995 NIOSH [1995] REL policy specifies that "NIOSH RELs will be based upon risk evaluations using human or animal health effect data, and on an assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques." To this end, technical feasibility has been addressed by providing data from a microwave popcorn plant that reduced the exposures to most workers below the REL using engineering controls. The inclusion of feasibility of analytical methods [NIOSH 1994] and achievability of engineering controls into REL development is not always recognized by users of the NIOSH RELs. A common misperception is that all RELs are based solely upon the quantitative risk assessment, when, in fact, some RELs are based on analytical limitations or the inability to routinely control exposures with engineering controls. For example, the existing policy has resulted in some RELs being based on the limit of quantitation (LOQ), LOD, or reliable quantitation limit (RQL) of the analytical method, which can be at a higher exposure concentration than the derived health-based REL. In 2006, NIOSH published the criteria document on refractory ceramic fibers that included the terminology "feasible" and "achievable" when controlling exposures to the REL [NIOSH 2006]. The terminology of "achievability" and achievable has been used to describe engineering

			controls in the criteria document for hexavalent chromium [NIOSH 2013] and the draft criteria document for diacetyl/2,3-pentanedione [NIOSH 2011a]. In addition, NIOSH has expanded the engineering achievability discussion in Chapter 7 of the revised criteria document.
EC-50	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	Consider making it clearer in the criteria document that most of the logic behind engineering control technology comes from two primary industries: flavor manufacturing and microwave popcorn manufacturing. This is only fair to other food manufacturing industries that have not been thoroughly investigated. It is important because other sectors of the food manufacturing industry must not choose to be silent on sharing effective engineering control technologies. Consider stating in the criteria document the need for such information and how it assists NIOSH in the development of a REL in addition to how it assists OSHA as they move forward in promulgating a health standard (i.e. Occupational Exposure to Food Flavorings Containing Diacetyl and Diacetyl Substitutes). Obtaining the aforementioned information assists OSHA in there statutory requirement to set a 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."	While the evaluations of engineering controls completed by NIOSH have been conducted in the flavoring and microwave popcorn industries, the use of these controls for standard processes extends to other industries including food production. For instance, mixing of ingredients is done in the flavor production and food production (such as industrial bakeries). As the commenter mentions, appropriate control approaches should be shared between companies and NIOSH, with industry and labor also sharing a role in making sure that this information is properly disseminated.

EC-51	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	Table 8.2 on page 242, recommends the use of a full-face air purifying respirator (FFAPR) for workers exposed at or above the proposed REL (8-hr TWA). It is understood that this logic comes from the NIOSH Respirator Selection Logic; however, consider also allowing the use of a half-face air purifying respirator (HFAPR) with goggles (and, if applicable, the use of a face shield). A feasible alternative to a FFAPR is a HFAPR with goggles, as determined by Annex I of ANSI Z87.1-2003. Goggles are effective at protecting workers eyes from exposure to butter flavoring vapors, liquids, and particulates.	NIOSH policy is to recommend only full facepiece respirators when there is the potential for eye irritation. Half mask respirators with goggles are not being recommended because NIOSH is not aware of any standards for gas-tight goggles that would permit NIOSH to recommend such goggles as providing adequate eye protection. This policy is from the NIOSH Respirator Selection Logic [2004b], page 21.
EC-52	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	The cover photograph is inappropriate. It shows a worker pouring what appears to be a liquid butter flavor without the use of engineering controls. The fact that the worker is shown wearing a respirator compounds the problem by implying that personal respiratory protection is acceptable as the primary means of exposure control. The cover photograph contradicts the advice provided in the document. FEMA requests that the cover be revised to either include no photograph or a photograph showing appropriate exposure controls.	The cover of this document has been revised in response to comments.
EC-53	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Nearly all of the recommendations in this chapter are consistent with recommendations made by FEMA in training workshops conducted by FEMA for flavor and food manufacturers in 2005 and 2007. As noted by FEMA (FEMA, 2004), flavor manufacturing facilities are extremely diverse in size and number of employees, facility design and layout, and products manufactured. For flavor manufacturing, one size does not fit all. Furthermore, the large majority of flavor manufacturers in the U.S. qualify as small businesses under the definition of the Small Business Administration - businesses with less than 500 employees. In fact, the majority of flavor manufacturing companies in the U.S. have less than 100 employees. The use of the term	NIOSH RELs are based currently on the technical feasibility and not “reasonably achievable.” The current NIOSH [1995] REL policy specifies that “NIOSH RELs will be based upon risk evaluations using human or animal health effect data, and on an assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques.” To this end, technical feasibility has been addressed by providing data from a microwave popcorn plant that reduced the exposures to most workers below the REL using engineering controls.

		"reasonably achievable" in the context of exposure controls to achieve the proposed REL for diacetyl of 5 ppb therefore clearly becomes a relative term. "Reasonably achievable" to a large flavor manufacturer with corresponding financial resources will mean something far different to the majority of flavor manufacturers in the U.S. that are relatively small in size. A small flavor manufacturer seeking to comply with the exceedingly low RELs suggested for diacetyl and 2,3-pentanedione may seek to employ respirators routinely as an alternative to engineering controls which, as explained by NIOSH in Chapter 8, are the preferred option consistent with the hierarchy of controls. Whether the recommended exposure limits are reasonably achievable for flavor manufacturers has not been demonstrated. FEMA requests that NIOSH review and revise its recommendations to address whether they are likely to be reasonably achievable in relation to the low proposed RELs by the majority of flavor manufacturers that are in fact small businesses.	
EC-54	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	NIOSH discusses engineering controls in Section 8.2. It is important to focus on engineering controls that are carefully considered and demonstrated to result in reductions in exposure because while some controls may appear to be likely to reduce exposure, they may in fact increase exposure. Of particular importance are engineering controls intended to capture or dilute vapors and powders. The installation and operation of engineering controls must be carefully and fully evaluated to assure that they result in reductions in potential exposure. One system that works well in one flavor manufacturing facility may not work in another because of differences in facility design and operation. It should be stressed in this chapter that controls must be validated by the operator for each specific facility. For example, one type of powder control may work in a	Controls need to be fitted to individual processes by each plant and cannot be a “one-size-fits-all” approach. Controls need to be evaluated after being installed. Evaluations should be completed to quantify exposures after controls have been implemented to ensure that target goals have been reached.

		facility that uses drums for shipping but may not work in another facility that uses a different transfer process or a different shipping container.	
EC-55	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	NIOSH discusses work practice controls in Section 8.3. It is important to focus on work practice controls that are carefully considered and that may result in reductions in exposure because while some actions may appear to be likely to reduce exposure, they may in fact increase exposure. For example, NIOSH recommends the use of HEPA vacuums to clean up flavoring powders. However, this may actually increase exposure due to evaporation from the HEPA filter itself. NIOSH recommends the use of wet sweeping methods in areas where powdered encapsulated flavors are present that may actually increase exposure as water dissolves the encapsulation material releasing its contents.	The statements referenced relate to properly cleaning up after spills. The use of high-efficiency particulate air vacuums and wet cleaning methods are still considered the best method of cleaning up spills to prevent the dispersion of contaminants throughout the work environment. As mentioned in that section, all personnel involved in cleaning up spills should be wearing appropriate personal protective equipment and should be properly trained. This combination should best protect the person cleaning up the spill and others in the facility.
EC-56	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	NIOSH discusses hazard communication in Section 8.3.7. Hazard communication is not just a key part of any workplace safety program for flavor manufacturing, but it is a legal requirement as noted in the Criteria Document (Section 8.3.7). FEMA recommends that this section be expanded to remedy several deficiencies. In 2007, OSHA published hazard communication guidance for diacetyl (OSHA, 2007). This important document is not described or referenced in the Criteria Document and must be. FEMA provided specific information related to hazard communication for "high priority" flavoring substances (FEMA, 2004) that can also be referenced in this section of the Criteria Document.	NIOSH has updated the diacetyl/2,3-pentanedione criteria document to provide additional information on hazard communication. This includes providing GHS classifications for diacetyl, 2,3-pentanedione, and mixtures containing these substances, based on the toxicological and physical-chemical data that are presented in the criteria document. This has resulted in classification of these compounds under several GHS human health endpoints and one physical hazard endpoint. NIOSH has also updated this document with recommendations with guidance on how these chemicals should be labeled as part of product labels and SDSs so that workers are informed of the potential hazards associated with exposure to these chemicals in neat form and in mixtures.

EC-57	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Economic Impact Sensient Flavors has already established excellent engineering controls to minimize employee exposure to diacetyl and 2,3-Pentanedione. Nevertheless, the additional economic cost to the company and, presumably, to other flavor manufacturers to attain the proposed REL will be significant. It is estimated that the cost of additional engineering controls for Sensient Flavors' single manufacturing location in Indianapolis will be in the range of $4 - $6 million. These costs would be incurred without a clearly defined benefit for the incremental reduction in potential employee exposures. There will also be additional, ongoing operating costs associated with the design changes, as employee productivity decreases and scheduling conflicts arise.	NIOSH RELs are based currently on the technical feasibility and not economic feasibility. See also response to EC-11.
EC-58	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page 236: "For some processes, employers may need to provide workers with showers and require them to shower before leaving work." In Sensient Flavors' view, this comment either needs to be fully developed or deleted. No benefit is derived from NIOSH suggesting a possible showering requirement for "some processes," but never identifying what processes, specifically, might make showering necessary. The Criteria Document provides the reader with no practical guidance. Given the potential implications a showering requirement could have on employers under the Fair Labor Standards Act, the OSHA Act and other federal and state statutes, if NIOSH is not prepared to specifically identify the "processes" in issue, this language should be deleted.	The bullet addressing showers has been deleted.
EC-59	Jacqueline Nowell on behalf of the United Food and Commercial Workers Union, CLC	The picture of a worker wearing a respirator on the cover of the document should be replaced with engineering control technology.	The cover of this document has been revised in response to comments.

EA-1	Eastern Research Group, Inc.	As part of the review, we compared the measurement ranges listed in Table 2 to the diacetyl exposure results obtained from surveys performed at each facility (i.e., OSHA A through OSHA L). We determined that all exposure level ranges identified in Table 2 accurately represent the reported levels and no revisions are necessary.	No response required
EA-2	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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 [po 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.	In the publication regarding the first survey of the sentinel microwave popcorn facility, the only exposure information available was from area samples, because the NIOSH industrial hygienists did not anticipate that flavoring chemicals might be responsible for health effects. We agree with the commenter that area samples are not the best representation of individual worker exposure. In the subsequent surveys, personal samples were collected in addition to area samples. These data from eight subsequent visits to NIOSH index facility G [NIOSH 2006] were used to model the relationship between area and personal measurements, as described in Appendix 4. With this model, the personal exposures of workers before the company undertook interventions to lower exposure were estimated. These estimations of personal exposure formed the basis of the exposure characterization used in the risk assessment. Because this approach to using personal exposure estimates is already described in the document, no changes have been made as a result of this comment. The section on page 55 that the commenter refers to is a description of the literature and is not pertinent to the risk assessment.

EA-3	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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, 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	Seven peer reviewers and five public commenters made mention of the LOD or LOQ issue. These comments were mixed and addressed the analytical methodology as well as the use of the LOD/LOQ data. We contend that air samples < LOD are informative; in fact, they are among the most precisely known exposures (when based on full-shift sampling) and are vital for statistical modeling as they drive the intercept (baseline) estimate in a regression analysis. They represent low or very-low exposed workers to be compared with higher exposed workers—exactly the desired contrast. The primary problem with exposures < LOD in the diacetyl risk assessment concerns the humidity correction that is required due to the limitations of NIOSH Method 2557. Not applying the correction for samples < LOD could result in underestimation of exposure if actual concentrations were > LOD/2; on the other hand, if non-detects mostly represent very low exposures (<< LOD), the diacetyl determinations would largely represent analytical noise, and applying the humidity correction would potentially create overestimates of the true values. New analyses in which the humidity correction was applied to all air samples, not just those above the LOD, produced very little change in the regression estimates of the exposure response to diacetyl. Revisions were made in this section of the criteria

		samples has the potential to double the lowest value used to calculated mean exposures.' 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.	document to report these additional analyses.
EA-4	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	**Chapter 2 - Assessing Exposure** This section includes an excellent and very detailed discussion about the pros and cons of a long list of sampling and analytical methods. However, it takes a close reading to determine which of these methods have been validated. We suggest more clearly indicating the validation status of each method, such as by indicating the status in parentheses when each method is first introduced in the text Also, although this section mentions that there are currently no validated sampling and analytical methods to adequately assess powder or mixed powder/vapor exposures, it is important that this section clearly address the limitations this lack of methodology places on assessing and controlling exposures to workers.	The status of methods for air sampling for diacetyl and 2,3-pentanedione has been clarified. A sentence has been added in section 2.2 regarding the limitations of vapor methods for measuring powder or mixed exposures. Measurement of airborne dust particles according to their size (e.g., inhalable, thoracic, and respirable) can help explain where they may deposit in the respiratory tract. Several types of sampling devices are available (e.g., inhalable dust samplers, impactors, cyclones, and sampling cassettes) to provide measurements of different size fractions of airborne dust. Currently validated sampling and analytical methods to determine airborne vapor concentrations of diacetyl and 2,3-pentanedione are presented in Appendix 1.

EA-6	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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. 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. *I* 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	NIOSH agrees that personal exposure data are preferable to area data when personal data are available. However, this preference does not preclude the use of area data. Typically area exposure information is supplemental to personal data when samples are collected in the general work environment. In other instances, such as when area samples are collected near a point of contaminant generation, this is normally apparent in the site report. Exposure misclassification for the period prior to 2000 probably also occurred in both directions—overestimation as well as underestimation, as the extent of diacetyl use was unknown, especially before the introduction of low fat products. Most of the surveyed workers were not employed at GMLC in the 1980s or early 1990s. Detailed justifications for the methods used to estimate personal exposures at the index plant appear in Appendix 4. However, when reviewing this appendix to respond to comments, omissions were found in the descriptions of the procedures in Appendix 4, section 1.3 titled “Creation of job categories and estimation of arithmetic means” and in Table A 4.3. These likely led to the commenter’s concerns, and they have been modified in the appendix. Specifically, the mean of the area samples collected in the first survey for workers with job titles in the warehouse, outside/inside and polyethylene areas were used to

		process, we request that NIOSH provide a detailed rationale and/or formulas for how it extrapolated area to personal breathing zone samples.	estimate personal samples because those job titles had too few personal samples and/or a large percentage of personal samples with measurements below the LOD during the subsequent surveys 2–9 (rather than only surveys 2 and 3, as was incorrectly specified in the body text). Inconsistencies existed between the body text and the table on how exposure estimates were made for microwave mixers, microwave line, and quality control job categories. The estimates were all made by modeling personal to area concentrations from surveys 2–9 and applying the model to the survey 1 area samples, as is currently reflected in the revised appendix.
EA-7	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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.	The significance of changes made between July 1986 and November 2000 is unknowable; the changes consist largely of scaling up production with the addition of more packaging lines. The introduction of local exhaust ventilation to a mixing room salt dumping operation in the summer of 1999 was unlikely to have changed flavoring exposures in the mixing room, which was the source of flavoring exposure to packagers (along with the unvented tanks of heated flavoring in oil on the packaging area mezzanine that supplied each line). In the presence of these strong sources, the introduction of wall fans in the large packaging area, also in the summer of 1999, had an unknowable overall effect on exposure to flavoring chemicals, but the fans could be expected to have some reductive effect on exposures in the packaging area at

			the same time that scaled-up production was likely increasing exposures there. The fans were not used during cold weather.
EA-8	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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. 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. iii) Although the HHE report states that relative humidity data were collected during the surveys, only the first interim report, dated August 200 I, documents that such samples were collected. Furthermore, there is no discussion of the relative	NIOSH industrial hygienists collected temperature and humidity data in multiple area baskets during every survey at the index facility G and at all other facilities during every shift in which measurements of flavoring concentrations were conducted. These area- and shift-specific average measurements were used in the published procedure to correct the measurements analyzed by NIOSH Method 2557, along with days to extraction, which were provided for every measurement by the analytical chemistry laboratory providing the concentrations. This information is included in Chapter 3 of the revised criteria document. With respect to measurement concentrations, only eight samples were above 25 ppm. These eight samples were not corrected because they fell outside the range of concentrations in the chamber studies used to develop the correction procedure. The measurement of 1,200 ppm was in the headspace of a heated flavoring tank and was not used in any subsequent analyses of mean exposures, in the job exposure matrix, or in

		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 1 200 ppm. NIOSH needs to clearly disclose how they took into account the problem of correcting for values higher than 25 ppm.	the risk analyses. Thus, the correction of this measurement was also not undertaken.
EA-9	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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 aI., 20 I 02 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	Animal studies have been reviewed and are discussed in the document. Not only was there no consensus among peer-reviewers of the NIOSH document that epidemiological studies are insufficient for risk assessment, a modest majority of reviewers were in favor of basing risk assessments on human data when adequate studies are available. The available human datasets were carefully evaluated by NIOSH and one particular one, from a NIOSH health hazard evaluation (HHE), [NIOSH 2006] was found to have a very extensive follow-up of respiratory status as well as a reasonably well described exposure history. NIOSH concluded that this study was appropriate and sufficient for a quantitative risk assessment for diacetyl. The criteria document explains in detail the basis for these judgments. Several analyses were performed to examine the robustness of this

		remains in the exposure reconstruction NIOSH utilized, we tend to agree with Maier et al.	approach and they affirmed the findings, as reported in the revised criteria document. Animal studies recently completed were also examined and provide supporting evidence for the human-based risk assessment. See also response to comment RA-45.
EA-11	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**The lack of predicted cases in the food processing industry is likely attributable to the significant difference in exposure scenarios. In addition, NIOSH relies on the wrong set of exposure data for microwave popcorn facilities.** The lack of cases in food manufacturing (aside from microwave popcorn production facilities without appropriate engineering controls) is likely due to the fact that use of flavorings in food production presents very limited opportunities for biologically relevant levels of exposure. We believe the prediction of widespread disease did not ta1<e into account this important difference in exposure between the industries that did seem to be affected and the industries that were anticipated to show effects. In spite of the lack of widespread disease in food manufacturing facilities, NIOSH continues to focus, including in this criteria document, 011 a single microwave popcorn manufacturing facility in which several cases of bronchiolitis obliterans were identified. A considerable body of data has been developed and published from several other microwave popcorn and food manufacturing plants but is virtually ignored in this criteria document. These data have demonstrated a considerable difference between the original microwave popcorn plant where disease was first identified, other	Other non-flavoring exposures would not explain the significant association between diacetyl and declining lung function. A detailed retrospective exposure assessment was made for the NIOSH index plant (facility G) [NIOSH 2006] that concluded that exposure conditions were probably fairly uniform prior to 2000, in part because plant management believed there was no problem. Cal/OSHA provided industrial hygiene monitoring results from a Flavoring Industry Safety and Health Evaluation Program evaluation in 2006 and 2007 at a food flavoring manufacturer for the production of vanilla dry blend product [Widess 2013]. In this evaluation, task-based personal breathing zone sample concentrations of diacetyl collected over 19 minutes ranged from 3.5–5 ppm during dispensing of dry powder containing 0.14% diacetyl by weight. If a TWA exposure was calculated over an 8-hour work shift, assuming no other diacetyl exposure during the work shift, the 8-hour TWA exposure would have been 0.19 ppm. Additionally, NIOSH has documented diacetyl

		microwave popcorn plants and an even greater difference between microwave popcorn plants and other areas of the food industry. For perspective on the difference between microwave popcorn facilities and other areas of the food industry, consider that at the time the problem was discovered in the first microwave popcorn plant, microwave popcorn manufacturing plants were using flavorings containing uniquely high concentration of diacetyl (greater than 15-30% in some flavoring formulations). Levels of this magnitude are not typical of use in the manufacture of other foods (and are no longer used even in the manufacture of microwave popcorn). Additionally, the diacetyl-containing flavorings were added to hot oil that was then mixed into the popcorn, often under open conditions, conditions, which promoted volatilization of diacetyl into the workplace air. Furthermore, these plants operated on a continuous basis, and microwave popcorn was the only product they produced. Thus the potential for cumulative and relatively high exposure was great. By contrast, according to GMA member companies, the **majority** of food flavorings in use today generally contain less than 1% diacetyl by weight. Only small amounts of such flavorings are added to food products with the concentration of diacetyl in a food product formula typically contain <0.1 % diacetyl by weight. Even considering that substitutes such as 2,3-pentanedione could also be present in formulations, it is common practice in the food industry that only small amounts of such flavoring are added to food products. Additionally, most food processing operations operate on a batch (intermittent) basis and do not produce the same product continuously. A plant will produce different products at different times, and not every product formulation will involve a buttery flavoring component. More specifically, none of these flavors will contain	exposures in investigations where employees worked with flavoring mixtures with < 1% diacetyl by weight resulting in exposures over the REL [NIOSH 2008a, b, 2009a, b]. One laboratory-based study also identified emissions of diacetyl from natural butter and butter flavor powders, pastes, and liquid products in a laboratory environment [Rigler and Longo 2010]. Determinations show that even in the butter flavoring containing the lowest amount of diacetyl in the bulk flavoring (1.01% by weight), heating this flavoring to 37.5°C released vapor concentrations of diacetyl as high as 13.67 ppm. This suggests that even if diacetyl is present in bulk concentrations of <1%, vapor concentrations of diacetyl could greatly exceed the NIOSH REL. See also response to comments G-18 and RA-52. It is quite unlikely that any systematic surveillance for diacetyl-related pulmonary impairment has been conducted in a food processing industry. If it had been, it should have been reported to the Occupational Health and Safety Administration (OSHA) during the rule-making process. To do meaningful surveillance employers would have to assess loss of breathing capacity for current workforces (including baseline evaluations), employees leaving employment, former employees and retirees with a high level of participation/ascertainment. To identify actual cases of obstructive lung disease and relate them to employment conditions would require accurate diagnosis

		more than a low percentage of diacetyl. Lastly, the potential for diacetyl (or any of the volatile buttery flavoring components) in a food flavoring to volatilize into the workplace air is limited by the fact that food is manufactured under closed conditions to the maximum extent feasible in order to prevent or minimize the introduction of physical, chemical and microbial contamination, in accordance with the federal Good Manufacturing Practice regulations. Finally, the majority of subjects (57%) evaluated in the original microwave popcorn plant reported having exposures outside the popcorn plant to other possible causes of occupational lung disease (Kreiss et al, 2002). This publication describes farming, grain dust, irritant gases and nitrogen oxide exposures but this fact is dismissed (or ignored) in subsequent publications by NIOSH and these authors. A further source of uncertainty in the data from the original microwave popcorn plant is that many of the sentinel cases from this plant had symptom onset between 1993 and 1998 (Ackpinar, 2004). That is, the symptoms developed at a time when NIOSH acknowledges it has no accurate exposure data and, in fact, could have significantly underestimated exposure. Trying to correlate data from this one plant with disease and compare these findings with any aspect of food production in other plants is, simply, not a scientifically defensible approach. Based upon these considerations, the focus of exposure estimates in this criteria document on a single microwave popcorn facility where disease was originally identified is not scientifically justified especially in light of the large amount of credible data available for many other plants.	of a rare disease, often in employees who have already left employment and who may have other plausible explanations for their breathing problem. In many food manufacturing applications, the diacetyl levels could be quite low, making most pulmonary changes within the range of normal and obstructive lung disease incidence quite rare.

EA-12	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	The low-level exposure scenarios in the food industry are not readily apparent to the reader due to the way the table that discusses this topic is constructed (Table 2 page 57 of the draft Criteria Document). [Table 2 is pp 44 & 45.] There is evidence for the low-level exposure in the food production industry in the reports cited in the criteria document, but it is not clearly considered. Table 2 (page 57 of the Draft criteria document) conveys ranges of diacetyl measured in workplaces that used or produced diacetyl. However, with the table in the current format, the actual measurements and, thus exposures, are not clear to the reader. To this end, we ask NIOSH to consider clarifying Table 2. We also believe that clarifying Table 2 will be beneficial to NIOSH in their interpretation of these data. A good example of how clarifying and adding more detail to the existing table brings value and impacts interpretation of the data can be seen in the Eastern Research Group (ERG) report on baked snack food production (ERG 2008d). To the reader of the draft document as it exists, Table 2 conveys that workers in the baked snack industry have time-weighted average (TWA) exposures ranging from below the detection limit to 164 parts per billion (Ppb). In actuality, the ERG report indicates that the sample representing the upper end of this range (164 ppb) was collected over 57 minutes: however. when the entire shift of 7.7 hrs was accounted for, the calculated full-shift TWA was 30 ppb. Further, diacetyl was not detected in samples collected on the two other workers sampled and, in fact, diacetyl was detected in only 3 of 16 samples. This is an important clarification because the casual reader might assume that the typical 8-hr exposure in this type of industry could lead to much higher exposures than what the data actually demonstrate. Without these clarifications, the casual reader is led to a conclusion that is not supported by the available data. Because the	Table 2.2 was modified to clarify the sample duration issue in the "Measurement Range" column. More discussion about this reviewer's issues with Table 2.2 is given in the response to comment EA-13.

		modification makes the table quite lengthy we have attached the suggested option for reconstruction as Attachment I to our letter. We feel this modified Table 2 will more accurately convey the data values in an easy to understand format. [See Rachman letter for Attachment]	
EA-13	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**Following the current best approach and validated methodology, the most commonly reported limit of quantification values (LOQ)'s exceed the proposed REL for diacetyl as well as the proposed action limit.** Before providing the details related to our concern listed above, it is important to mention that the terminology used by NIOSH in Table 2 (page 58) is confusing. NIOSH defines "ND" as "no limit of detection was reported". A review of the OSHA -ERG reports used to populate this table indicates that "ND" is actually defined by the authors of those reports as "not detectable" which was used when "there was no indication of the analyte in the sample". Since these are very different meanings, we would appreciate NIOSH clarifying this definition for consistency purposes. Relative to our concern listed	As discussed in both the draft and revised criteria documents, NIOSH recommends the use of OSHA Method 1012, which is a validated analytical method that can be used to effectively measure worker exposures to diacetyl. The RLQ for this method is 1.3 ppb, which is below the proposed REL for diacetyl. While the OSHA-ERG reports may have defined ND as “there was no indication of the analyte in the sample” in those reports, the lack of a minimum concentration value that would have been necessary to produce such an indication was not reported. In Table 2.2 that lack of information is noted as “ND” meaning, as mentioned, no minimum

		here, using the modified Table 2 in Attachment I, one can better see that many of the air monitoring values for the food production industry fall into the "ND" and <LOQ categories. Since the "not detectable" designation would indicate no presence of analyte, the fact that quite a few of the TWA values resulted in "ND" designation demonstrates again, the lack of exposure in many job categories in the food industry. Further, we believe that the modified table allows one to better see that in many cases, the LOQ exceeds 5 ppb (the proposed REL). Discussions with certified industrial hygienists at our member companies have highlighted the concern that if one is to follow the strict interpretation of the currently available validated method (OSHA 1012) for sample time and flow rate, the LOQ will often exceed the newly proposed REL. The problems with achieving an LOQ that is below the action limit need to be more openly discussed with validated examples/labs that are capable of delivering relevant and accurate results using methods reasonably anticipated to be available in work areas. Another more practical option would be to consider using a performance based approach that requires employers to ulilize good administrative practices and to apply existing guidance such as that available from FEMA (2004), NIOSH and OSHA under special emphasis programs. Following such guidance would also help provide direction to employers when handling butter flavor substitutes.	concentration to produce an indication (limit of detection) was reported. The format selected for the data presentation in Table 2.2 is a compromise to allow sufficient information for the reader (with references if additional detail is desired) to establish the points being discussed, and to present that information in a succinct manner.

EA-14a	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**The risk assessment utilizes exposure data that are limited in scope and based on data values that have many underlying uncertainties. The risk assessment cannot be considered scientifically sound if the data critical to the exposure metric (cumulative in this case) is highly uncertain.** As stated in the public transcript "the trick in risk assessment is to come up with the appropriate exposure metric and then do statistical models that relate the metric to the outcome". Unfortunately, we believe that the determination of the exposure metric is flawed due to the major uncertainty associated with historical exposure reconstruction. The draft REL relies on the metric of cumulative exposure. In order to reconstruct cumulative exposure for workers affected, NIOSH chose to use data based primarily on exposure information from one facility: the Gilster- Mary Lee Corporation in Jasper, Missouri ("index plant''). Although NIOSH conducted nine surveys at this facility between November 2000 and July 2003 and nearly 400 personal and area samples were collected during these surveys, there are serious questions as to the adequacy of these data for use in risk assessment. NIOSH acknowledges on page 116 of the draft that, "The characterization of historical exposures was limited by the absence of air sampling prior to the NIOSH HHEs." Thus, for purposes reconstructing exposures, NIOSH assumed that: Diacetyl was used at the index plant beginning July I, 1986 (p. 118) or more than 14 years prior to the initial survey in November 2000.	Exposures prior to 2000 may have been underestimated and overestimated. With the advent of low-fat popcorn, diacetyl concentrations were increased considerably (some time before 2000 but after 1986). As explained in Chapter 3 of the criteria document, there was one study of a facility that provided relatively detailed and sufficient information on both exposures and outcomes. The number of facilities included in a risk assessment does not determine its validity; rather, the quality of the data is what is important. We acknowledge that there is some uncertainty associated with our analysis, but we do not think it is substantial. The one shortcoming on exposure assessment was the absence of air sampling information prior to the time of the study. This omission was present in all the candidate populations for analysis.

EA-14b	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	It was appropriate to apply the exposure estimates gathered at the first survey to the entire 14-year prior time period. To this point, NIOSH stated, "For work history prior to the first industrial hygiene survey, exposure estimates from the first time period were: used." (p. 117). No engineering controls or process changes were made at the index plant between the years 1986 and 2000. NIOSH notes that " . .. .it was assumed that there were no significant exposure control changes prior to the first survey." (p. 117). These assumptions are fraught with uncertainty as well as a lack of consistency and transparency, the most important of which are highlighted below.	See response to EA-7.
EA-14c	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	In contrast to the draft criteria document, NIOSH notes in the August 22, 2001 interim report that, "In the summer of 1999, a local exhaust ventilation system was added to the microwave mixing room to control salt dumping operations. Roof air intake systems were also added to the microwave area in the summer of 1999." (p. 62 of HHE Report No. 2000- 0401-2291). NIOSH acknowledges that, "In the late October- November survey, 17/79 (22%) of the workers currently in microwave packaging and mixing operations reported that the addition of ventilation in the summer of 1999 had improved the work environment; an additional 33% reported that the environment had stayed the same; and the remainder (46%) didn't know." (p. 69 of HHE Report 2000-0401-2991). Although NIOSH concludes that "volatile organic compounds, such as diacetyl, may not have been affected by past ventilation interventions," they provide no basis for that conclusion and, at a minimum, their choice of wording implies that NIOSH recognized that diacetyl concentrations could have been affected. Given that the highest exposures were measured in the mixing room, if these engineering measures did reduce diacetyl concentrations in this area	See response to comment EA-7.

		of the plant, then the historical exposures for workers of the plant could have been greatly underestimated	
EA-14d	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	NIOSH relied on area samples to estimate personal exposure. NIOSH acknowledges that, " . . . for the first industrial hygiene survey (November 2000), only area samples were collected, and thus personal sample-equivalent exposures were estimated (Appendix 4). (p. 117, 1. 15- 16). This is a critical point because it means that the vast majority of the estimated cumulative exposure over a period of up to 1 7 years (198 6 to 2003) is based on a single survey in which no personal samples were collected! NIOSH employed a variety of methods for converting the area samples to personal samples, without providing any explanation or justification as to how these methods were applied and to what data (see Appendix 4, p 4-5). For example, the mean of the area samples collected in the warehouse were used as personal samples, whereas in the Microwave Packaging Area, personal samples were estimated based on a model of area and personal samples for two of the other surveys whereas for the Microwave Mixing area, a model of area and personal samples for all surveys was used.	Detailed justifications for the methods used to estimate personal exposures at the index plant appear in Appendix 4. However, when reviewing this appendix to respond to comments, omissions were found in the descriptions of the procedures in Appendix 4, section 1.3 entitled "Creation of job categories and estimation of arithmetic means" and in Table A-4.3.These likely led to the commenter's concerns, and they have been modified in the appendix. Specifically, the mean of the area samples collected in the first survey for workers with job titles in the warehouse, outside/inside and polyethylene areas were used to estimate personal samples because those job titles had too few personal samples and/or a large percentage of personal samples with measurements below the LOD during the subsequent surveys 2–9 (rather than only surveys 2 and 3, as was incorrectly specified in the body text). Inconsistencies existed between the body text and the table on how exposure estimates were made for microwave mixers, microwave line, and

			quality control job categories. The estimates were all made by modeling personal to area concentrations from surveys 2–9 and applying the model to the survey 1 area samples, as is currently reflected in the revised appendix.

EA-14e	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	Air samples collected during the nine surveys were analyzed by NIOSH Method 2557, which is now known to be affected (underestimated) by humidity and time to extraction (p. 115). Accordingly, the sampling results from these were adjusted based on an adjustment procedure published by NIOSH staff (Cox-Ganser et al. 2011). As noted in the publication, the upper end of the range to which the adjustment is applicable is approximately 25 ppm, and it is unknown if the adjustment is appropriate for concentrations greater than 25 ppm, which were found during the first survey of mixers (p. 69 of HHE Report 2000- 0401-2991). This is another example where historical exposures to mixers may have been underestimated. Despite these fundamental uncertainties, the draft criteria document barely addresses the uncertainty and/or sensitivity of the assumptions used.	As indicated in the response to comment EA-8, only eight samples had results above 25 ppm. These samples were not corrected. (See EA-8.) A total of 299 samples were used to create the job exposure matrix. Both the uncertainty and sensitivity of various methods used in the document are discussed.
EA-14f	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	Section 5.5 of the draft criteria document is entitled "Sensitivity Analyses and Alternate Hypotheses." This section is less than two pages and most of it addresses "alternate hypotheses" for the apparent variability in susceptibility in a subset of the index plant workers. Regarding their sensitivity analysis, NIOSH simply states: "NIOSH evaluated many different statistical models and procedures using continuous and discrete outcomes based on different definitions of impairment, different exposure metrics, and data from different plants. For Company G [index plant], the risk estimates are surprisingly similar for the different modeling	The Sensitivity Analyses and Alternate Hypotheses section has been expanded to examine the impact of additional assumptions made in the risk assessment. For example, peak exposures were not addressed in the risk analysis, and new results support that decision. A smoking interaction was investigated and found to not enhance the diacetyl effects. In the original analyses, the humidity correction was not applied to air samples determined to be below the limits of detection. The impact of this choice was

		approaches and the diacetyl levels estimated for a given level of life-time prevalence or risk are generally pretty close, within an order of magnitude." (p. 133) No further explanation or discussion is provided to allow the reader to understand what was done and/or which assumptions were most sensitive.	examined by applying the humidity correction to all samples less than 25 ppm; it made very little difference and this is presented in the revised criteria document. This section has also been revised to conform to the new interpretation of the observed high risk with short employment duration. Of the various choices behind the risk analysis, model specifications probably have the largest impact, with preferences based on statistical fit.
EA-14g	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	NIOSH provides no discussion as to why the exposure estimates were based solely on its own data, even though NIOSH acknowledges and discusses other worker exposure data (e.g., Lockey et al. 2009) in an earlier chapter of the draft criteria document.	NIOSH conducts quantitative risk assessments based on the best available data. NIOSH determined that the data collected in a specific health hazard evaluation [NIOSH 2006] was the best available data for the diacetyl quantitative risk assessment: (a) there was extensive exposure assessment over the 3-year period of longitudinal medical evaluations, (b) manufacturing conditions had not changed substantially prior to the investigation (and plant management claimed there was no reason to have made changes on health hazard grounds), and (c) large numbers of workers were evaluate over eight successive evaluation cycles during which diacetyl levels were declining rapidly due to interventions. NIOSH reviewed the Lockey et al. [2009] data and determined it is not suitable for quantitative risk assessment as it had no exposure data prior to ventilation improvements, the first respiratory assessment was in 2003 when exposures were already quite low, and the likelihood for exposure misclassification in this study is

			high. The earlier health hazard evaluation conducted at NIOSH Plant L [NIOSH 2004a], (included in the [Lockey et al. 2009] study of four plants) was analyzed in the NIOSH document but appeared to have had significant reductions in diacetyl exposure levels prior to the environmental assessment conducted by NIOSH. This source of exposure misclassification would cause a higher estimate of the exposure response and a lower proposed REL than that ultimately selected by NIOSH.
EA-14h	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	Based upon NIOSH's own data, engineering controls added to the mixing room also impacted other areas of the plant clearly indicating that diacetyl exposures across this entire plant were influenced by activities in the mixing room. These observations further support the difference between the index plant and other microwave popcorn plants and, especially, other food manufacturing facilities.	Kanwal et al. [2006] describes in detail the similarities and differences between the six microwave popcorn facilities that NIOSH visited. The index plant was one of four plants that had nonisolated or inadequately isolated mixing rooms. No changes to the document were necessary based on this comment.
EA-15	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Comment 1: NIOSH's recommended TWA of 5 ppb for dlacety/ is not justified.** The NIOSH recommended exposure limit of 5 ppb for diacetyl as an 8-hour time-weighted-average (TWA) is based in part on an inappropriate interpretation of exposure data. **NIOSH's claim that diacetyl is a threat to workers' health at levels just above 5 ppb is justified neither by exposure data or precedent in toxicology.** The upper end of the measured range of airborne concentrations of diacetyl at which some workers are reported to show adverse respiratory changes appear to be approximately 50 ppm, or 50,000 ppb. The four orders of magnitude (i.e., 10,000-fold) difference between what NIOSH suggests as nonhazardous to human health (i.e., S ppb) and a point where adverse respiratory changes occur in some	See responses to comments on odor threshold (e.g., RA-11) and on popcorn consumption EA-17.

		workers (i.e. 50 ppm) appears to be an arbitrary, unconventional and unexpectedly wide range. A TWA of 5 ppb with an action level of 2.5 ppb would likely be experienced by every short-order cook and baker in the country who uses real butter, margarine, or butter flavoring. The Rosati data suggest that a 5-ppb REL and 2.5 ppb action level would include those millions of workers who make popcorn at the office. At the very least, they would have to be included in a worker monitoring program to determine their exposure under this proposed rule. Further, the NIOSH proposed RELs and action levels are near or below the odor threshold for diacetyl and 2,3-pentanedione. If the proposed rule is finalized in its current form, anyone who can smell the odor of butter in their workplace would need to be included in a compliance program because, by this rule, they would be overexposed. The odor threshold of diacetyl, which is incorrectly reported in the Criteria Document (NIOSH 2011b, pp. 16-17), is correctly reported at 4.37 ppb (Devos et al. 1990) and 1.42-7.39 ppb (Rychlik et al. 1998). The implication of this simple analysis is that miilions of Americans are at or above the proposed REL when they smell butter odor.	
EA-16	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**NIOSH's proposed 2.3-pentanediane REL of 9.3 ppb Is unjustified bv the science.** As part of Its HHEs for flavoring compounds, NIOSH did not develop an exposure profile or hazard analysis for 2,3-pentanedione. In fact, NIOSH has only measured 2,3-pentanedione in one flavoring HHE that we were able to identify. At a bakery mix producer, NIOSH found extremely low detectable air concentrations of 2,3-pentanedione, which was introduced to the facility as a substitute for diacetyl a few months before NIOSH's evaluation; hence, no association could be found between 2,3-pentanedione and adverse respiratory changes. Lacking any data, NIOSH has set the REL at the	We do not disagree with the reviewer that there is little HHE data on 2,3-pentanedione exposure. The basis for concern for 2,3-pentanedione is not the NIOSH HHE studies but rather the animal toxicology studies showing effects parallel to those of diacetyl and compelling mechanistic considerations. See also responses to comments RA-46 and G-18.

		reliable quantitation limit for the analytical method. Similarly, NIOSH's proposed 2,3-pentanedione STEL of 31 ppb is unjustified by the science. Lacking any data, NIOSH has set the STEL at the reliable quantitation limit for the shorter sampling period.	
EA-17	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Consumer and office worker exposure levels provide a reality check on the RELs** In the matter of Newkirk v Conagra Foods, the Plaintiff claimed that his BO was the result of airborne exposures to diacetyl from making and eating large quantities of diacetyl-containing microwave popcorn. Judge Rosanna Peterson found this to be an unbelievable stretch of logic. Judge Peterson excluded the plaintiff's expert witness, writing: "..... There is simply too great an analytical gap between the existing data, indicating that exposure to butter flavoring vapors in the occupational setting can cause bronchiolitis obliterans, and Dr. Egilman's opinion that a consumer of microwave popcorn is exposed to a vaporized substance equivalent to production plant butter flavoring vapors at levels sufficient to cause bronchiolitis obliterans ....." (Detroit Legal News 2010). In fact, **a person's exposure to diacetyl when eating butter-flavored popcorn as Mr. Newkirk did, may exceed NIOSH's proposed TWA of 5 ppb for diacetyl**. Rosati, Krebs and Liu, scientists at the USEPA, measured diacetyl in air when bags of fresh microwave popcorn were opened. Although not an exposure study, they found that an average of 779 ug of diacetyl were emitted from each bag of popcorn, mostly in the first few minutes of opening the bag. If a person were a frequent popcorn eater and inhaled diacetyl while standing in a small 15 m^3 kitchen, they would experience a potential concentration of (779 ug)/{15 m^3) = 52 ug/m^3, or 15 ppb. This is an airborne level 3 times higher than a worker exposed at the NIOSH proposed level of 5 ppb. Therefore, it is unlikely that ppb levels of diacetyl actually cause BO, for If that assumption were	The NIOSH mission is to provide national and international leadership to prevent workplace illnesses and injuries. NIOSH publishes criteria documents with RELs to fulfill our legislative mandate and protect workers from occupational exposures and disease. Consumer exposures are not under the NIOSH purview. However, if we shifted the hypothetical scenario presented in the comment to workers involved with quality control of microwave popcorn, NIOSH can comment on the situation presented. In an occupational environment, i.e., a microwave popcorn quality control laboratory, qualified industrial hygiene personnel could collect samples on workers over a 15-minute time period or over the course of the entire work shift. These sample results would be compared to the 15-minute short-term exposure limit (STEL) or 8-hour REL as appropriate. It is inappropriate to compare an instantaneous measurement to a STEL or REL. It should be noted that occupational disease has been observed previously in workers from the microwave popcorn quality control laboratory.

		valid, the incidence of BO would have reached epidemic proportions In the general population by this time from the frequent popping of popcorn in home and office microwave ovens.	
EA-18	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Many of the industrial hygiene studies involve multiple chemical exposures All of the industrial hygiene monitoring studies used to justify the proposed rule for diacetyl and 2/3-pentanedione involve workers who were also simultaneously exposed to other toxic chemicals that cause damage to the respiratory tract.** These include exposures to acetic acid, acrolein, and acetaldehyde. These chemicals cause irritation in the airways, but acrolein itself can cause cumulative damage. It is likely that the bronchiolar damage attributed to exposure to diacetyl reflects the combined effect of damage to the respiratory tract from multiple chemicals. **The recommended occupational standards for a chemical should represent the effect of the chemical of interest alone**, rather than the aggregate effects of a chemical mixture. It Is our contention that the proposed standards, while targeted at diacetyl and 2,3-pentanedione, are based on effects and worker exposure settings in which it is difficult to unravel the individual effects of one chemical from another. While **some of these additional chemicals may not necessarily cause BO, they may exacerbate the effects of diacetyl and 2,3-pentanedione.** For example, exposure to a chemical that inhibits the enzyme pathway that metabolizes diacetyl or 2,3-pentanedione, may become the chemical that actually causes the damage to the airway. Accordingly, the proposed rule would effectively regulate a single chemical based on data gathered in a mixed chemical environment. Animal testing data show a NOAEC for obstructive lung disease from inhalation exposure to diacetyl near 200 ppm for short-term exposures (Hubbs 2008; Morgan et al. 2008) and 5O	The reviewer's point that may of the industrial hygiene studies involved mixed exposures to diacetyl and 2,3-pentanedione is an observation that is true for the overwhelming majority of all human exposures to all compounds, not just diacetyl and 2,3-pentanedione [Callahan and Sexton 2007; Løkke et al. 2013]. In formulating this criteria document, NIOSH recognized and addressed the issue of the expected mixed exposures in the workplace by using converging lines of evidence from multiple different human populations, animal toxicology studies, and the basic chemistry of reactive α-dicarbonyl compounds. Thus, in addition to the human studies, the animal toxicology studies involved vapors of butter flavoring, single agent exposures to diacetyl and exposures to 2,3-pentanedione. In addition, the animal studies involved rats and mice and exposures of varying durations. The mechanistic conclusions from the animal studies of diacetyl and 2,3-pentanedione make the identification of diacetyl as the causal agent in human populations quite compelling and demonstrate that these agents are capable of injuring respiratory epithelium as single agents. In regard to species differences in diacetyl sensitivity, hybrid computational fluid-dynamics-physiologically based pharmacokinetic models predict that the diacetyl dose to the

		ppm subchronic inhalation exposures 6 or 12 weeks in duration. It is difficult to accept that there would be such disparity with worker medical surveillance data to support a proposed TWA four orders of magnitude below this latter NOAEC. A likely explanation would be the combined effects of other chemicals in expressing BO and prior unmeasured exposures of workers to higher levels before PPE and engineering controls were implemented in the workplace. As described In the NIOSH criteria document, every study to date has found exposures to multiple chemicals in the workplace such that the respiratory conditions identified could not be tied to exposure to a single chemical.	bronchiolar epithelium of a working person can vastly exceed the dose to the rodent bronchiolar epithelium [Gloede et al. 2011; Morris and Hubbs 2009].
EA-19	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Some of the studies Include older workers who were "historically-exposed." Some workers who display or were observed to have respiratory symptoms in recent years from exposure to flavoring agents worked before 2001 when work conditions were more adverse and exposures were less controlled. Thus, their symptoms probably reflect higher long-term levels that may have permanently damaged their respiratory tract in the past.** Current functional measurements would not be able to separately account for previous long-term exposures. This would lead to underestimation of the concentrations of diacetyl or 2,3-pentanedione that would need to be present to cause the currently-observed functional deficits in respiratory function. Because the respiratory tract changes from these two chemicals are permanent (i.e., irreversible), currently observed functional deficits may reflect primarily long-term damage In workers with exposure experience before 2001. There is a lack of baseline spirometry measurements for workers in some studies. Measurements of airborne levels and lung function measurements would not be able to discern between pre-existing permanent obstructive lung disease and	We agree with the commenter that the respiratory impairment observed in November 2000 in the first cross-sectional study was the result of exposures over the work tenure of most workers. For this reason, we devised a job-exposure matrix, assuming that historical exposures were the same as those measured in November 2000. With this job-exposure matrix, we estimated cumulative diacetyl exposures over employment tenure for each worker studied. No baseline spirometry existed in this or any other microwave popcorn facility because medical surveillance was not deemed necessary in the absence of a known respiratory hazard in the industry. However, some historical information on spirometry is available on the former worker sentinel cases [Akpinar-Elci et al. 2004] showing the decline in pulmonary function available after these workers sought medical attention for their symptoms. When exposure controls began to be put in place in December 2000 with

		effects caused by contemporary exposure conditions. For example, in the quantitative human health risk assessment section of the draft criteria document (NIOSH 2011b), the risk assessment relies on an analysis of the index study recently published as Kanwal et al. (2011). In the study a total of sixty-six percent of mixers, maintenance workers and quality control workers who were hired after exposure controls were put into place reported respiratory symptoms suggests that pre-existing respiratory impairment already existed. If true, this group may not represent the typical newly hired employee working under current industry practices.	respiratory protection and in January 2001 through August 2003, diacetyl levels began to decrease in many jobs, as documented in Kanwal et al. [2011]. However, the highest risk group of mixers and maintenance workers hired after the controls began to be put in place were never thought to be protected by the controls introduced. The average exposures of mixers in the last 2003 environmental survey were still in the range that had resulted in disease in the packaging room in 2000. It was for this reason that we continued to recommend medical surveillance for these workers. The quality control workers' exposures were reduced to below detection limits during the 2.7 years of interventions, but considerable time elapsed before this was the case. Because the company did not introduce preplacement spirometry testing, our finding of abnormal spirometry in newly hired workers might reflect either pre-employment impairment or lung damage in the up-to-6-month intervals of employment before we tested them. In retrospect, there is no way to know which is the explanation, but lung function in the group hired after interventions began was much better on average than lung function for those hired by November 2000 and excessive declines were much less prevalent.
EA-20	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Worker exposure monitoring data do not suggest a clear dose-response curve.** In the index study, the mean length of employment for workers hired after exposure controls were implemented is 6 months. The affected workers with suspected pre-existing obstructive lung disease had an average length of employment of six	It is difficult to construct a systematic risk assessment based on the data in the reviewer's comment. The variations discussed by the reviewer would not detract from an appropriate retrospective exposure assessment and regression analysis as long as

		years, indicating a work period before exposure controls were implemented, most likely associated with significantly higher airborne concentrations of diacetyl and other chemicals. These two groups of workers also vary significantly in age. Workers hired after exposure controls were implemented were on average 10 years younger than the older workers with pre-existing lung disease. Per the testimony of Dr. Kathleen Kriess of NIOSH at the August 26, 2011 public hearing (p.59) in Washington, DC, four companies that used at least 800 lbs. of diacetyl per year employed workers with moderate to severe obstructive lung disease who had worked for 9 years, compared to 1.5 years for those with only mild degrees of obstruction. Eighteen of the 467 Individuals employed and exposed at these "heavy-use" facilities showed spirometric obstruction. A few individuals of these 18 exhibited "severe" obstruction based on the spirometric measurements. These factors make it difficult to compare or combine the health outcomes of these groups. Further, in this study and others, the general expectation that job categories or locations that would normally be associated with the highest concentrations of diacetyl would be associated with the highest incidences of obstructive lung disease was not consistently the case. In the index study, and in other studies, job categories with the highest airborne levels of diacetyl and other flavoring chemicals are not necessarily the jobs associated with the highest incidence of obstructive lung disease. Thus, **the basis of NIOSH's dose-response and quantitative risk assessment is a set of skewed data that likely does not represent the effects of current exposures with contemporary PPE and engineering controls in place.** It is difficult to understand how NIOSH could propose a numerical value for a recommended standard for	there is no selective removal of individuals that jointly depends on exposure history and health status. Such selective removal could occur if workers believed the diacetyl exposure was contributing to their health impairment in which case bias would be introduced causing an underestimate of the exposure response. The likely presence of variable susceptibility would introduce systematic bias as discussed in some detail.

		occupational exposure when a clear dose-response is lacking in workers.	
EA-21	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**<u>The exposure parameters used by NIOSH in its deliberations are incorrect.</u>** Per the testimony of Dr. Ann Hubbs at the August 26, 2011 public hearing (p. 85) in Washington, DC, it is cited that by light exercising, workers can absorb a 40-fold greater dose to the bronchiolar epithelium than experimentally-exposed rats. NIOSH should consider what portion of the day the worker is involved in light exercise and what portion at more sedentary or standing inhalation rates. It is likely that most of the work day is spent at lower inhalation rates, and that calculation of a time-averaged inhalation rate across an 8-hour work day would reflect this. Thus, arbitrarily inferring that workers would obtain a 40-fold greater dose than rats is unfounded and unlikely. **NIOSH needs to reconsider and update its exposure parameter data from more recent sources, such as the newly-released Exposure Factors Handbook from the U.S. Environmental Protection Agency.**	The potentially 40-fold greater exposure of the bronchiolar epithelium of man under light working conditions as opposed to the resting rat was based upon the ICRP calculation of minute volume for light exercise which is 25 liters per minute (L/min) and mouth breathing [Gloede et al. 2011]. The models in the cited study also calculated a 5-fold increase in bronchiolar epithelial concentration in sedentary nose-breathing humans versus the rat, while a 7-fold increase in bronchiolar epithelial concentration was predicted for mouth-breathing sedentary humans, using the ICRP calculation of 9 L/min for sedentary humans. This provides a range for the species extrapolation of 5- to 40-fold greater exposure to bronchiolar epithelium of workers versus rats, depending upon activity level and form of breathing of the worker. When calculating a permissible exposure limit (PEL), OSHA uses a minute volume of 20 L/min for the standard “light activity” of workers, closer to the light exercise model than to the resting worker. This appears to be the result of the estimation that a workday consists of 5.5 hours of light exercise breathing 25 L/min, and 2.5 hours of sedentary activity breathing 7.5 L/min [ICRP 1994]. The exposure parameters used by NIOSH for the diacetyl

			risk assessment, did not assume that a worker would have 40 times the exposure of a resting person for the entire workday. Instead, the Gloede et al. [2011] exposure estimate for light exercise for 5.5 hours/day, and the Gloede et al. [2011] exposure estimate for sedentary activity for the other 2.5 hours of the workday were used, based upon the accepted "light activity" model.
EA-22a	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	Chapter 2: Assessing Occupational Exposure in Workers Consider researching nationwide AIHA accredited laboratories and their ability to measure to the reliable quantitation limit (RQL) for OSHA methods 1012, 1013, and 1016 before publishing a recommended exposure limit (REL). •It is known that the OSHA Salt Lake Technical Center (SLTC) can meet this need mainly for OSHA compliance reasons. However, since there is not a regulation on these substances and you are recommending a limit for employers to meet, it is only fair to say in the criteria document that the reliability to measure to this REL lacks confidence and cannot be achieved by most laboratories across the U.S at the current time. •NIOSH's approach to publishing a REL without assuring laboratories can measure to the RQL is prudent, in that it is technology forcing; however, I believe it would be better received by the flavor manufacturing and food manufacturing industries if the REL can be measured to confidently by "most" laboratories prior to publication of the final criteria document.	Current NIOSH REL policy requires that a validated analytical method exist to measure the compound of interest. The criteria document describes the three OSHA Methods (1012, 1013, and 1016) and the associated RQL for each method in Chapter 2, section 2.2. NIOSH policy does not require that "most" laboratories across the United States can obtain the method as this pertains to laboratory quality control and assurance.

EA-22b	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	•Because the proposed REL for 2,3 pentanedione is set at the RQL of OSHA method 1016 brings into question whether or not NIOSH fulfilled their charge in conducting a proper quantitative risk assessment (QRA) on 2,3 pentanedione. •I say this because if the toxicological effects 2, 3 pentanedione have a strong correlation to the toxicological effects of diacetyl as NIOSH states in the criteria document, then why stop at the RQL of OSHA method 1016 (?). •It appears that the proposed REL for 2, 3 pentanedione needs more research and validation. •If the research is not there to conduct a proper QRA, then remove it from the criteria document. •NIOSH's main charge for setting a REL is to determine a "safe" level for exposure to workers. The way it is currently written, it appears that NIOSH is going outside the scope of the criteria document and proposing a REL for 2,3 pentanedione based "mostly" on analytical feasibility.	NIOSH notes that the 2,3-pentanedione risk assessment in the external review draft has been updated on the basis of new information. This new chapter has undergone an additional peer review and public comment process. The 2,3-pentanedione REL is still set at the limit of quantitation. NIOSH believes that a health-based REL set at an exposure level too low to measure would not be practical to implement in the workplace. Historically, NIOSH has made a practice of setting RELs at the analytical limit under these circumstances.
EA-22c	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	•Continue efforts on developing a traditional industrial hygiene personal sampling method for quantifying powdered diacetyl, and 2, 3 pentanedione (e.g. powdered butter flavorings) because it can be assumed that occupational exposure inhalation risks are underestimated since encapsulated butter flavorings are most likely liberated once they come into contact with moisture when entering the body via inhalation routes (mouth, nose, tracheal, pulmonary lining, etc.)	The analytical scheme for measuring diacetyl and 2,3-pentanedione in bulk powder food flavorings has been developed and validation of the analytical scheme is currently underway. A sampling train involving a cassette with a filter followed by a silica gel sorbent tube has been proposed to collect airborne dust. The sampling process will be evaluated after the analytical method is fully validated. The proposed sampling and analytical procedure will allow for total diacetyl/2,3-pentanedione to be measured.
EA-23	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	**Appendix 6: Typical Protocol for Collecting air samples for Diacetyl and 2,3 Pentanedione** •On page 4 of Appendix 6, line 18 under "Focused Sampling' replace the word "fibers" with "vapors".	The document was revised as suggested.

EA-24	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	In Section 3.1.2.2 it appears that NIOSH used area samples to associate exposure to diacetyl with the development of illness in terms of workers' personal cumulative exposures. This is contrary to sound industrial hygiene practice (AIHA, 2006), is contrary to NIOSH's recommended sampling strategies (Leidel et al. 1977), and is inconsistent with NIOSH's recommendations in the Criteria Document regarding compliance with the NIOSH REL for diacetyl. **It is a well-recognized industrial hygiene principle that area samples are not reliable representations of potential exposures that may be more accurately estimated by personal breathing zone samples.** A misplaced reliance on area sample data can be a serious flaw and can call into question quantitative risk assessments. **FEMA requests that NIOSH explain their use of area sample data and why the use of such data do not adversely affect the accuracy of the risk assessments described in the Criteria Document.**	See Appendix 4, section 1.3, entitled **"**Creation of Job Categories and Estimation of Arithmetic Means "for a detailed explanation of how NIOSH used the area sample data. Also see NIOSH response EA-2 which addresses similar comments.
Epi-1	Dana M. Hollins, MPH, ChemRisk, LLC	***The epidemiology data do not support the conlusion that diacetyl is a cause of obstructive effects*** Diacetyl has been manufactured and used in bulk quantities in the United States since the early 1900s. According to a 2004 Flavor and Extract Manufacturer's Association (FEMA) report, approximately 21 1,000 pounds of diacetyl were used by American industries in 1995 (FEMA 2004). In the mid- 1980s, microwave popcorn became a highly popular snack item and diacetyl containing artificial butter flavoring (ABF) was a frequent additive for a substantial fraction of the microwave popcorn products. Diacetyl is also used in numerous other food-related industries, such as baked goods, candy, cake mixes, some syrups, certain cheeses and other dairy products. As described below, workers in popcorn packing and other food industries have been studied to assess the	The commenter raises many items to question the conclusion that diacetyl is a cause of obstructive effects. The first is that the use of National Health and Nutrition Survey III (NHANES III) data may not be an adequate reference population and that internal comparisons are preferable, as would be local community comparisons. We addressed possible confounding exposures at Facility G in rural Missouri, showing that the internal comparison group had statistically significantly higher proportions of non-popcorn plant exposures that might contribute to obstructive lung disease from farming, grain dust, irritant gases, and nitrogen oxides, than the production workers with flavoring exposure. In addition, the

		possible role of diacetyl as a risk factor for obstruction and other respiratory disorders. To date, these studies, individually and in aggregate, have failed to demonstrate a causal relationship between diacetyl exposures and respiratory disorders, particularly obstruction. BO is an obstructive disease and therefore it stands to reason that, if diacetyl is truly causing BO in workers in popcorn plants, flavoring facilities, and diacetyl manufacturing facilities, There would be a measurable increase in obstructive effects in the workplace. Thus far, the published studies on worker health in diacetyl and flavorings facilities have relied exclusively on the National Health and Nutritional Examination Survey (NHANES) III data as a source of "general population" information for comparison purposes. While NHANES is arguably the largest available source of "background" health status in The U.S., it may not adequately represent a relatively small, blue-collar population in a discrete geographical area, particularly one in a farming or agrarian setting (where many of the popcorn packing facilities are located). Agrarian populations are often exposed to numerous respiratory toxicants not related to their profession that affects pulmonary health, such as: organic dusts, endotoxins, fungal toxins, silo gases, microbial toxins, pesticides, fertilizers, disinfectants, and feed additives (A TS, 1998). Accordingly, and as described in detail in the American Thoracic Society's "Respiratory Health Hazards in Agriculture" (and many other publications), it is well understood that Those who live and work in agrarian settings typically have a higher incidence of numerous respiratory disorders, including decreased FEV1 and FVC:	worker quartiles of increasing cumulative exposure to diacetyl had decreasing rates of farming exposures [Kreiss et al. 2002]. Thus the internal local comparison group (which was very small with 20 persons) was likely to have led to underestimations of the effect of flavoring exposures. These points about possible confounding exposures are more pertinent to differential diagnosis of individual workers' conditions than to epidemiologic comparisons. Basically, we see no reason why persons with other risk factors for obstruction would select into jobs with flavoring exposure risks, and we documented in Facility G that the opposite was the case. We agree with the commenter that NHANES III is the most robust source of general population comparison information. The extent of excess obstruction in the Facility G population far exceeds any geographical variability in obstruction rates across the country or between rural and urban populations. The second item of the commenter is that the internal control group and the flavoring-exposed group did not differ statistically in some symptoms. While this is correct, all symptom prevalences were much higher in the flavoring-exposed group compared to the small internal control group (likely inadequate power to detect differences). The symptoms most likely associated with constrictive bronchiolitis were statistically significantly higher: exertional shortness of breath, regular trouble with breathing, two or more respiratory symptoms, unusual fatigue, one

		"Increased prevalence rates for chronic bronchitis have been reported in farmers and agricultural workers in many parts of the industry (page 29)." "Dosman and colleagues also reported significantly lower FV, FEV1, and FEV1/FVC in farmers compared with control subjects (page 29)." Thus, for diacetyl and flavorings workers who live in a farming community, a more apt comparison group would be an internal reference group (e.g. office workers at the facilities that are not exposed to diacetyl) or a comparison group of individuals from communities that represent the diacetyl workers. **Kreiss et al. (2002)** was the first study to examine respiratory disorders in a group of popcorn workers (as opposed to case reports of single individuals). The authors [that are from the National Institute for Occupational Safety and Health (NIOSH)] evaluated 117 workers from the Gilster Mary-Lee (GML) facility in Jasper, Missouri via spirometric analyses and questionnaire responses. Over one hundred VOCs were measured in the mixing room; many of which are known respiratory irritants. The authors reported a statistically significant increase in the prevalence of airway obstruction (defined simply as a "low" FEV1/FVC ratio) and self-reported symptoms (e.g. chronic cough, wheezing, shortness of breath, asthma, and chronic bronchitis) when the workforce was compared to expected rates from NHANES. However, when the prevalence of these respiratory disorders was compared to those in an internal reference group of unexposed workers (office workers, etc.), many of the symptoms were no longer significantly	or more systemic symptoms, and skin irritation. Thus the commenter's argument that the NHANES III comparison of symptom prevalence was flawed was addressed by internal comparisons, which substantiated that the distribution of chest symptoms associated with constrictive bronchiolitis was greater among the exposed workers. The commenter states that Kreiss et al. [2002] did not present a statistical comparison of the abnormal spirometry prevalence in flavoring-exposed workers compared with the internal control group, which is correct. Instead, Kreiss et al. [2002] showed an exposure response relationship by quartile of cumulative exposure to diacetyl. The lowest quartile includes the internal control group. The commenter states that no information was provided for how this figure or the underlying dose calculations were derived, but the methods section of the paper describes the assumptions made in creating a job exposure matrix from exposures measured during the first survey, which was used to calculate cumulative exposure from job tenure in various areas. In the revised criteria document, we have corrected the underestimates of exposure that resulted from use of NIOSH Method 2557 [1994] for diacetyl in recreating the prevalences of abnormal and mean FEV_1 by quartile of cumulative exposure. In the draft criteria document, estimated personal measurements by job were derived from area measurements for use in calculating cumulative exposure. The commenter states

		increased in exposed workers (chronic cough, phlegm, wheezing, attacks of wheezing, chest tightness, fever, chills, night sweats, influenza-like achiness, and mucus membrane irritation). This change strongly suggests that the NHANES comparison was confounded by the aforementioned higher prevalence of respiratory disorders in those living in farming communities. Indeed, Kreiss et al (2002) noted that: "5 7% of the participants had exposures outside the popcorn plant to other possible causes of occupational lung disease; the leading sources of exposure were farming (40%), grain dust (32%), irritant gases (14%), and nitrogen oxides (8 %)." As noted earlier, nitrogen oxides are the primary cause of bronchiolitis obliterans in humans. Unfortunately, it does not appear that NIOSH seriously evaluated alternative risk factors in this or study any of the Human Health Evaluations (HHE) that they conducted soon after their investigation of the GML facility. Also, it is clear that even the internal control group had a much higher than normal prevalence of respiratory disorders. For example, as can be seen in Table 4 of the paper, 25% of the control group reported wheezing, and 5 0% reported mucous membrane irritation. Given the fact that 1) the majority of the study participants reported that they had been exposed to known respiratory toxicants outside the popcorn plant, and 2) even the internal control group (unexposed to diacetyl) had a very high rate of self-reported symptoms, it is clear that NHANES was not an appropriate reference group for this cohort. Indeed, it could be argued that most or all of the respiratory disorders in these workers were entirely unrelated to the GML facility. In short, the	that airborne dust and chemical levels were similar in distribution to diacetyl and objects to Kreiss et al. [2002] implicating diacetyl as a cause. The Kreiss et al. [2002] paper does not claim that diacetyl is the cause of the respiratory impairment in the facility but may be a marker of another cause. Only the subsequent investigations, including those in diacetyl manufacture and experimental animal studies, narrowed the range of potential causes to implicate diacetyl specifically. The comment that diacetyl levels of short-term animal exposure were higher than average levels in the facility, experienced over years by most workers, is irrelevant and ignores differences in metabolism, airway diameter, nasal scrubbing, and subsequent animal work that account for differences in human and animal response to diacetyl. Finally, the commenter compares the 12.5% decrease in FEV_1 at the highest quartile of diacetyl-exposed workers in comparison to the lowest exposure quartile to the American Thoracic Society (ATS) statement that FEV_1 changes of 12% or less are likely due to natural variability in the participant and instrumentation. This comparison is completely inappropriate. An average measurement of a group of about 30 people is a much more stable measurement than a measurement in an individual, which is what the ATS guidance refers to. The fact that the group in the highest quartile of diacetyl exposure had an average FEV_1 of about 84% predicted suggests that, on average, this group had lost 16% of their lung function,

		results of Kreiss et al. (2002) likely reflect the predictable outcome of an investigation of respiratory effects in an agrarian, blue collar cohort that routinely worked with heated organic vapors under poorly ventilated conditions. In short, most or all of the "increased prevalences" of self-reported respiratory symptoms are far more likely to have been the result of exposures to agents other than diacetyl. For reasons that are not explained, Kreiss et al. (2002) did not present a statistical comparison of the abnormal spirometry prevalence (airway obstruction) in workers versus the internal control group. Kreiss et al. (2002) present a figure which they believe indicates a statistically significant relationship between cumulative diacetyl exposure and decreased FEY I in the GML workers [see Hollins letter for figure] Unfortunately, no information was provided as to how this figure or the underlying dose calculations were derived. More importantly, the figure itself is relatively meaningless because the same figure could be derived for most or all of the analytes at the GML plant. Specifically, airborne dust and chemical levels were all highest in the mixing room, lower in the quality control areas, and lower still in other areas of the facility. Indeed, as shown in the NIOSH HHE report for the GML facility [NIOSH 2006], The figure below describes the relationship between cumulative dust exposure and decreased forced expiratory volume in one second (FEV_1) in these same individuals: [see Hollins letter for figure] Also, the diacetyl levels measured in the GML facility (overall mean = 8.1 ppm; mean in the mixing room = 32.3 ppm) are well below those that *failed to cause alveolar effects in animals* (up to 1800 ppm). Finally, it is important to note (in Figure 3 above) that the FEV_1	which should have been 100% of predicted had they suffered no occupational insult to their lungs.

		decreases in most of the workers were low even though the diacetyl exposures were very high: the highest quartile of exposure (11 -126 ppm-year) was associated with only a 12.5% decrease in FEV1. As noted earlier, the ATS states that a change of less than 12% in FEV1 or FVC is likely due to natural variability in the participant and instrumentation rather than due to a change in lung function (Pelligrino et al., 2005). In summary, regarding Kreiss et al. (2002) [see comments Epi1a thru g]	
Epi-1a	Dana M. Hollins, MPH, ChemRisk, LLC	use of the NHANES database as a "control group" was problematic due to: 1) the high percentage of GML workers with non-occupational exposures to known respiratory risk factor (including known inducers of BO), and 2) the high prevalence of respiratory symptoms in GML workers who were not exposed to diacetyl	The NHANES population was used in two ways: (a) to develop prediction equations [Hankinson et al. 1999] for a normal healthy population, which required excluding smokers and others with environmental risk factors; and (b) as a typical population in which to predict impairment prevalence (falling below lower limit of normal) with increasing diacetyl exposure based on the regression model at the NIOSH index plant (Facility G) [NIOSH 2006] plant. It is not known if workers at this facility had a “high percentage... with non-occupational exposures to known respiratory risk factor,” but if they did, that would increase the intercept in the regression model and reduce the effect estimate for diacetyl unless those other exposures were highly correlated with it (unlikely). Some of these other risk factors would be negatively correlated with diacetyl exposure (corn dust, printing).

Epi-1b	Dana M. Hollins, MPH, ChemRisk, LLC	when the more appropriate internal control group was used as the basis of comparison, there were few significant differences between the exposed versus unexposed workers	As discussed in comment Epi-1a above, the NHANES population is considered appropriate. No citation is cited for the conclusion presented in this comment.
Epi-1c	Dana M. Hollins, MPH, ChemRisk, LLC	this study provided no evidence of a statistically significant increase of abnormal spirometry in the workers versus the internal control group	All the regressions in this risk assessment used only internal comparisons; that is workers from one plant were compared on their exposure status. The regression analyses NIOSH reported show very

			significant effects: pulmonary function declines with increased cumulative exposure to diacetyl in a cross-sectional analysis. This indirectly implies a statistically significant increase in prevalence of abnormal performance (below the lower limit of normal). On the other hand, the analyses of incidence of falling below the lower limit of normal, as reported (Table 5.24), directly show a statistically significant effect of increasing incidence of abnormal pulmonary function with diacetyl exposure as well as a profound apparent selection of responders out of the population.
Epi-1d	Dana M. Hollins, MPH, ChemRisk, LLC	the results of Kreiss et al. (2002) likely reflects the predictable outcome of an investigation of respiratory effects in an agrarian, blue collar cohort that routinely works with heated organic vapors under poorly ventilated conditions	We believe there is sufficient specificity within and among the studies, including the cited Kreiss work, to indicate the cause of bronchiolitis obliterans is diacetyl and not the generic heated organics mentioned in the reviewer's comment.
Epi-1e	Dana M. Hollins, MPH, ChemRisk, LLC	there was inadequate consideration of alternative causes; the prevalence of respiratory symptoms in these workers could also be explained by exposures to non-occupational toxicants or other compounds (e.g., VOCs, dusts, endotoxins) in the facility	There is no evidence that “nuisance dusts” or any of the other listed substances cause bronchiolitis obliterans. Endotoxin (and cigarette smoke) may be protective for diacetyl effects.
Epi-1f	Dana M. Hollins, MPH, ChemRisk, LLC	there is no evidence of a causal relationship between diacetyl exposure and prevalence of respiratory disorders in the GML workers	See responses to reviewer’s comment RA-39 and RA-46.
Epi-1g	Dana M. Hollins, MPH, ChemRisk, LLC	the decreased FEV1 values were not biologically significant even at very high exposures; this study therefore suggests that diacetyl did not pose a respiratory risk in these workers	It is not clear which study is being cited. See response to comment 5086 in the peer review comment response document.
Epi-2	Dana M. Hollins, MPH, ChemRisk, LLC	Kanwal et al. (2006) examined 708 workers across six microwave popcorn plants, including the workers from the Kreiss et al. (2002) study. Hence, this study is a far	This summary of the Kanwal et al. [2006] paper is selective and misleading. The commenter does not recognize that average

		more robust version of the original Kreiss et al. (2002) analysis. Airborne diacetyl levels were much lower in the other five facilities (relative to the GML facility). Unlike Kreiss et al. (2002), Kanwal et al. (2006) compared the spirometric outcomes in the exposed workers versus internal control groups. This is arguably the most valid approach for assessing whether diacetyl-related respiratory obstruction is occurring in the workforce. The cohort was stratified in several ways, thereby permitting numerous evaluations of the potential contribution of diacetyl to obstructive disease: 1) "ever mixers" versus "never mixers," 2) smoking status, 3) mixers who worked > 12 months versus those who worked < 12 months, and 4) individuals who worked in the packaging area in plants with isolated tanks versus those who worked in the packaging area in plants with non-isolated tanks. *In every case, there was no difference between the exposed and control groups*. Specifically, there was no difference in % obstruction on spirometry in: smokers who had worked as mixers versus those who had never been mixers non-smokers who had worked as mixers versus those who had never been mixers smokers who had worked as mixers <12 months versus those who had worked as mixers > 12 months nonsmokers who had worked in the as mixers < 12 months versus those who had worked as mixers> 12 months smokers who had worked in the packaging area in plants with isolated tanks versus those who had worked in plants with non-isolated tanks nonsmokers who had worked in the packaging area in plants with isolated tanks versus those who had worked in plants isolated tanks In short, no matter how many different ways the authors "sliced the deck", there was no relationship between chemical exposure and obstruction in a pooled cohort of 708 workers from six	percent predicted pulmonary functions cannot be compared to percent predicted in individuals with respect to abnormality. The average percent predicted for a healthy workforce should be 100% predicted, and Kanwal et al. [2006] show substantial decreases in the percent predicted in relation to exposure category. No changes were made in the document as a result of these comments.

		different popcorn-packing facilities. Furthermore, a majority of the comparisons involving % predicted FEV1 also showed no difference between control and exposed groups, i.e., there was no difference in % predicted FEV1 in: smokers who had worked as mixers versus those who had never been mixers nonsmokers who had worked as mixers <12 months versus those who had worked as mixers> 12 months nonsmokers who had worked in plants with isolated tanks versus those who had worked in plants with non-isolated tanks smokers who had worked in plants with isolated tanks versus those who had worked in non-isolated tanks Finally, there was no difference in a majority of the exposed versus control comparisons involving self-reported symptoms such as shortness of breath, chronic cough, and wheezing. In summary, the study by Kanwal and colleagues demonstrates a clear lack of evidence that exposure to diacetyl is a risk factor for obstruction. Its results are arguably more relevant than the initial study at the GML facility (Kreiss et aI, 2002). As was the case in Kreiss et al. (2002), the reported % predicted FEY 1 values in Kanwal et al. (2006) represented relatively healthy individuals. Further, the small FEV1 decrements that were observed could be due to oils, other components of ABF, dusts, endotoxins, and many other toxicants that would be elevated in the mixing room relative to other parts of the facility.	

Epi-3	Dana M. Hollins, MPH, ChemRisk, LLC	*3* Similar to Kanwal et al. (2006), Lockey et al. (2009) examined a pooled cobort of over 700 individuals from multiple facilities that used flavoring chemicals. Also, like Kanwal et al. (2006), they evaluated the prevalence of obstruction in different job categories relative to an internal control group comprised of workers with little or no mixing experience (and therefore little to no occupational exposure to flavoring chemicals). Unlike Kanwal et al. (2006), however, Lockey et al. (2009) claim to have measured a high prevalence of obstruction in workers (mixers) exposed to diacetyl. The reasons for this inconsistency can likely be explained by the very different methodologies used to characterize the findings. Kanwal et al. (2006) presented direct comparisons between % obstruction in those with high diacetyl exposures (ever mixers, mixers > 12 months, workers near non isolated tanks) versus those with relatively less or no diacetyl exposures (never mixers, mixers < 12 months, and workers near isolated tanks, respectively). Lockey et al. (2009) does not present any such transparent comparisons. Instead, they present a "logistic regression model" that is claimed to "explain" how respiratory function of the different workers is influenced by various factors. The problem is that the reported statistic for model fit, r^2, was poor across all the tested models. The largest reported r^2 values associated with the tested regression models (0.41 and 0.16, respectively) accounted for an insignificant amount of variability in the data. Therefore, variables that were not included in the regression models better predict pulmonary health decrements in the workers, so no conclusions can be drawn from the reported effect estimates. In other words, the values are so low they indicate that a vast majority of the variability in the respiratory function measurements *cannot* be explained	See response to Epi-4.

		by smoking status, diacetyl exposure, job title, or any other of the variables that are input to the model. It is worth noting that in the one instance in which Lockey et al. (2009) do directly compare number of cases with obstructive respiratory function in the cohort versus the expected rate from NHANES (stratified by smoking status and age), there is no difference. Differences only arise when the Lockey et al. (2009) model is employed. It is also critical to note that all five of the "obstructive cases" reported in the pre-PAPR mixing group (mixers that never used respirators) could have been due to pre-existing asthma, smoking, or some other condition. Specifically, as noted by the authors, one individual had pre-existing asthma and another had respiratory symptoms prior to work. There were current and former smokers in the group, and all of the individuals who were tested (three of the five) with a bronchodilator showed a positive response (individuals with BO do not respond to bronchodilators). There are many other shortcomings present in the Lockey et al. (2009) analysis, and it is beyond the scope of this submittal to detail them all, but I believe that Lockey et al. (2009) fails to provide compelling evidence of either an increased risk of obstruction in mixers or a causative relationship between diacetyl exposure and obstruction for the following reasons: In Table 2 of the paper, it can be seen that Asian females, who have almost no mixing experience, have the worst FEV1 % pred and FVC% pred values; this suggests a lack of association between diacetyl exposure and decreased respiratory function in this study. The results of Table 2 (in Lockey et al., 2009) indicate that cumulative diacetyl exposure (ppm-years) does not correlate at all with either FEV1% pred or % obstructive PFT pattern, but smoking (pack-years) correlates very well with both of these respiratory endpoints. In Table 3 of the paper it can be seen that, in	

		non-Asian males and females (the vast majority of the workforce), diacetyl exposure does not correlate at all with FEV1% pred (e.g., in non-Asian males, intermittent pre-PAPR mixers actually have a significantly increased FEV1% pred and FVC% pred). Lockey et al. (2009) reported a mean FEV1 decrement of almost 13% in non-Asian females; this is a group that essentially had no diacetyl exposure. This decrement is larger than every other decrement that Lockey et al. (2009) attempt to ascribe to diacetyl. There was actually a greater % of obstruction PFT pattern (3/20= 15%) in the PAPR group than in the pre-PAPR group (5/39=13%); this suggests that diacetyl exposure is not associated with obstruction. As shown in Table 6 from the paper, diacetyl exposure does not correlate with obstructive PFTs in non-Asian males.	
Epi-4	Dana M. Hollins, MPH, ChemRisk, LLC	The van Rooy et al. (2009) study is unique in that it is the only study tbus far to examine diacetyl *manufacturers*. Also, the study took place in the Netherlands. Hence, this study avoided the problems of confounding exposures to numerous other workplace respiratory irritants (dusts, endotoxins, hundreds of other VOCs, etc.) and also tbe NHANES-related shortcomings (described earlier) inherent in the NIOSH studies. The findings can be summarized as follows: when the worker population was compared to national averages or an internal reference population, there was no difference in the % with self-reported symptoms for a vast majority of the symptoms contrary to the claims of Kreiss et ai. (2002) and Lockey et al. (2009), there was no clear association between FEV1 (% predicted) and exposure to diacetyl contrary to the claims of Kreiss et al. (2002) and Lockey et al. (2009), lung function was actually *better than predicted* with diacetyl exposure Like the Kanwal et al (2006) study, van Rooy et al (2009)	The commenter selectively summarizes the van Rooy [2009] article and neglects the earlier publication from [van Rooy et al.] 2007 which documents four cases of severe disease. The discussion of the Lockey et al. [2009] paper is similarly selective. Every paper has limitations, and the commenter seems to take no account of the aggregate evidence from workforce and animal studies. No changes were made in the document as a result of these comments.

		examined PFT results as a function of diacetyl exposure using many different comparisons: smokers vs nonsmokers, years worked at the plant post-1995, number of years worked at the plant, and cumulative weighted number of years. Like the Kanwal et al (2006) study, in every case the authors failed to find a causative relationship: In short, the van Rooy et al. (2009) study certainly does not indicate that cumulative diacetyl exposures are associated with an increased risk of serious respiratory disorders.	
Epi-5	Dana M. Hollins, MPH, ChemRisk, LLC	There are three relatively robust studies that have evaluated respiratory disorders (including obstruction) in workers potentially exposed to diacetyl: Kanwal et al. (2006), van Rooy et al. (2009), and Lockey et al. (2009). Kanwal et al. (2006) reported no increase in % obstructive patterns in workers. van Rooy et al. (2009) actually reported that lung function improves as a function of diacetyl exposure. Lockey et al. (2009) claims to have observed an increased risk of obstruction in mixers who had no respiratory protection. An unbiased weight of evidence evaluation of these studies would reach a conclusion that the preponderance of data do not show a relationship between diacetyl exposure and serious respiratory disorders. When one then considers the animal data (discussed previously), wherein numerous studies have failed to show evidence of any deep lung effects even following very high diacetyl exposures, it appears that diacetyl is unlikely to be a cause of 80 or any other serious respiratory disease in humans	See responses to comments 5135 and 5114 in the peer review comment response document. Also, none of the studies cited in the comment accounts for selection of workers with declining pulmonary function out of the workforce and/or variable susceptibility.
Epi-6	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**Historical epidemiological data suggest that cases of bronchiolitis obliterans have been observed in workers handling flavors at flavor manufacturing sites and/or in food production only where microwave popcorn was manufactured when appropriate PPE or environmental controls were not in place.** The occurrence of the	In the absence of a clear standard and prevention efforts, evidence of respiratory impairment would not be expected to appear in non-rejected workers' compensation claims. No systematic investigation was found prior to 2000. None of the investigative

		cluster of lung obstruction cases among workers at microwave popcorn plants identified in the year 2000, and the initial absence of a timely regulatory response, led to a situation in which political demand for action on this issue was ahead of the science needed to responsibly develop an appropriate standard. The presumption that latent cases of fixed obstructive lung disease would be discovered throughout the food manufacturing industry has not been borne out in spite of II years of experience. If one considers that the first cases of bronchiolitis obliterans in the flavoring manufacturing industry were reported in 1985 (NIOSH, 1985), then the timeframe for discovery of cases is actually 26 years. Furthermore, the presumption of risk in the food manufacturing industry as a whole has not been supported by data on workers' compensation claims, which our members believe provide no indication of a problem. It is also noteworthy that despite the increased awareness of diacetyl usage in food flavorings, not only in California due to their emphasis program and subsequent rulemaking, but also by the federal Occupational Safety and Health Administration (OSHA), **there is still no evidence of incidence or pattern of diacetyl-associated illness in general food manufacturing, including a lack of development of new disease in microwave popcorn plants (Kanwal, 2011).**	efforts has addressed selection issues, which would require full enumeration of exposed populations hired and then follow up including for departing and former employees. Work-relatedness would be difficult to prove in the case of moderate respiratory impairment in an isolated case without prior precedent.
G-1	David Egilman, MD, MPH, Brown University	If you have any questions please do not hesitate to get in touch with me. I often can access information that companies are forced to produce in legal discovery but fail to report to the EPA under TOSCA. I believe BASF may have reported its study to the EPA. I know some companies did report health information to the EPA including Chemtura	No response necessary

G-2	Eastern Research Group, Inc.	PAGE 43 Line 13: Replace the words "…flavorings, including diacetyl…" with "…formulated flavorings, including flavorings that contain diacetyl…". This change will more clearly indicated that diacetyl-containing flavorings (but not pure diacetyl) were either used or manufactured by all facilities described in Section 2.5.6 and Table 2.	The document was revised as suggested.
G-3	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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.	No response necessary
G-4	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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	The scope of the document is indeed broad in some respects, due primarily to the nature of the industry being discussed. Considerable care has been taken to use appropriate references when discussing substances or groups of substances. For example, the terms "alpha-diketones" and "alpha-dicarbonyl compounds" have specific meanings, while phrases such as "chemicals with structural similarities," "moieties that are biologically active," and "capable of producing similar toxic effects," etc., convey a more general but still limited meaning. This document is 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.	review of some quite sophisticated technical literature and portions of that literature, and by extension this criteria document will be at a level not expected of all potential readers.
G-5	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	We believe the current scientific evidence indicates that diacetyl may be a possible marker for workplace conditions causative of occupational lung disease. However, we findit difficult to accept the agency's claim it is sufficient to establish causation between diacetyl, 2,3-pentanedione, or other specific flavorings and 80. 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	We agree with much of this comment and in areas such as exposure characterization, risk quantification and control assessment there are statements in the criteria document describing future work and research needs. We disagree with the reviewer's opinion that bronchiolitis obliterans exposure is unrelated to diacetyl exposure for reasons presented in the document.

		assessments, and control technology should be addressed to Mr. Leslie J. Ungers.	
G-10	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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	See responses to reviewers' comments RA-52, RA-46, and G-18.

		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.	

G-11	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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. 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 N IOSH 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 N lOSH 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.	We believe the exposure limits established in this document are based on sound science, and that the meeting from which this and other comments from this reviewer originate provided the opportunity for interaction and discussion requested.
G-12	Dana M. Hollins, MPH, ChemRisk, LLC	I, Dana Hollins, am submitting comments regarding the August 12 , 2011 DRAFT NIOSH criteria document regarding a proposed occupational exposure limit for diacetyl. I attended the public meeting on August 26, 2011 in Washington, DC and presented oral comments at that meeting. The enclosed written comments are a follow-up to these oral 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	No response required

		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.	
G-13	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	The California Departrnent of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA), and the California Department of Public Health (CDPH). Occupational Health Branch, have prepared these technical comments based on our joint work over the past several years regarding flavoring-related illness. The draft Criteria Document on Diacetyl and 2, 3-Pentanedione is a very comprehensive, detailed compilation of available information on these flavoring chemicals. It is a valuable resource for employers and workers and for Federal OSHA standard setting as well.	No response necessary
G-14	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	We have two general concerns. The first is that throughout the document there should be greater emphasis on the hazard stemming from the powder forms of diacetyl and other butter flavoring ingredients. This greater emphasis on the powder forms is most necessary during discussion of engineering, administrative (particularly with regard to considerations of temperature effects), and personal protective equipment (PPE) controls. The document should also make it clear that the proposed Recommended Exposure Limits (RELs) for diacetyl and 2,3-pentanedione apply only to vapor exposures and may not be protective for mixed-phase exposures (i.e .. where exposures to both vapors and particulates exist).	Diacetyl can also be contained in a powder, either by encapsulation or adherence to a substrate. Air sampling for diacetyl-containing dust that may be generated during handling of powders can be achieved by current sampling methods. Chapter 8 also reviews appropriate personal protective equipment necessary for both forms. Regarding considerations of PPE and the two forms, Table 8.4 in Chapter 8 includes air-purifying respirator recommendations for protection against diacetyl and 2,3-pentanedione in which all of the listed air-purifying respirators are equipped with combination organic vapor/P100 or organic vapor/high efficiency filter cartridges, which are capable of protecting wearers against vapor and particulate hazards. NIOSH P100 filters are designated as 99.97% efficiency

			level filters, which are effective against all particulate aerosols. NIOSH high efficiency filters are designated as high efficiency particulate air filters for powered, air-purifying respirators. NIOSH regulations at Title 42 Code of Federal Regulations Part 84, section 84.114 and section 84.194 require that particulate filters used in conjunction with chemical cartridges or canisters shall be located on the inlet side of the cartridge. This would prevent any blockage of sorbent pores by particulate matter, and also would prevent any adsorbed vapor on particulate matter from passing through the cartridge by having the sorbent downstream to remove it.
G-15	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	The second concern is that the Criteria Document should include a comprehensive list of all the known substitutes for diacetyl, including the trimer form (which is not listed in the draft). At the same time, the document should make clear that other proprietary substitutes not on the list may also be in use. We also have the following comments on the individual sections. The Executive Summary should include more key information about the conclusions and "take home messages." This would make the findings and recommendations more accessible to a wider range of people who may not have the technical background necessary to follow the detailed information on toxicological risk assessment or industrial hygiene analytical issues. But who need to understand the hazards of working with diacetyl and related substances. Given the length and technical nature of this document, many people will not read the entire document, making a statement of the key public health messages in the summary more critical.	Because the list of compounds used in place of diacetyl or 2,3-pentanedione is both extensive and ever changing, and is also application specific, it is not practical to try to include such a list in this document. The executive summary has been revised significantly to serve as a stand-alone summary. We have added references and important take-home messages as suggested.

G-16	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Cal/OSHA and CDPH are very appreciative of the opportunity to submit technical comments on this complex and thoroughly researched draft Criteria Docurnent. We are sure that this document will provide invaluable guidance to manufacturers, employers, workers, physicians and regulators in making safer workplaces with exposures to diacetyl and its substitutes. We look forward to its publication in final form in the near future. Any questions related to these comments may be directed to Deborah Gold, MPH, CIH, Cal/OSHA Deputy Chief for Health, at dgold@dir.ca.gov or 510-286-7013, or Barbara Materna, PhD, CIH, CD PH Occupational Health Branch Chief, at barbara.materna@cdph.ca.gov or 510-620-5730.	No response required
G-17	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	Based in Washington, D.C, the Grocery Manufacturers Association (GMA) is the voice of more than 300 leading food, beverage and consumer product companies that sustain and enhance the quality of life for hundreds of millions of people in the United States and around the globe.Founded in 1908, GMA is an active, vocal advocate for its member companies and a trusted source of information about the industry and the products consumers rely on and enjoy every day, The association and its member companies are committed to meeting the needs of consumers through product innovation, responsible business practices and effective public policy solutions developed through a genuine partnership with policymakers and other stakeholders. In keeping with its founding principles, GMA helps its members produce safe products through a strong and ongoing commitment to scientific research, testing and evaluation and to providing consumers with the products, tools and information they need to achieve a healthy diet and active lifestyle.	No response required

		The food, beverage and consumer packaged goods industry in the United States generates sales of $2.1 trillion annually, employs 14 million workers and contributes $1 trillion in added value to the economy every year. GMA sincerely appreciates the opportunity to submit comments to the National Institute of Occupational Safety and Health (NIOSH) Docket #245 concerning the draft Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-pentanedione (draft criteria document). Our comments represent the collective view of GMA and six additional associations representing the food manufacturing industry: the National Coffee Association, American Bakers Association, American Beverage Association, The International Dairy Foods Association, the National Confectioners Association and the Snack Food Association. Our collective members recognize the importance of worker health and safety. We support and encourage the work done by NIOSH to help employers, industrial hygienists and employees understand and manage risks in the workplace. Furthermore, we support a science based regulatory process that incorporates the best available science. We appreciate the effort that the NIOSH staff has exerted to pull together the extensive draft criteria document and we want to commend NIOSH for publishing the transcript and presentations from the recent public stakeholder meeting as part of this docket. The nature and availability of these types of documents has been valuable in our review process.	

G-18	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	NIOSH stated during the public stakeholder meeting (8/26/11) that their goal was to develop a document that is scientifically sound, has relevance and utility and is developed according to a rigorous, consistent, and transparent process. After reviewing the draft criteria document, we feel compelled to raise multiple concerns that call into question the rigor, consistency, transparency and validity of NIOSH's analysis. We are particularly concerned with the exposure estimates developed for the quantitative risk assessment based on worker data, which forms the basis for NIOSH's proposed criteria. As a result of these concerns, we believe that the proposed recommended exposure limits (RELs) and short-term exposure limits (STELs) put forward by NIOSH are overly conservative and inappropriate when applied to any worker handling food or flavors. Further, we request that NIOSH take into consideration these concerns (presented in detail below) before finalizing the criteria document. Attention to addressing these concerns is critical because the criteria document is a recommendation to OSHA that a standard be issued and, prior to any subsequent rulemaking, the finalized criteria document could be considered guidance.	Concerns have been raised in several public comments about affected industries having insignificant or "naturally occurring" diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxins, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.
G-19	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	toXcel, LLC is pleased to submit the following comments on the proposed rule relating to the establishment of recommended worker exposure standards for the chemicals diacetyl and 2,3-pentanedione. These chemicals are of considerable economic importance in the U.S. food and food flavorings industry. According to NIOSH, there is a literature accumulating that would paint a presumably compelling picture of severe irreversible lung effects resulting from worker exposures to diacetyl and/or 2,3-pentanedione primarily in the food and food flavoring industries. NIOSH asserts that diacetyl exposure is associated with severe obstructive	No response required

		lung disease, morphological changes known as Bronchiolitis Obliterans (BO), and decreases in lung function. NIOSH has also raised concern regarding 2,3-pentanedione because it is an alphadiketone, and because inhalation studies in laboratory animals indicate similar morphological effects on the respiratory tract. This literature, which is often inconsistent and conflicting, consists of anecdotal evidence, experiments in laboratory animals, epidemiological studies involving relatively small populations of workers, and industrial hygiene surveys of affected sites. The proposed rule sets recommended 8-hour time-weighted-averages (TWAs) of 5 ppb for diacetyl and 9.3 ppb for 2,3-pentanedione. The latter is based in part on the lowest reliable quantification limit for 2,3-pentanedione. In addition, NIOSH is proposing to set short-term-exposure-limits (STELs) of 25 ppb for diacetyl and 31 ppb for 2,3-pentanedione. STELs are not-to-exceed maximum allowable air concentrations in the workplace for a 15-minute period. NIOSH is also proposing an action level of 2.6 ppb for diacetyl to proactively protect worker health. No action level is being proposed by NIOSH for 2,3-pentanedione. Our comments focus on the following primary issues: Whether the recommended exposure limits (RELs) for diacetyl and 2,3-pentanedione are supported by available science; The extent to which the recommended exposure limits (including TWA, STEL, and action levels) are feasible; The role of multiple chemical exposures in confounding the attribution of effects to diacetyl and 2,3-pentanedione; Whether the current lack of full understanding of the role of dlacetyl and 2,3-pentanedione in the development of obstructive respiratory disease in the workplace permits defensible promulgation of standards at this time; The	

		complications of older workers who contracted obstructive lung disease in previously uncontrolled job environments, in terms of estimating the actual impacts of contemporary exposure; Available dose-response information; The appropriateness of the benchmark dose approach used by NIOSH; The expansive scope of the rule; and Whether the role of NIOSH in promoting substitutes at this time is appropriate.	
G-20	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	**The Flavor and Extract Manufacturers Association of the United States** FEMA, founded in 1909, is the Washington, D.C.-based national association of the U.S. flavor industry. FEMA's members include flavor manufacturers, flavor users, flavor ingredient suppliers, and others with an interest in the U.S. flavor industry. FEMA's flavor manufacturing members include all of the twenty-five largest flavor manufacturers in the U.S., and FEMA's flavor manufacturing members produce >95% of all flavors consumed in the U.S. FEMA and its members are committed to assisting flavor manufacturers in having the safest workplaces possible. **FEMA's Program on Respiratory Health and Safety in Flavor Manufacturing** FEMA has been very active in assisting flavor manufacturers on respiratory health and safety matters since the initiation of FEMA's efforts in 1997 (FEMA, 2004). Since 1997, FEMA has sponsored four workshops (1997, 2002, 2004, and 2007), with the 2004 and 2007 workshops including extensive training sessions for flavor and food manufacturers on the safe handling of flavors, proper medical surveillance of workers, and hazard communication. In addition to the workshops, since 2001 FEMA has held numerous information sessions for its members and others in an effort to share relevant information in a timely manner.	No response required

		Since 2001, FEMA has had extensive meetings and discussions with NIOSH, the Occupational Safety and Health Administration (OSHA), and the California Department of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA) on these matters and has shared extensive information with these agencies in cooperative and collaborative relationships. Representatives of NIOSH, OSHA, and Cal/OSHA have attended FEMA meetings and workshops, and have also made presentations at a number of these sessions. FEMA supported the regulatory efforts of Cal/OSHA which resulted in 2010 in the implementation of the first workplace safety regulation related specifically to flavor manufacturing. **Flavoring Substances and Their Regulation and Use** The inclusion of flavoring substances in food is an important part of food processing and manufacturing in the U.S. Many individual flavoring substances, such as diacetyl, are commonly present in food as natural constituents. For example, diacetyl is commonly found in butter, dairy products, and in many other foods often as a product of fermentation. Diacetyl is endogenous in humans and is the single substance most responsible for the human perception of the taste of butter. The "compounding" of flavors and how they are used in food manufacturing was described by Hallagan and Hall (2009). Compounded flavors typically contain individual flavoring substances at levels well below 1.0% of the compounded flavor. Compounded flavors are in turn most often added to foods also at levels below 1.0%. So, the concentration of individual flavoring substances in food is most often in low ppm concentrations (i.e. 10-200 ppm).	

G-21	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Before they may be marketed and added to food, flavoring substances must comply with the requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA) through the premarket approval requirements instituted by the Food and Drug Administration mandating that these substances be safe for ingestion. In most instances, flavoring substances permitted for use in the U.S. have regulatory status as substances determined by FDA to be approved food additives or substances determined to be "generally recognized as safe" (GRAS), or as flavoring substances determined to be GRAS by FEMA (Hallagan and Hall, 1995; 2009). About 600 flavoring substances, including diacetyl and 2,3-pentanedione, have both explicit FDA regulatory status and FEMA GRAS status. Both diacetyl and 2,3-pentanedione are permitted for use in food by FDA (21 CFR 184.1278 as a GRAS substance and 21 CFR 172.515 as an approved food additive, respectively). Like the vast majority of flavoring substances, this regulatory status means that they may be added to food consistent with good manufacturing practices (GMP). The use of flavoring substances and other food ingredients consistent with GMP means that the substances should be used in the minimum amount to achieve their desired technical effect in food.	It is understood that diacetyl and 2,3-pentanedione are on the Food and Drug Administration (FDA) generally recognized as safe list, although the FDA was not considering the exposure of the workers who were manufacturing these compounds or using them in the manner discussed in many situations in this document. The use of good manufacturing practices, however, will minimize these occupational exposures when those manufacturing practices include the control measures described.
G-22	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	**General Comments on the Criteria Document and Requests for Revisions** Much of the advice and many of the recommendations contained in the Criteria Document are consistent with the advice and recommendations that FEMA has provided to flavor and food manufacturers for many years through reports (e.g. FEMA, 2004) and workshops. Some of the general comments and requests for revisions below are elaborated in the following sections of these comments.	The glossary was expanded to include *priority flavoring* with reference to the Flavor and Extract Manufacturers Association. Other terms such as "chemicals with structural similarities" have meanings within the profession, and others yet are general terms with meanings in context.

		Priority Flavoring Chemicals The term "priority flavoring chemicals" or "priority substances" appears in several places in the Criteria Document (e.g. Section 8.3.6) but is not defined. The concept of prioritizing flavoring substances to indicate suggested areas of focus for potential workplace exposures was developed by FEMA and first appeared in the NIOSH Industry Alert (NIOSH, 2003 - with attribution to FEMA) and the FEMA report "Respiratory Health and Safety in the Flavor Manufacturing Workplace" (FEMA, 2004). The Criteria Document also includes other terms such as "other flavoring chemicals," "chemicals with structural similarities," and "agents of concern," none of which are defined or included in the glossary. FEMA requests that the Criteria Document provide definitions of these terms and assure consistency in their use.	
G-23	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	**Summary of Requests for Revisions and Responses** In summary, FEMA requests that NIOSH make the following revisions to the Criteria Document. If NIOSH decides not to make the revisions requested by FEMA then we request that NIOSH fully explain its reasons.	No response required
G-23a	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that the cover of the NIOSH Criteria Document be revised to either include no photograph or a photograph showing appropriate exposure controls.	The cover of this document has been revised in response to comments.
G-23b	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH clarify statements describing food and beverages that contain diacetyl by deleting reference to wine and beer. Standard wine is not permitted to contain added flavors. Beer may contain added flavors only if clearly labeled as such. FEMA also requests that NIOSH include information in the Criteria Document explaining the distinction between diacetyl which may be present in foods naturally (i.e. through natural occurrence or through natural fermentation processes and not through addition) and diacetyl	Concerns have been raised in several public comments about affected industries having insignificant or “naturally occurring” diacetyl exposures. Other “naturally occurring” chemicals (e.g., aflatoxins, endotoxins, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e. naturally occurring or not).

		present in foods through intentional addition to provide flavor.	While wine, beer, or other food products, labeled or not, may contain "naturally occurring" diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.
G-23c	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH review and revise accordingly the recommended exposure limits (REL) proposed in the Criteria Document to address whether they are reasonably achievable by flavor manufacturers, especially in light of the fact that the majority of flavor manufacturers that are small businesses	See response to EC-11.
G-23d	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH make it clear throughout the Criteria Document that any recommended exposure limits (RELs) for diacetyl or 2,3-pentanedione do not apply to facilities where exposure to either of these substances may occur solely through exposure to naturally occurring diacetyl or 2,3-pentanedione in foods and beverages.	See response to G-23b.
G-23e	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that the Criteria Document be carefully reviewed for consistency when the illness at issue is described and make appropriate revisions to assure that the illness described is supported by the reported clinical findings. If the variety of terms currently used is to be used in the final version of the Criteria Document then FEMA requests that each term be fully defined to allow clear distinction among the descriptive terms.	The commenter asks for consistency in descriptions of the illness and the terms used to describe it. Section 3.1.1 has an extensive description of terminology and our use of terms in the articles cited. Other commenters have been critical of our use of the term bronchiolitis obliterans without pathologic confirmation, which is not possible in NIOSH field studies. In our revision, we have indicated where findings are consistent with constrictive bronchiolitis or pathologically confirmed. Historically, the term "bronchiolitis obliterans" was used by pathologists for proliferative bronchiolitis, and we have attempted to use the term "constrictive bronchiolitis," which may be

			less confusing to both pathologists and pulmonary physicians.
G-23f	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH revise the Criteria Document to describe the relationship between diacetyl and respiratory illness, including bronchiolitis obliterans, as an association and not as a causative relationship.	Section 3.7 has discussion of the criteria met for causal associations. Accordingly, we have not changed the description of the relationship between diacetyl and respiratory illness to an association in contrast to a cause.
G-23g	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA also requests that NIOSH revise the Criteria Document throughout to make it clear that there are no known cases of respiratory illness associated with exposure to 2,3-pentanedione.	We agree that there are no known cases of respiratory disease associated with 2,3-pentanedione exposure. When manufacturers of butter flavorings changed formulations to decrease use of diacetyl and include diacetyl substitutes, they did not advise their clients of the new ingredients, which were claimed to be trade secret. Accordingly, populations with 2,3-pentanedione exposure without previous diacetyl exposure are difficult to identify. The basis of the recommended exposure limit for 2,3-pentanedione is animal toxicity data. We have inserted a paragraph at the beginning of Chapter 3 to indicate that illness in relation to 2,3-pentanedione exposure alone has not been studied.
G-23h	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that the NIOSH Criteria Document include definitions of terms such as "priority flavoring chemical," "priority substance," "other flavoring chemicals," "chemicals with structural similarities," and "agents of concern," none of which are defined or included in the glossary. FEMA requests that the Criteria Document provide definitions of these terms and assure consistency in their use.	See response to G-22.

G-23i	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that the available medical surveillance data from workers described in Table 3.1 on Page 47 of the NIOSH Criteria Document be analyzed and reported together with standard descriptions of the findings because as the information is currently reported it is limited in usefulness because of the highly variable descriptions of the findings. This table would also be the ideal place to describe the total number of workers examined, the total number with possible and confirmed lung disease, and if available, data on the presence of diacetyl in the facilities.	We have added Table 3.2 to address the commenter's request for more information. This new table indicates the number of workers tested by plant, the publication from which the information was derived, the number and percentage of those tested with abnormal spirometry, and the numbers classified with restrictive, obstructive, and mixed restrictive and obstructive abnormalities. In populations in which we tested former workers, we have presented the information for current and former workers separately. In a flavoring plant in which we tested a substantial number of nonproduction workers, we have presented the information separately for current production and nonproduction workers. In NIOSH medical surveys, we don't have diagnosis confirmation of the abnormalities in workers that we identify as having abnormal spirometry. Accordingly, we are not able to provide the information requested on probable and confirmed cases. Diacetyl exposure data for these facilities are summarized in Table 2.1 and are available in the primary health hazard evaluation reports.
G-23j	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH explain their use of area sample data in Chapter 3, Section 3.1.2.2 and why the use of such data does not adversely affect the accuracy of the risk assessments described in the Criteria Document.	The commenter requests explanation of the use of area samples in section 3.3.2.2, which describes the initial cross-sectional exposure survey at Facility G. NIOSH industrial hygienists conducted only area measurements on this initial survey because they did not know that flavorings were a potential causal agent. Because area samples are often a poor reflection of personal exposures, these measurements were not

			used directly for the risk assessment. For the risk assessment, OSHA and NIOSH staff estimated personal exposures in the initial November 2000 survey by modeling personal to area measurements for subsequent surveys and applying the model to the first survey which had only area measurements. This information is included in Chapter 5 and Appendix 4, which describe the derivation of the job exposure matrix for Facility G.
G-23k	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH explain the following statement on Page 51, Chapter 3: "Because of concerns for patient welfare and the invasive nature and low sensitivity of lung biopsy for diagnosing constrictive bronchiolitis obliterans, most patients have been diagnosed upon clinical findings." Please explain, with supporting references, the statement regarding the "low sensitivity of lung biopsy" which most pulmonologists consider the gold standard for the diagnosis of constrictive bronchiolitis obliterans.	That sentence has been modified for accuracy.
G-23l	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that in Chapter 3 NIOSH explain the absence of a thorough discussion of smoking histories and other potential confounding factors for the evaluation of the existence of employment-related obstructive lung disease. Important factors that should be addressed include pre-existing asthma and whether pre-employment spirometric data are available.	See responses to public comments RA-2, RA-9 and Med-22.
G-23m	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA request that NIOSH clarify its definition of "rapid decline" in lung function as used in Chapter 3 and elsewhere in the Criteria Document.	In section 9.5, definitions of excessive decline are made, providing alternatives for determination based on spirometry quality, population-based normative values, and a NIOSH software program which can adjust for spirometry quality. Because these definitions are already included in Chapter 9, we have not repeated the information in Chapter 3,

			but have indicated where different approaches are discussed in section 9.5.
G-23n	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH include in Chapter 3, Section 3.3 an explanation of the role that factors such as body mass index may play in evaluating pulmonary restriction.	The issue of body mass index is discussed several times throughout this chapter (specifically in sections 3.1.2.5, 3.1.2.7, 3.2.3, 3.3 and 3.7) and we feel it is not necessary to address this issue again.
G-23o	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Recognizing that the analysis presented in Chapter 5 of the NIOSH Criteria Document is almost exclusively based on data from the sentinel microwave popcorn manufacturing plant, FEMA requests that NIOSH explain the relevance of the quantitative risk assessment presented in this chapter to flavor manufacturing facilities.	See responses to reviewers' comments RA-52, RA-46, and G-18.
G-23p	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH revise Chapter 5 of the Criteria Document to report an analysis of the application of the Cox-Ganser et al. (2011) correction methodology to samples reported in this chapter to be below the limit of detection. If the analytical results for these samples were corrected and used by NIOSH the risk assessment may have yielded a much different outcome resulting in a higher and more reasonably achievable REL for diacetyl.	The document was revised as suggested.
G-23q	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH, in both Chapters 5 and 6 on its risk assessments, and in Chapter 7 on the basis of its REL for diacetyl compare the results of its risk assessments yielding an REL of 5 ppb (8hr. TWA) for diacetyl with the OEL of 0.2 ppm recommended by Maier et al (2010) and thoroughly explain its rationale for the substantial difference.	See response to comment RA-45.
G-23r	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that Chapter 8, Section 8.3.7 on hazard communication be revised to include a description of OSHA's hazard communication guidance for diacetyl (OSHA, 2007).	The criteria document has been updated to include information that address some major requirement of the new OSHA hazard communication standard based on the GHS [OSHA 2012].

G-23s	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA requests that NIOSH explain in Chapter 9 how it would address concerns associated with individual small business company resources and worker privacy issues resulting from the implementation of medical monitoring programs. We would be pleased to respond to any questions and comments, and requests for additional information that you may have. We look forward to continuing a productive relationship with NIOSH. My email address is Hondobear@aol.com and my direct telephone number is 202.331.2333	This comment regarding small business company resources and worker privacy issues has been addressed above in responses to EC-48 and Med-25.
G-24	Azita Mashayekhi, M.H.S. on behalf of the International Brotherhood of Teamsters	The IBT commends NIOSH for presenting a comprehensive review o f scientific literature, a quantitative risk assessment, and valuable guidance to reduce occupational exposures to diacetyl and 2,3-pentanedione. The information presented in this document will serve as a very useful tool to adequately and effectively reduce or eliminate significant risk o f health impairment from exposure to these toxic chemicals and to prevent flavorings-related lung disease in the working men and women of this country. While the focus of this document is on diacetyl and 2,3-pentanedione, the IBT fully supports NIOSH's concern about "other flavoring substitutes with structural similarities to diacetyl. .. and capable of producing similar toxic effects as diacetyl," and NIOSH's recommendation "that such exposures also be considered and controlled to as low as reasonably achievable."] Our comments are to serve as a statement of support for this effort and to urge NIOSH to move ahead with finalizing the criteria document. We will submit additional comments to the NIOSH docket at a later date.	No response required

		The IBT represents more than 1.4 million workers nationwide, hundreds of whom are employed in industries and jobs where diacetyl and 2-3,pentanedione, and other alpha-diketones are used. Our members perform a variety of jobs in the manufacturing of flavorings, foods, baked goods and snacks, dairy, candy, confectionary, and baking products. □ Forty-one years ago, when the Occupational Safety and Health Act of 1970 was enacted, it declared that "the Secretary of Health and Human Services, on the basis of such research, demonstrations, and experiments, and any other information available to him, shall develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods o f employment, including but not limited to the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result o f his work experience."[2] It was in 1985, over 16 years ago, that NIOSH conducted a health hazard evaluation at a plant in Indiana that produced flavorings for the baking industry and found severe fixed obstructive lung disease among workers in a mixing room.[3] And it was on January 15, 2004, over seven years ago, that NIOSH recommended in an Alert "that employers take measures to limit employees' occupational respiratory exposures to food flavorings and flavoring ingredients in workplaces where flavorings are made or used."[4] Since 2006, the IBT, and its local union affiliates, have been in the forefront of efforts to encourage and assist federal and state agencies in research and regulation of occupational exposures to diacetyl and related flavoring ingredients.	

		In 2006, the IBT, along with the United Food and Commercial Workers International Union (UFCW), pointed to "compelling epidemiologic and toxicological evidence linking exposure to diacetyl to severe respiratory impairment and disease" and called upon the Occupational Safety and Health Administration (OSHA) to issue an Emergency Temporary Standard (ETS) and to initiate formal rulemaking to protect workers exposed to diacetyl and other harmful flavoring-related chemicals.[5] In 2008, a Teamster local union submitted a request for a health hazard evaluation (HHE) at a flavorings manufacturing facility in Indiana.[6] Also in 2008, NIOSH received another union request to perform an investigation of possible health hazards at a Teamster-represented bakery mix facility in Los Angeles, CA. These investigations have resulted in important findings which are described in the draft criteria document. At both plants, NIOSH found a pattern of spirometric restriction, significantly higher than the prevalence for the U.S. adult population. At one of the plants "Employees with higher potential for exposure to flavorings had greater average annual decline in lung function and a 7- fold higher chance of abnormal lung function decline than employees in other areas with lower potential for exposure."[7] These findings, and previous reports, suggest that the spectrum of health effects related to flavorings may be broader than fixed obstruction, and include restrictive lung disease.[8] And in both cases, NIOSH could not find "the results of any in-depth medical evaluations resulting from abnormal findings identified by the	

		monitoring and surveillance program,”[9] to determine if those with restrictive spirometry have occupational lung disease. We urge NIOSH to continue exploring this possible association. In light of the range of possible health effects, we fully embrace NIOSH's objective, in recommending exposure limits, "to reduce the risk of decreased lung function and the severe irreversible lung disease constrictive bronchiolitis obliterans associated with occupational exposure to these chemicals, and to help prevent other adverse health effects including but not limited to irritation of the skin, eyes, and respiratory tract in exposed workers." At one of the plants, although "none of the applicable Material Safety Data Sheets for the evaluated bulk flavorings listed diacetyl or its alpha-diketone substitutes,”[10] NI0SH's analytical results of bulk samples of liquid and powdered flavorings indicated that, aside from diacetyl, five of six contained the alpha-diketone substitute compound, 2,3-pentanedione, and three contained other alpha-diketones.[11] This finding confirmed the use of 2,3-pentanedione as a substitute for diacetyl in artificial butter flavorings. Research by both NIOSH and the National Institute of Environmental Health Sciences (NIEHS) "suggests that, in rats, 2,3-pentanedione causes airway epithelial damage similar to that produced by diacetyl," signifying that " ... all too often, substitution is an unreachable panacea."[12]	

G-25	Azita Mashayekhi, M.H.S. on behalf of the International Brotherhood of Teamsters	Given NIOSH's comprehensive revIew and quantitative assessment of human exposures, supported by animal risk assessments, the IBT supports the recommended exposure limit (REL), the action level (AL), and the short-term exposure limit (STEL) for diacetyl proposed by NI0SH; we also agree with NIOSH "that the use of an AL in conjunction with periodic monitoring of worker exposures ...is helpful to protect workers."[13] In view o f the capabilities and constraints o f the analytical method, the IBT also supports the REL and STEL recommended by NIOSH for 2,3-pentanedione. As NIOSH notes, these limits are supported by validated analytical and sampling methods that can be used to effectively measure worker exposures at the selected level, and by achievable engineering controls based on "information from OSHA-sponsored site visits [Eastern Research Group 2009c] where diacetyl is used or handled." Since, however, the analytic method capabilities may advance in the future, we recommend that NIOSH clearly state in this document, to the extent that improvements in analytic feasibility would permit, that the recommended limits for 2,3-pentanedione should be based upon data from human and animal studies and the quantitative risk assessment. In addition, in view of new research findings, NIOSH should explain in this document if and how it could be amend the criteria document and provide new references, so stakeholders are informed of and have convenient access to all relevant documents. We thank NIOSH, once again, for this opportunity to comment on behalf of our members, and all affected workers, and for producing criteria of a recommended standard for the recognition, evaluation, and control of hazards impairment from exposure to diacetyl or 2,3-	No response required

		pentanedione and other potentially hazardous flavoring chemicals. This criteria document is, at last, a great step by NIOSH towards fulfilling its mandate to use scientific evidence to protect American workers from debilitating lung disease.	
G-26	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Sensient Flavors LLC (Sensient Flavors) is pleased to respond to the request for comments on the document "Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione" ("Criteria Document") published by the National Institute of Occupational Safety and Health (NI0SH). 76 *Fed. Reg*. 44338. 25 July 2011.	The public commenter suggests that the 1985 HHE [NIOSH 1986] (Facility A) should be omitted from the criteria document because no cause was identified for the two cases of fixed obstructive lung disease. While this is correct, the report documented that diacetyl was frequently used in the facility and that one case reported preparing “cinnabutter” flavoring on the day of symptom onset. In

		In addition to the comments contained herein, as one of the larger members of The Flavor and Extract Manufacturers Association of the United States (FEMA), Sensient Flavors also adopts FEMA's comments to the Criteria Document. [1] Sensient Flavors is a part of Sensient Technologies Corporation, a global, publicly traded company with operations in more than 30 countries including the United States. Sensient Flavors' headquarters is in Indianapolis, Indiana. Sensient Flavors offers flavor solutions to help our clients bring life to their products. The company's approach to advanced product development capabilities are reknown in the industry. With an extensive portfolio of proprietary technologies, Sensient Flavors creates custom flavor solutions and products. Continuous development of our product range and ongoing investment in state of the art technology and production facilities allows Sensient Flavors to create innovative products, tap new markets and meet the innovation needs of our customers. Since its inception, Sensient Flavors has had an unwavering commitment to the health and safety our workforce. Indeed, our Indianapolis facility has an excellent record of compliance with all applicable state and federal regulations relative to workplace safety. Sensient Flavors has actively supported and participated in FEMA's efforts in the area of respiratory health and safety since it began offering programs in 1997. **General Comments on the NIOSH Criteria Document** The 1985 Indiana Bakers Study The Criteria Document makes multiple references to the 1985 NIOSH evaluation of a baking facility in Indiana that used flavorings with diacetyl, and where "two workers with fixed obstructive	every flavoring manufacturer with batch operations, such as International Bakers (which manufactured flavorings for the baking industry), the multitude of chemical exposures makes causal attribution difficult, if not impossible. The inclusion of this HHE investigation documents that flavoring manufacturing workers performing similar tasks have rapidly developed severe lung disease in the industry for decades now. Many cases of biopsy-documented constrictive bronchiolitis have been documented in flavoring manufacture in many plants, in contrast to the incorrect allegations of the public commenter. No changes were made in the document.

		lung disease *suggestive* of bronchiolitis obliterans were observed." (emphasis added) This document did not identify diacetyl or any other chemical as a causative agent. Indeed, a fair reading of this document indicates that N IOSH was unable to reach any conclusions whatsoever as to the cause of the respiratory condition of these two workers. In Sensient Flavor's view, to suggest that the 1985 baking facility study is somehow germane to the establishment of a recommended standard for diacetyl and 2,3-Pentanedione is a stretch, at best. Moreover, if NIOSH intends to use this study in the Criteria Document, it should explain why there are no case reports of respiratory disease in the flavor manufacturing workplace for at least 10 years following the study, despite the fact that the use and production of flavors containing diacetyl and 2,3-Pentanedione continued without interruption in multiple companies and in multiple contexts across the country. For these reasons, Sensient Flavors believes all references to the 1985 Indiana baking facility study should be removed from the Criteria Document.	

G-27	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page 19: "When the encapsulated powder comes into contact with water, or saliva, a 'flavor burst' occurs where the release of the flavor from the encapsulation is generally fast and complete upon contact with the moisture." This is a gross overstatement and oversimplification of the functionality of encapsulated powder flavorings. While this may be true of ***some*** flavoring encapsulated technologies, it is not true of all of them. And it is certainly not true that contact with common saliva will always trigger a "flavor burst" and "release" of the flavor. Indeed, most encapsulated flavorings that Sensient Flavors manufacturers will not release unless heated and exposed to moisture at levels well beyond the temperature of saliva or even hot water. Sensient Flavors believes this statement should be significantly modified to reflect the highly variable nature of the different encapsulated powder flavoring products made by companies in the flavoring industry.	The document was revised as suggested.
G-28	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page 21: "For example, respiratory issues have been anecdotally reported for cheese production (Wisconsin), yogurt production (Ohio), and potato chip manufacturing." Sensient Flavors does not believe that a scientifically based document like the Criteria Document should contain anecdotal report information without more. Especially when, as here, the anecdotal reports do not attribute the purported respiratory issues to exposure to flavoring chemicals or, more specifically, diacetyl and 2,3-Pentanedione.	We agree that anecdotal data should not be used for the determination of the exposure limits or similar purposes, however this instance is in a section of the document on "Potential for Exposure," and is clearly designated as anecdotal. In this context, we believe the inclusion of this information is justified.
G-29	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page 294: "What proportions of excess obstructive lung disease in food production workers and in cooks are attributable to flavorings exposure?" Sensient Flavors understands that some study has already been performed in this area involving workers employed by ARAMARK. If the results of that study are discussed	Sensient Flavors requests an answer to a research needs question regarding what proportions of excess obstructive lung disease in food production workers and in cooks are attributable to flavorings exposure. This research need was listed because of the

		somewhere in the Criteria Document, please identify where that is. If it is not in the Criteria Document, NIOSH should explain why it is not.	excess of bronchitis symptoms or measured obstruction in three population-based epidemiologic studies referred to in Kreiss [2007], Hnizdo et al. [2002], Fishwick et al. [1997], and Zock et al. [2001]. The commenter wants to know if the results of the health hazard evaluation involving cooks at Aramark are included in the criteria document. These results are [NIOSH 2009b] in Chapter 3, page 78 of the draft criteria document. This investigation does not answer the question posted in the research needs.
G-30	Jacqueline Nowell on behalf of the United Food and Commercial Workers Union, CLC	The UFCW International Union supports the draft document "Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-pentanedione." The Union has been involved almost from the beginning of NIOSH's seminal work on flavorings. NIOSH researchers and scientists, clinicians and industrial hygienists have conducted site investigations of cases and exposures and have developed methods and materials for both measuring and controlling exposures. This is exactly the role for the agency charged with researching workplace hazards. **History** In 2001, NIOSH contacted my office to inquire if we represented workers in the microwave popcorn industry. They informed us of lung disease among workers and they were investigating the link to butter flavoring. We found no microwave popcorn companies among our represented plants. However, later, we found plants that used butter flavoring - cooking, snack foods, frosting, flavored oils. We obtained MSDSs and examined OSHA 300 log data and held meetings with officials from companies we identified who were using butter flavorings to discuss our concerns. Throughout	No response required

		this process, we were working closely with NIOSH, asking and answering questions and reviewing our information. They conducted research. They worked closely with California, the OSHA state-plan state that took this occupational hazard very seriously. We found almost no Diacetyl used in our food manufacturing plants and we found no sick workers. However, it did raise our awareness specifically of the thousands of food manufacturing workers who were potentially exposed. There was important press on the issue during this time. There were law suits on behalf of injured workers. Cal OSHA began its work, partnering with NIOSH. But Federal OSHA was doing almost nothing. In 2006, the UFCW and the IBT along with the support of 40 occupational doctors and scientists filed a petition with OSHA for an Emergency Temporary Standard. The petition called on OSHA to require employers to: Control airborne exposure to diacetyl to below 0.05 ppm, averaged over an eight-hour work period; Provide air-purifying respirators to all exposed employees above 0.05 ppm; Provide medical surveillance to all employees exposed Provide medical surveillance and consultation to all employees exposed above 0.05 ppm; Conduct monitoring of airborne exposure to diacetyl. In addition, we asked that OSHA immediately issue a bulletin to all employers and employees potentially exposed to diacetyl stating that exposure may result in severe illness; conduct inspections at facilities where workers are exposed to Diacetyl; and begin rule-making proceedings to establish a permanent standard to protect workers from exposure to all flavorings that should include a permissible exposure limit that protects workers against a significant risk, methods of	

		compliance, a detailed medical surveillance program, appropriate exposure monitoring, training and information. OSHA denied our petition and but under the Obama Administration, OSHA has finally begun rulemaking. **Cal/OSHA and FISHEP**Cal/OSHA aggressively pursued investigations and standard setting for butter flavorings. They identified California-based manufacturers of flavorings, conducted investigations, pursued cases of flavorings-related lung disease, working closely with NIOSH and the Department of Health. In 2006, the unions similarly petitioned Calf OSHA for an Emergency Temporary Standard. In 2010, they promulgated the first standard, which covers diacetyl and substitute butter flavorings where a case **Prevention and control, training, medical surveillance and monitoring** With the exceptions listed below, we support the recommendations in these sections.	
G-31	Jacqueline Nowell on behalf of the United Food and Commercial Workers Union, CLC	Further investigations should be conducted in food manufacturing facilities that use flavorings One example is the use of slurries sprayed on snack foods tumbled in drums. To date, the research has been limited. For over 1 1 years, NIOSH has done preeminent work on this issue. Research scientists across multiple divisions have been involved. This criteria document amasses the data and research as well as that of other institutions and organizations, including National Jewish Health and FEMA and goes beyond our petition to reduce or eliminate significant risk of health impairment from exposure to not only diacetyl but 2,3-pentanedione and prevent flavorings-related lung disease. NIOSH also recommends that exposures to other flavoring substitutes with structural similarities to diacetyl or moieties that are biologically active and capable of	We agree that additional work would benefit the knowledge regarding exposure and effects of exposure and control of flavorings as well as other areas of this subject. See response to comment RA-41 and Chapter 11, Research Needs.

		producing similar toxic effects as diacetyl be considered and controlled to as low as reasonably achievable. This document is based on sound science. It serves as a basis for an OSHA standard. Thank you for the opportunity to comment on the recommended standard.	
G-32	private person (from a brewing company)- No other information provided	About two years ago a study group that included members of various safety organizations of government and several members of mostly food industries such as bakeries, cheese-makers, snack food producers including popcorn, and breweries addressed the concern of diacetyl, which in high concentrations, had been found to produce "popcorn lung" in exposed workers. The industries represented were among those who use diacetyl in their products or produce it due to their various processes. After six months it was determined that breweries would not be a target industry because the diacetyl concentrations obtained within their process were too low to cause concern: that is parts per billion instead of the dangerous, parts per million. Now NIOSH has proposed an action level for the food industries of 5 parts per billion diacetyl at which point safety breathing apparatus must be used by those exposed to those levels for most of their work shift.	Concerns have been raised in several public comments about affected industries having insignificant or “naturally occurring” diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxins, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.

		What this means to the pub brewer and to any bar that serves beer and whiskey products is that workers will have to wear SCUBA gear. This is alarming. I move that the proposed regulation be shelved until there is a thorough discussion by all stakeholders of all ramifications including economic impact and consumer responsibilities and liabilities.	
G-33	Charles Schroeder, private citizen	The release of volatile chemicals: when this occurs in trace quantities it is recognized as flavor or fragrance, yet the release of concentrated vapors has the potential to be harmful. In reality, all flavors and perfumes are simply blended chemicals (mixtures of natural and/or artificial ingredients). Only when an aromatic compound volatilizes can it be enjoy as a flavor or fragrance - it can not be detected if confined or bound physically or molecularly. Across the gamut of flavors and fragrances, one could infer that any blend of chemicals can be safe, yet can also be harmful at highly concentrated levels. Currently OSHA/NIOSH is faced with the challenge to determine a level above which a volatilized diacetyl and related compounds can be injurious. In lieu of the many opinions expressed during this assignment, this task has proven daunting. In the late 1920's, diacetyl was identified as the key flavorant in high-quality butter. Dairymen knew that fresh cream butter was bland and often used salt for flavor, yet if the cream was allowed to "sour" before churning, it was rich with flavor. Many cold-processing food manufacturers (specifically dairies) have long used diaeetyl-containing flavors without incident. Typically their HACCP plans and operations feature cold processing, they use flavors with less than 1.5% diacetyl, they handle the flavor for only a short period of time,	This comment provides a discussion of flavor industry practices and nomenclature that in some respect differ from the nomenclature used by the environmental health profession. Most notably, the reviewer seems concerned by the use of the concentration expression of parts per million. The terminology used throughout the diacetyl criteria document is standard professional vernacular and should be clear to not only the health and safety professional but also to any scientific audience.

		and the final product contains trace quantities of diacetyl. Today, those skilled in the art of flavor/fragrance creation are aware of the many virtues of diacetyl and its derivatives, and their importance in buttery notes, cream notes, caramel notes, ripe berry profiles, maillard-reaction flavors, and their uses as crucial flavor modifiers. Within the flavor/fragrance industries, the terminology "15X" represents 15,000 ppm, or 1.5%. Many other flavor compounds may be present in said flavor, yet the flavor/fragrant "strength" has been standardized using diacetyl as an effective benchmark. Brewers and vintners also familiar with diacetyl as a natural metabolite, encountered when fermenting eukaryotes (yeast) and prokaryote (bacteria) It can be found in beer, wine, and many other fermented foods. Wthin these cells, diacetyl is a natural metabolite, part of butylene glycol biochemical pathway, mixed-acid fermentation pathway. In addition, it develops naturally as certain fruits ripen. And as a ubiquitous bacterial metabolite, standard microbiological classification systems test for the production of diacetyl in its reduced form - better known as acetoin (Voges-Proskauer method). Again, these food and beverage industries have long dealt with diacetyl and diacetyl-containing flavors without incident. A food-related occupational hazard was first reported with diacetyl in the relatively young industry of microwave popcorn. Manufacturing this convenience-food item used highly concentrated flavor (up to 30% diacetyl) in a heated mixing process. This is in stark contrast to the 1.5% diacetyl found in more traditionallyused butter or other dairy flavors. For microwavc popcorn production, the flavor was blended	

		into hot fat, that, once dispensed into a final container (bag), would then solidify. Heating has the effect of increases vapors by decreasing liquid viscosity and increasing flavor evaporation. Subsequently, microwave popcorn plant QC methods repeatedly pop bags in a microwave oven throughout the day: this exposed the flavored oil again to liquefaction, heat, as well as the steam and pressure generated by popping corn kernels. Such conditions can exacerbate the release of any volatile component of a flavor or fragrance. In general, heating a flavor in oil, influences flavor solubility and affects the partition coefficients of the flavor molecules. In contrast to dairies and other food processing plants that use the cold flavors with 1.5% diacetyl, popcorn plants used heated flavors with up to 30% diacetyl. While food manufacturing plants feature cold processing (e.g., dough handling), production lines in microwave popcorn plants added highly concentrated diacetyl-containing flavors to high-temperature melted fats, then maintained high temperatures to prevent the fats from solidifying before being dispensed. Once the possibility of an occupational hazard was identified, diacetyl quickly became a scapegoat within the flavor/fragrance industry, diverting attention away from other more common or lucrative volatile compounds. And since diacetyl is the quintessential, and characteristic note of butter, many butter, cream, and caramel flavors rapidly fell under the same ire and scrutiny. NIOSH has made concerted efforts to assess the safety of diacetyl-containing flavors. With the help of scientist, scholars and testing, NIOSH has offered exposure limit values, yet the misunderstanding and misinterpretation of the relevance of this published information is causing unnecessary fear and confusion.	

		Worker safety equates to exposure to vapors, yet the food industry is more familiar with values relating to concentrations in solution. Regarding diacetyl, these concentrations are quoted as parts-per-million (ppm). In reports focusing on worker safety, NIOSH is recommending extremely low parts-per-billion (Ppb) for both short-term exposure limits (STEL) and time-weighted averages (TWA). With orders-of-magnitude difference between ppm and ppb, many in the food industry confused.	
G-34	Charles Schroeder, private citizen	To best serve the food industry, NIOSH should generate tables that allow food manufactures to better access their potential risks to workers. These tables could be structured as follows: [See Schroder letter for Table] Similar tables as shown above should be generated to provide information on vapor release at different temperatures for different concentrations, bases, and forms, since liquid flavors are available in many concentrations (e.g., 0.1 % - 30% diacetyl), in various bases (i.e., water vs. oil vs. alcohol), and forms (e.g., emulsions vs. homogeneous blends). Provided with these data, any manufacture can identify their flavor strength, recognize their process temperatures, and better assess their manufacturing operations. Again, any chemical or blend of chemicals can be used safely, yet has the potential to be harmful at high concentrations if handled inappropriately. By providing information similar that that shown in the tables and data above, manufactures, occupational safety professionals, and should prove to be an invaluable tool to all pertinent industries.	A study of the air concentrations that are evolved from heating of different concentrations of diacetyl has not been completed by NIOSH. This type of study would provide some information but would not be directly applicable to exposure assessments.

G-35	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	The U.S. Department of Agriculture, Food Safety and Inspection Service (FSIS) requests that NIOSH:	No response required
G-35a	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	recognize poultry and meat industry workers and inspectors as potentially exposed to diacetyl or related compounds	The criteria document recommends a maximum inhalation concentration for anyone exposed to diacetyl or 2,3-pentanedione in a work environment, but it is impossible to list all occupations where this may occur. A search of current literature does not indicate any published connections between poultry and diacetyl.
G-35b	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	explicitly consider diacetyl's irritant effects in setting occupational exposure limits;	See responses to comments on odor threshold (e.g., RA-11).
G-35c	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	consider the economic impact/feasibility of implementing the recommended medical monitoring program across a large, geographically diverse organization or company	Consideration of economic impact is purposely not included in a criteria document, but is considered in the OSHA standards setting process.
G-36	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	FSIS recently identified the use of butter flavored starter distillate in a poultry slaughter and processing establishment. In this instance, waste marinade containing starter distillate was discharged into open trenches that ran beneath the poultry inspection stands. No odors consistent with butter flavorings were reported at any time, but highly prevalent eye and upper airway irritation among the inspection workforce ceased the day after the use of starter distillate was	See response to comment G-35a.

		discontinued. Previously, there was no documented evidence of diacetyl's inclusion in poultry or meat marinades. Based on available information about the consumer of this specific poultry product, we estimate that the number of birds marinated in starter distillate for this retail outlet alone approached one million annually, with product distributed to about 1,000 retail stores for rotisserie roasting. Anecdotal information from poultry industry managers suggests that the use of diacetyl is much more widespread than was observed in this single case. We believe it is plausible to expect diacetyl or diacetyl substitutes are used in a variety of meat and poultry product lines. This could entail exposure potential for several thousand federal meat and poultry inspectors, and tens of thousands of industry workers. We believe these populations should be identified as potential exposure groups in the Criteria Document and any subsequent flavorings research. FSIS thanks NIOSH for your attention to these issues. The potential for adverse health effects and reduction in productivity and the quality of work life due to diacetyl exposure exist outside of the popcorn and flavorings industries. Diacetyl's strong irritant and dermal effects, while not as devastating as BO or chronic lung disease, can have a very real and significant impact on workers and organizations. Due consideration is needed to ensure that they are addressed in the current body of research on diacetyl and related butter flavorings.	

Med-1	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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.	The commenter objects to the word "related" for a statistical association, saying that the wording implies causation. The wording is that of the peer-reviewed publication, which does not claim causation for the statistical association. No change was made in the wording in relation to this comment.
Med-2	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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 issuers) 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.	The commenter objects to the wording "conferred" as implying causation. We have changed the wording in Table 3.1, as requested, to "Cumulative diacetyl exposure of ≥0.8 ppm-year was associated with an odds ratio of 9.2 for obstruction." Reference NIOSH 2009d was included in Table 3.1 because it was a flavoring manufacturing facility that had both flavoring operations and bacterial products workers. We have revised the comment for the van Rooy [2007] paper to insert the word "syndrome" indicating that no pathologic confirmation was obtained or sought.

Med-3	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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.	This comment duplicates part of Med-20, and the response is found there.
Med-4	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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.	Some workers in flavoring manufacturing plants have biopsy evidence of constrictive bronchiolitis, contradicting the suggested wording by the commenter. The van Rooy et al. paper [2007] regarding diacetyl manufacturing had no biopsy documentation. We have corrected the wording in describing the diacetyl manufacturing cases to indicate that they had findings consistent with constrictive bronchiolitis.

Med-5	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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.	The document was revised as suggested.
Med-6	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	*6* **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] There are medical reports that describe the microwave popcorn workers as having "restrictive lung disease, as well as airways obstruction.'" 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.	The commenter correctly states that equating bronchiolitis obliterans with fixed airways obstruction is too simplistic. The revision clarifies the terminology and these issues of definition. The specific page and line triggering the comment (page 79, line 14) is a section on asthma, and the paragraph has been simplified to agree with the commenter in making the point that persons without bronchodilator response are unlikely to have asthma and may have been misdiagnosed. The revised chapter clarifies that constrictive bronchiolitis can manifest with normal, restrictive, or obstructive physiologies based on case series of biopsy-documented constrictive bronchiolitis.
Med-7	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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	We have revised wording to more precisely indicate whether pathologic evidence is available to support the diagnosis of bronchiolitis obliterans, where appropriate. We do not agree that follow up is necessary, because progressive disease is not a characteristic of all bronchiolitis obliterans or fixed obstruction consistent with bronchiolitis obliterans due to toxic inhalation, in contrast to the experience with bronchiolitis obliterans syndrome in transplant recipients.

		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.	We do not agree with the commenter that we have insufficient evidence for the conclusions in Chapter 3.
Med-8	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	**Chapter 9 - Medical Monitoring and Surveillance** The Criteria Document should provide clearer guidance on what should trigger inclusion of specific workers in the medical monitoring program. The current guidance seems more applicable to flavor manufacturing jobs; how should food production facilities determine who to include? What does "regular" exposure mean? Since disease develops quickly, please provide any guidance on how frequency of exposure should be considered (e.g., some standards such as the lead standards specify a more specific trigger for including workers without daily exposure). Should the percentage of diacetyl in the flavorings used be a factor to consider in deciding which workers should be included in medical monitoring, and if so, how?	The commenter requests inclusion of guidance on what workers should be included in medical monitoring across industries in which exposure occurs, specifically asking for a definition of “regular” exposure, frequency of exposure, and whether percentage of diacetyl in source flavorings should be a factor. We have eliminated the adjectives “regular” and “frequent” in our revision so that all workers with any exposure are included. (One could argue that the prudent health-conserving response to defining regular exposure is any exposure above the action levels for the recommended exposure limits or short-term exposure limits for diacetyl and 2,3-pentanedione, regardless of frequency of such exposure over a work year. Because measurements are done intermittently and may not be representative, the potential presence of airborne diacetyl or 2,3-pentanedione by virtue of using flavor chemicals or flavored products in manufacture should trigger inclusion in a medical monitoring program until respiratory health has been assured by medical surveillance results over a period of surveillance that takes into account the number of persons exposed and the power to detect excess respiratory ill health.) The percentage of diacetyl in flavorings is not a

			consideration, because air concentrations are affected not only by the percentage of diacetyl in the source but also temperature, ventilation, and work practices. When diacetyl percentages were decreased in some California food production facilities, substitutes for diacetyl were increased or introduced that may have comparable toxicity. It is possible that a mixture of substitutes and diacetyl may have additive effects that are not reflected in recommended exposure limits of individual flavoring chemicals. The medical surveillance chapter has not been changed in response to this latter comment, omitting any consideration of the percentage of diacetyl in flavorings.
Med-9	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	A medical monitoring program director (or supervising physician) may work with a team of providers such as spirometry technicians. Section 9.1 suggests that the physician him- or herself will be in face-to-face contact with workers. Is NIOSH recommending that each employee have a baseline physical exam performed by this lead physician? Or would this contact happen only if screening identifies an abnormality or symptoms requiring follow-up? This ambiguity should be clarified. If no baseline physical exam is recommended, language could be added to emphasize that the person(s) administering spirometry and questionnaires should be trained to ascertain worker knowledge of risks, assess PPE use, explain findings in an understandable way to workers, etc.	The public commenter asks whether the medical monitoring director is required to have face-to-face contact with workers and to conduct a physical examination. In no place does NIOSH suggest that a physical examination is needed. The criteria document states that the physician should review and interpret questionnaire and spirometry results, including assessing spirometry quality. The most important component of an effective medical monitoring program for workers exposed to diacetyl and similar flavor ingredients is the careful comparison of spirometry test results over time to identify excessive declines in lung function [California Department of Public Health 2012]. While we continue to recommend physician involvement in test and questionnaire review, we have clarified

			that the physician director can delegate the review of the questionnaire and spirometry quality, ascertainment of worker knowledge of risks, assessment of PPE use, and explanation of findings to appropriately trained technicians. However, the written communication to the worker and employer should be by the physician overseeing the staff designated to perform aspects of medical monitoring.
Med-10	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Section 9.5 provides guidance intended to ensure that surveillance results get transferred when a company makes a change in medical surveillance provider. In our experience, this is an important issue and one that was not handled optimally by many flavor manufacturing companies we worked with in California. We recommend the following as a preferred method of addressing this situation: on the next surveillance visit for spirometry/questionnaire following a change in provider, the new provider should have employees sign a release allowing the new provider to request previous surveillance records from the previous provider. This approach allows providers to avoid any potential liability related to privacy laws and still obtain previous results that are critical to detecting any decrements in respiratory health over the course of employment.	The public commenter suggests that a new provider of medical services seek a signed release from the worker to allow the previous provider to provide surveillance records to the new provider. We have included this suggestion in section 9.5, strengthening it by suggesting that the company use contractual requirements that will result in obtaining previous records and comparing them to spirometry measurements conducted by the new provider.
Med-11	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**Decrease In FEVI Is Not Specific To DiacetyJ 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 ").	We concentrated in our historical reports and manuscripts on obstructive lung disease because the sentinel former worker cases had diagnoses of constrictive bronchiolitis or findings compatible with constrictive bronchiolitis. However, three papers of

		Although not entirely clear from the document, it appears that NIOSH emphasized decrement in FEVI1 (Case Definition I) as a measure of diacetyl impact, as opposed to case definition 2 ... The selection of decrease in FEV1 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 FEV1 as the end point **since reduction in FEVI is 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 FEV1< LLON and FEV1/FVC < LLON (case definition 2). Nevertheless, it appears in the draft criteria document that NIOSH chose instead decrement in FEV1 without considering decrements in vital capacity, as the critical health effect metric for conducting the risk assessment. The use of FEV1 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 FEV1 are observed with exposures to many agents that do not cause BO. b) The decreases in FEV1 observed in response to inhalation of reactive VOCs is thought to occur as the result of an immediate and direct effect of airway	biopsy-confirmed constrictive bronchiolitis now available on toxic exposure-related constrictive bronchiolitis document that spirometry can be obstructive, restrictive, both obstructive and restrictive, and even normal. In the risk assessment, we had chosen FEV_1 indices as the outcome because it is the most repeatable measurement among the spirometry measurements, and we did not have consistent information regarding bronchodilator response. Thus, although FEV_1 abnormalities and decrements are not specific for constrictive bronchiolitis, our choice covers both obstructive and restrictive manifestations of constrictive bronchiolitis and is the only feasible health outcome from our field studies. The excesses of obstruction in the sentinel facility are such that most cases are not background cases that are found in the general population from prevalent conditions such asthma and cigarette smoking. In addition, our models used in risk assessment controlled for cigarette smoking. Although the commenter is correct that unanswered questions remain regarding individual cases and the nature of their abnormality, the findings are robust in that persons with excessive FEV_1 decrement will eventually have impairment that is associated with increased mortality. No change in the risk assessment approach has been made in response to this comment

		irritation. This is not the case for BO. c) Many cases of decrease in FEV1 are reversible. BO is not considered to be reversible. d) Decreases in FEV1 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 FEV1 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 FEV1, decline remains unknown*."	
Med-12	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	An additional concern with the choice of FEV1 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. NIOSH found that the quality of the spirometry data was questionable. In the HHE report 2000-0401-2991 (page II) 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% FEV1 cutoff may work in some situations, but they allow for significant over or underestimation of the 95th 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.	This comment overlaps with that of RA-34 regarding the alleged poor quality of spirometry in the sentinel microwave popcorn facility. The quotation has to do with the NIOSH assessment of company spirometry following NIOSH testing in the facility, none of which was used in risk assessment. As in the response to RA-57, NIOSH only used high quality NIOSH spirometry testing in its quantitative risk assessment. The use of available field data, without clinical diagnoses, can be justified because the 3.3-fold excess of obstruction observed in the first cross-sectional evaluation of the sentinel facility suggests that the vast majority of cases were occupational in nature.

		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 FEV1/FVC and FEV1 less than their respective LLofNs." (p. 119 of draft criteria document). However, 57% percent of the cases defined using FEV1 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.	
Med-16	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**We are concerned that NIOSH has not and will not use appropriate caution when addressing the investigation of flavor exposure and the potential for development of restrictive lung disease.** NIOSH points out in Section 3.1 that "the most significant health consideration for flavoring-exposed workers is the development of lung airways obstruction. Airways obstruction is characterized by a decreased FEV1 and a decreased FEV1 to FVC ratio on spirometry testing." It is further mentioned that the magnitude of decline in FEV1	Both obstructive and restrictive effects are considered in the risk assessment, and the RELs implied by either outcome are very similar. There is considerable evidence for a restrictive effect as well; this is now presented in the revised criteria document.

		determines the severity of the disorder. To this end, in our opinion, the peer-reviewed, publicly available science to date has been focused on trying to understand the association between diacetyl and irreversible obstructive disease (i.e., BO). It is therefore concerning to us that NIOSH appears to be emphasizing in the Draft Criteria Document their concerns regarding decrement in lung function associated with diacetyl exposure based solely on a decrease in FEV1 < LLON as opposed to using the definition of FEV1 < LLON and FEV1/FVC< LLON. Using this less specific definition (FEV1 <LLON) allows for an inappropriately broader "pull of cases" into consideration which includes restrictive disorders. We recognize that NIOSH wants to ensure a broader spectrum of potential health effects is included, but are concerned that the Draft Criteria Document could be misinterpreted if other confounding factors in the workplace that could lead to a false association of flavors with restrictive disorders are not considered when assessing risk. Further concerning to us it that NIOSH incorrectly cites (p 114) the work of Lockey et al., 2009, in support of a statement that "diacetyl may cause restrictive ventilator impairment". We have reviewed this paper and, although there is a borderline loss in FVC (Table 4), the authors note in the manuscript that this is not statistically significant. Thus, despite NIOSH noting that 1) poor quality spirometry can lead to the finding of a restrictive abnormality because the test subject did not exhale long enough during the maneuver (p 280), and 2) a future research need is to determine whether "... the spectrum of diacetyl-related lung disease include restrictive lung disease" (page 306), NIOSH proposes that restrictive abnormalities be further investigated in medical surveillance programs. This is inappropriate because the chance of false positives for this endpoint is likely high and NIOSH itself by identifying the research	

		need is not convinced an increase in risk of developing restrictive disease is associated with exposure to flavors. Thus, NIOSH must proceed with extreme caution when alleging that diacetyl and flavor exposures may lead to restrictive disorders to avoid the appearance of a biased perspective. Further we suggest that: 1) NIOSH publicly address the management of potential confounding factors related to making an association between flavor exposure and the risk of developing a restrictive lung disorder and 2) be clear that clinical signs of apparent lung restrictive disorders in workers are not to be attributed to flavor exposure based upon currently available science and other factors must be taken into consideration. For NIOSH to remain relevant, it is imperative that the organization remain objective on the science and not lead society to draw inappropriate conclusions based upon limited data.	
Med-17	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**We believe the above-identified concerns (low level exposure, lack of-observed cases in the food production industry to date) and uncertainty in the risk assessment exposure reconstruction collectively indicates that the proposed REL is not scientifically sound or justified. These points also clearly indicate that the food industry does not fit the overall criteria that NIOSH uses to justify the need for the standard.** NIOSH begins to outline the criteria "which are often used to determine if the results of multiple studies indicate that an exposure is the likely cause of a specific health effect" on p. 82. Although these criteria-simplified in the table below-appear to meet the flavoring and microwave popcorn industries, they do not apply more broadly to the food production industry: [See Rachman letter pg. 12 for Table] **In conclusion, we are confident, based on an independent review of the available data, that the**	See response to reviewers' comments G-18, and RA-45 (in this document) and 5130 in the peer review comment response document.

		proposed REL is not scientifically sound and does not stand up to peer review scrutiny. We agree there Is a need for a base set of management principles. Available data indicate that low levels of diacetyl can be handled safely in food manufacturing and thus that diacetyl may be a better alternative to using high levels of potential substitutes. Given the current uncertainties we have Identified in the exposure assessment combined with the other concerns identified above a more sensible approach would be to either: 1) Adopt, as a guidance level for the food industry, the peer-reviewed, publicly available OEL approach of Maier et al, 2010, which suggests a 0.2 ppm occupational exposure limit (OEL) as an 8-hr TWA with no STEL required. Or 2) Implement a performance criteria approach instead of a REL. This may include a questionnaire to help employers identify workers at higher risk. To that end, many of our members have found the FEMA, NIOSH and OSHA guidance documents to be helpful in applying administrative controls to lower workplace exposure.	
Med-18	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	**NIOSH's Descriptions of the Relevant Illness** FEMA requests that the Criteria Document be carefully reviewed for accuracy and consistency when the illness at issue is described and make appropriate revisions to assure that the illness described is supported by the reported clinical findings. Sometimes the illness is referred to as bronchiolitis obliterans, sometimes as "fixed obstructive lung disease suggestive of bronchiolitis obliterans," "severe fixed obstructive lung disease consistent with bronchiolitis obliterans" and other descriptions. None of these terms, with the exception of "bronchiolitis obliterans," are defined in the glossary provided at Pages ix-xi of the Criteria Document. If this wide variety of terms is to be used in the final version of the Criteria Document then FEMA	The commenter requests that diagnostic terms be used consistently and defined. The King and Kinder reference has already been cited many times in the document and supports the utility of HRCT in classifying bronchiolar diseases in the following statement: “HRCT is an excellent way to examine the morphology of small-airway diseases. Consequently, it has become the method of choice for assessing these airways, often replacing the need for surgical lung biopsy.” We have reviewed and simplified the terminology concerning lung disease in the document by substituting constrictive bronchiolitis for bronchiolitis obliterans

		requests that each term be fully defined to allow clear distinction among the descriptive terms. King and Kinder (2008) describe the difficulties in accurately classifying these illnesses and the Criteria Document could benefit significantly from a more thorough use of this reference on this subject.	(which may be interpreted differently by pathologists and pulmonologists and has a wider historical definition). We have also indicated when findings are consistent with constrictive bronchiolitis and not confirmed by histopathologic examination.
Med-19	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	There also are inconsistencies in the Criteria Document in other aspects of the illnesses observed. For example, in some instances, workers are described as having "restrictive lung disease" and in some instances workers are described as having their illness stabilize which is inconsistent with the progression of bronchiolitis obliterans. In a number of instances, individuals described as having "developed bronchiolitis obliterans" would be more correctly described as displaying "clinical symptoms consistent with bronchiolitis obliterans" or as noted by King and Kinder (2008), as having a "clinical syndrome(s) associated with bronchiolitis."	The revision of Chapter 3 clarifies that restrictive disease is part of the spectrum of biopsy-documented constrictive bronchiolitis. The commenter is in error in indicating that bronchiolitis obliterans always progresses. While bronchiolitis obliterans syndrome that occurs in organ transplant recipients appears to progress, the illness seen in microwave popcorn workers consistent with constrictive bronchiolitis has been shown to often stabilize following exposure cessation. This natural history is now included in Chapter 3.
Med-20	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 3 - Effects of Exposures in Workers We request that this chapter be carefully reviewed for consistency when the illness at issue is described consistent with FEMA's concerns expressed above. An example of the problems created by the use of varied, imprecise terms and descriptions is presented in Section 3.1.2.7 in the discussion of the Lockey et al. (2003) report. The Criteria Document states that "A cluster of cases of bronchiolitis obliterans (emphasis added) among production workers at a flavoring manufacturing company was reported by Dr. James Lockey . . . After identification of an index case of bronchiolitis obliterans at this plant, a survey of the workforce identified an additional four workers with clinical findings consistent with bronchiloitis obliterans. All five workers with bronchiloitis obliterans (emphasis	The gist of this comment appears to be that our terminology does not distinguish between pathologically confirmed bronchiolitis obliterans and clinical bronchiolitis obliterans in describing the literature. In the example cited on the Lockey work described in section 3.1.2.7, we have indicated that only one of the five cases had a pathologic diagnosis, but in light of this comment we have revised the introductory sentence to indicate that there was a cluster of clinical bronchiolitis, thereby acknowledging that not all cases in the cluster were pathologically confirmed. Although the commenter is correct that Dr.

		added) . . ." According to the Lockey abstract (Lockey et al., 2003), there was one "index" case of a worker with bronchiolitis obliterans and four workers with clinical findings "consistent with" bronchiolitis obliterans but without pathological confirmation. Lockey also stated "After removal from exposure for four to five years, these patients have no further loss in their lung function." Furthermore, as NIOSH is aware, Lockey attributed the illness observed to possible exposure to acetaldehyde, not diacetyl. Cross-sectional data are briefly summarized in this chapter from workers from six microwave popcorn manufacturing plants, five flavor manufacturing plants, one baking mix plant, and three restaurants. FEMA requests that the available medical surveillance data from these workers be analyzed and reported together. The information presented in Table 3.1 (Page 47) is interesting but limited in usefulness because of the highly variable descriptions of the findings. This table would be much more valuable if the descriptions of the findings used standard terminology. This table would be the ideal place to describe the total number of workers examined, the total number with possible and confirmed lung disease, and if available, data on the presence of diacetyl in the facilities.	Lockey attributed the observed illnesses to possible exposure to acetaldehyde, not diacetyl, the attribution was made prior to understanding that diacetyl was a potential inhalation hazard, and diacetyl and was certainly present in the plant described. We have not changed the document in response to this comment. The commenter asks that cross-sectional data from all of the NIOSH studies be analyzed and reported together. We have published the combined data from the microwave popcorn facilities but do not intend to aggregate data from popcorn, flavoring, other food production facilities, and restaurants because the exposure assessment and medical information are not comparable across these differing industries. We have revised Table 3.1 in response to peer reviewer comments to indicate the facility studied as the basis for the literature contribution. Compilation of the information on total number of workers examined, numbers with possible and confirmed lung disease, and data on the presence of diacetyl in the facility can be done by the commenter on the basis of the original reports and is unnecessary for this criteria document. However, in partial response to this commenter, we have added a table to Chapter 3 showing the number of workers by facility with abnormal spirometry among those tested, including the proportions with obstruction, restriction, and mixed obstruction and restriction.

Med-21	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	On Page 51 of Chapter 3, NIOSH states, "Because of concerns for patient welfare and the invasive nature and low sensitivity of lung biopsy for diagnosing constrictive bronchiolitis obliterans, most patients have been diagnosed upon clinical findings." FEMA requests that NIOSH explain this statement, with appropriate references, especially the statement regarding the "low sensitivity of lung biopsy" which most pulmonologists consider the gold standard for the diagnosis of constrictive bronchiolitis obliterans.	While pathologic confirmation of constrictive bronchiolitis is a gold standard for diagnosis, biopsy may be insensitive because of the patchy nature of the abnormalities, the need for serial sections perpendicular to the bronchiole, special stains, and specific attention to evaluating the tissue sample for constrictive bronchiolitis. Indeed, NIOSH staff had the experience of an experienced chest pathologist missing the diagnosis until prompted to review tissue blocks again. A chest pathologist at the Armed Forces Institute of Pathology recommended that this diagnosis is a multidisciplinary diagnosis that whenever possible should integrate all possible diagnostic modalities, including physiology and radiologic studies, recognizing that biopsies may not be possible or confirmatory. In Chapter 9, we have included counsel from King and Kinder, which states “HRCT is an excellent way to examine the morphology of small-airway diseases. Consequently, it has become the method of choice for assessing these airways, often replacing the need for surgical lung biopsy.” We have revised our wording to indicate that the likely diagnosis can be made without pathologic confirmation in settings of disease clusters in flavoring-exposed workplaces in which there is supporting radiologic and physiologic evidence and other explanations are unlikely. We suggest that the pathologic confirmation of diagnosis is useful in cases with restrictive or normal spirometry.

Med-22	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	In Chapter 3, substantial information is provided regarding the symptoms and spirometric findings in several NIOSH investigations. However, there is inadequate reporting of smoking histories and other potential confounding factors for the evaluation of the existence of employment-related obstructive lung disease. Important factors that should be addressed include pre-existing asthma and whether pre-employment spirometric data are available. FEMA requests that NIOSH address these potential short-comings.	In NIOSH investigations that had study populations of sufficient size, smoking histories were used for adjustment of comparisons to national expected prevalences of symptoms and spirometric abnormalities, e.g., those in Facilities E, F, G, I, K, L, and N. In no facility investigated by NIOSH were there pre-employment spirometries because the inhalation hazards in the industry were not evident at the time of the NIOSH investigations. However, there is no reason to believe that workers in the industry have pre-employment respiratory illness in increased proportion compared to persons in the general population. No change in the document was made in response to these comments.
Med-23	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	In the discussion in Chapter 3 on rapid lung function decline, how many workers were affected? On Page 73, Wang and Petsonk (2004) are cited for the statement "a yearly decline in FEV1 greater than 8% of 330 ml. should not be considered normal" but it is not clear if this is what NIOSH means by "rapid decline." Precision in this discussion is important because this seems to be the basis for recommendations that flavor workers undergo spirometry testing every 3-6 months. FEMA requests that NIOSH clarify its definition of "rapid decline."	The medical surveillance chapter has information on alternative means of assessing abnormal declines in lung function in section 9.5. The criteria for an abnormal decline depend on spirometry quality, as discussed. The commenter can refer to the reports and publications to pursue actual numbers of workers with rapid lung function decline. The recommendation that flavor workers undergo spirometry testing every 3–6 months is based on observation of workers who have become abnormal in 4–6 months. Even poor quality spirometry can identify huge drops in pulmonary function measures, but the goal of prevention is to identify persons who have abnormal declines before they fall into the abnormal range of spirometry with consequent impairment. The reader of Chapter 3 is now referred to the

			section in Chapter 9, which contains the requested information.
Med-24	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	In Chapter 3, Section 3.3, NIOSH does not explain the role that various factors such as body mass index may have in evaluating pulmonary restriction. FEMA requests that NIOSH include an explanation of the roles that such factors may play especially because the data presented are being used to support recommendations for medical surveillance.	The public commenter is correct that restrictive spirometric abnormalities can result from obesity, as reflected in body mass index. For this reason, we now compare worker populations for prevalence of restrictive abnormalities to population data from the NHANES III, adjusting for body mass index. Our analyses take elevated body mass index into consideration, as described in the section 3.3 for NIOSH [2011b] (Facility I). In earlier work in Facility G, we did not make comparisons of restrictive abnormalities in relation to NHANES III because we were focusing on obstructive abnormalities. In Chapter 3, we have now included the range of physiologic abnormalities seen in bronchiolitis obliterans, and we have included the requested background on nonpulmonary causes of restrictive abnormalities, such as obesity, neuromuscular weakness, and inadequate quality spirometry with insufficient exhalation.
Med-25	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 9 - Medical Monitoring and Surveillance of Exposed Workers NIOSH's recommendations in this chapter are similar to recommendations made by FEMA for many years. However, unlike FEMA, NIOSH has not adequately addressed key facts about flavor manufacturing that make "one size fits all" proposed solutions unhelpful. Many flavor manufacturers are small businesses with limited resources. Some of the	The medical surveillance recommendations are consistent with the training of occupational medicine physicians in a specialty that is oriented to population health and prevention. Small companies needing these services can rely on the market to motivate such approaches by medical providers, who already often serve many

		recommendations in this chapter suggest that individual manufacturers establish what amounts to sophisticated epidemiology study programs. For example, in Section 9.3, NIOSH describes the creation of individual company databases on workers' medical findings that would require substantial expertise and resources unlikely to be available to small businesses. Furthermore, NIOSH fails to describe the implications of significant worker privacy issues associated with individual's confidential medical histories. FEMA requests that NIOSH explain in Chapter 9 how it would address these concerns.	small businesses with respect to injury care. We have found that even large employers are not undertaking population surveillance with their medical testing data. The revision of Chapter 9 addresses these issues with a paragraph after the examples of the utility of epidemiologic approaches. Medical providers are accustomed to safeguarding worker medical privacy in compliance with the Health Insurance Portability and Accountability Act of 2006 [United States Congress 1996], and we have incorporated suggestions from commenters about how this should be done, as in the response to Med-10 above.
Med-26	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Data Quality Concerns/Inconsistencies The Criteria Document indicates that spirometry data from the Indiana flavoring manufacturer was analyzed using software (SPIROLA) to adjust for data quality. This is the only reference to data quality in the draft report. It is curious - and inconsistent – that SPIROLA was not utilized to evaluate and adjust respiratory function data from the other studies and reviews conducted by NIOSH. What is NIOSH's rationale for using this software to evaluate only the Indiana data?	The spirometry data from the Indiana flavoring manufacturing company was supplied by the company's medical provider and not generated by NIOSH technicians. As a consequence, spirometry quality was poorer than that generated by NIOSH. Spirometry Longitudinal Data Analysis (SPIROLA) software allows adjustment for intra-individual data quality in assessing criteria for excessive declines in FEV_1. Indeed the company requested that we use a 15% decline in FEV_1 as the criterion for abnormal decline (rather than the 12.4% annual decline indicated by SPIROLA), and the odds ratios for exposure-related excessive FEV_1 decline increased to 8.3 from 7.5. We chose a much lower cutpoint for excessive FEV_1 decline in our historical work at the sentinel microwave popcorn facility from 2000–2003 because SPIROLA was not available at that point in time. We did not have serial NIOSH

			spirometry data from other flavoring manufacturers other than two measurements at 4–5 month intervals in two California facilities with fewer than 32 nonoffice workers. We also used SPIROLA in evaluating excessive declines in California Department of Public Health industry-wide surveillance of flavoring manufacturing workers [Kreiss et al. 2012].
Med-27	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page 274: "Smoking diacetyl-exposed workers appear to have lower excess risk of obstruction than never-smoking flavoring exposed workers." This needs to be explained. The notion that smoking could somehow have a protective effect for flavoring exposed workers seems, on its face, to make no scientific sense. Sensient Flavors requests that NIOSH explain how it believes this phenomenon can occur if in fact there is a dose-response relationship between diacetyl exposure and abnormal lung function.	The commenter asks us to interpret the finding that smokers have lower excess risk of obstruction than never-smokers. We are unable to explain this impressive finding: Smokers had less than 2-fold the risk of airways obstruction compared to the general smoking population, whereas nonsmokers had 10.8-fold the risk. The corresponding prevalences of obstructive spirometry in the cross-sectional Facility G workers were 25.0% in nonsmokers and 12.5% in smokers. The excess risk calculation takes into account competing causes of the incident condition. Smokers are more likely to experience respiratory impairment because of smoking, so that an increasingly smaller proportion of the smoking population is at risk for impairment from another cause, in this case diacetyl exposures.
Med-28	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page 275: "If a worker with asthma symptoms does not have changes over time on medical monitoring spirometry, a methacholine challenge test may be necessary to determine if the worker has airways hyper responsiveness as occurs in asthma." If Sensient Flavors understands this statement correctly, NIOSH is proposing that a methacholine challenge test be administered to a worker with stable medical	The commenter asks for scientific justification for performing methacholine challenge in a worker with asthma symptoms who has normal spirometry. The justification is that asthma is a disease characterized by intermittent symptoms, and the asthmatic may have normal spirometry between bouts of symptoms. In such instances, the way of

		monitoring spirometry results. If that understanding is correct, what is the scientific justification for this?	making the diagnosis of asthma is to assess airways hyperreactivity with methacholine challenge. Flavorings can exacerbate and even cause asthma, which would constitute work-related asthma, which should be of interest to employees and their medical providers in providing treatment and possible work restrictions. No change was made to the document in response to this comment.
Med-29	Jacqueline Nowell on behalf of the United Food and Commercial Workers Union, CLC	Medical Removal Protection. We believe this document should provide a stronger recommendation that workers who are found to have health effects from exposure to flavorings be removed from work. The food manufacturing industries are high turnover workplaces. Workers in these industries are paid low wages, they are often new immigrants and may be temporary workers. Any document recommending a standard that will impact this sector of manufacturing must stress the importance of follow-up for workers who have exposures to these flavorings. We would like to see in this document the recommendation that OSHA include specific steps companies must take, follow-up medical evaluation, and recordkeeping as to how that was done to follow up with exposed workers who develop health effects. This should be done for a minimum of 12 months.	The commenter wants a stronger recommendation that workers who are found to have health effects from exposure to flavorings be removed from work. This is already present in section 9.7, which states that respiratory protection is not adequate as a response and that such workers must be prevented from having further flavoring exposure. The commenter requests that the document recommend that workers with health effects related to flavorings receive follow-up medical evaluation for a minimum of 12 months after being severed from employment, in view of the vulnerability of workers in food manufacturing who are often paid low wages, are immigrants, or are temporary workers. The workers' compensation system is the provision for follow-up of work-related conditions. No changes in the document were made in response to this comment.

Med-30	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	FSIS is also concerned about the potential economic impact and narrow benefit of the proposed medical management program. While the specific testing protocols seem reasonable as screening for precursors to BO, we feel the inclusion criteria are unrealistic and potentially cost prohibitive. In the absence of criteria other than "ever/never enter a potential exposure area", and arbitrarily assuming a typical exam cost of $200, an agency of our size could expect to pay $1.2 million annually in medical expenses alone, not including time away from work or related intangibles. The potential cost to industry could be significantly higher. While these costs may turn out to be necessary and appropriate, there is not sufficient justification in the proposed Criteria Document to support the recommended inclusion criteria. Additionally, as with the setting of OELs, we do not see consideration given to exposure symptoms that are not precursors to BO aside from the suggestion that "additional questions (on the questionnaire) might inquire about work-related nasal, ocular and dermal symptoms." The proposed medical management program could potentially cost in excess of a million dollars annually, without having any direct relevance to the most predictable adverse effects of diacetyl exposure. Considerably more attention should be paid to justifying the proposed threshold for inclusion in a medical monitoring program, and considering the relevance of exposure effects which are not directly related to the incidence of BO.	The medical surveillance guidance is not informed by economic considerations. Our reason for broad inclusion of flavoring-exposed workers in medical surveillance is articulated in the opening paragraph of Chapter 9, indicating that medical surveillance serves as a safety net. A safety net is important in industries with risks of irreversible lung disease with premature mortality because workers may develop health effects as a result of insufficient control or monitoring, additive effects of chemicals, susceptibility, and unrecognized hazards (e.g., due to incomplete material safety data sheets or powdered flavorings). With the implementation of a thorough medical surveillance program including workplace-based data analyses, companies can create data-driven policies regarding how to modify the medical surveillance programs to target subgroups of workers at high risk, if they exist. Such experience can inform future considerations of medical surveillance requirements, taking economic feasibility into consideration, should OSHA develop regulations regarding permissible exposure limits and required medical surveillance. Because constrictive bronchiolitis may cause shortness of breath on exertion in the presence of normal spirometry and radiologic studies, symptoms are potentially important for managing respiratory health of a workforce. However, both in the index microwave popcorn facility and in the California industry-wide surveillance, many workers with obstructive abnormalities on

			spirometry had no chest symptoms. Our conclusion has been that those with and without chest symptoms need to be under medical surveillance. No changes in the surveillance document were made in response to this comment.
RA-1	David Egilman, MD, MPH, Brown University	Attached is a peer reviewed paper on the diacetyl TLV. It comes to the same conclusion as does your criteria document (safe level is below 1 ppB). Also attached are the PFTs and exposure measurements for ConAgra QA workers who were followed for 8-12 months. The importance of these findings are noted in the peer reviewed paper attached. Lockey's published paper asserted that none of the QA workers had obstructive lung abnormalities. http://erj.ersjournals.com/content/34/1/63.full As you can see this was not true. In addition NIOSH reported disease in QA workers in one of the ConAgra plants. These cases were excluded from Lockey's study. [See Egilman attachment for references] p	The NIOSH criteria document contains a quantitative risk assessment based upon data collected in health hazard evaluations. NIOSH has reviewed the previously published Lockey data and determined it is not suitable for inclusion in our quantitative risk analysis. There was no exposure data prior to ventilation improvements and the first respiratory assessment in 2003, and the likelihood for exposure misclassification in this study is high.
RA-1a	David Egilman, MD, MPH, Brown University	Since the criteria document calls for ALARA (detection limit TLV) for pentanedione this should be explained more clearly. NIOSH proposes ZERO exposure and you should say so.	NIOSH has described the rationale for the 2,3-pentanedione REL in detail in the revised Chapter 7, Basis of the Standard.
RA-2	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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	The role of agents like diacetyl or acrolein in smoking pathophysiology is largely unknown, but they could be significant contributors. The diacetyl content of cigarette smoke [Fujioka and Shibamoto 2006], subject of one peer and three public comments, raises some interesting questions, not the least of which is the impact on smokers' health of this possibly relatively recent (<20 years [yrs]?)

		definitive support for diacetyl as a marker chemical "associated" with adverse effects within a complex mix of workplace chemical 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.	additive. However, it is not clear how well the Fujioka and Shibamoto [2006] laboratory model predicts actual human exposure; airflow rates may be important determinants. A risk assessment to limit the consequences of smoking to 1/1,000 excess lifetime risk of respiratory impairment might indeed imply quite low smoking behavior, possibly considerably less than one cigarette per day. Also see response to reviewers' comments RA-39 and 5130.
RA-3	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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	The exposure concentration of diacetyl or 2,3-pentanedione established as the REL is independent of the source of that compound.. Absent some deterministic criteria such as particle size, valance state, etc., there is no reason not to include all sources in these RELs. See also responses to comments 5130 and G-18.

		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.	
RA-4	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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, anyone 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	See response to comment RA-52.

		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.'	
RA-5	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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 FEY, 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 FEY, in the studied population, regardless of the statistical significance achieved.	We disagree with the commenter that there is no basis for the conclusion that diacetyl causes bronchiolitis obliterans. The epidemiologic criteria for causation and animal experiments are sufficient to conclude a causative association, and these criteria are reviewed in Chapter 3.
RA-6	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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 (I) ppm diacetyl = 0.00352 flg/mL on the basis of diacetyl's molecular weight of 86.09, the proposed REL of 5 ppb translates into 0.0176 mg/ml. 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 IS years (a light smoker by definition) results in a daily dose of	The logic of the comment is fundamentally flawed. The proposed NIOSH REL for diacetyl is based on reduction in pulmonary function as opposed to the development of bronchiolitis obliterans; therefore, the incidence of bronchiolitis obliterans among smokers is not relevant to the REL. NIOSH notes that smoking is well known to cause reduction in pulmonary function, which is in fact consistent with the toxicity of diacetyl. The role of agents like diacetyl or acrolein in smoking pathophysiology is largely unknown,

		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.	but it is possible that they could be significant contributors.
RA-7	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	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.	The revised document clarifies the contention that the animal-based analyses were not the basis chosen for the NIOSH REL.
RA-8	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	*8* 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	See response to comment RA-52.

		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.	
RA-9	David Egilman, MD, MPH, Brown University and Hank Schilling- Never Again Consulting	2. Evidence supporting a lower REL It is our understanding that the REL for diacetyl (5 ppb) is derived primarily from quantitative risk analyses (BMD and lifetime risk estimates) of exposed workers. In particular the data from "Company G" was felt to have the "most extensive and representative diacetyl exposure data and largest body of respiratory outcomes data." (page 138). However, the BMD analyses from all companies support an REL lower than 5 ppb. As summarized on page 138 and Table 5.37, excess risk of 1/1000 for company G corresponds to 3 ppb for general population,S ppb for smokers, and 0.9 ppb for non-smokers. For the pooled Company K/L it is approx 0.4-0.5 ppb. The REL appears to be set at the level corresponding to the 1/1000 excess risk for smokers at Company G. All other excess risks of 1/1000 correspond to exposures <5 ppb. We feel strongly that the REL should be set at the level corresponding to excess risk for non-smokers (approx. 1 ppb), particularly since studies authored by NIOSH have noted the apparent health-protective effect of smoking in flavorings-exposed workers. It would be unprecedented for NIOSH to select an REL based on protecting only smokers, rather than the general population, or in this case the more sensitive non-smoking population. If there was any rationale for selecting the highest exposure level corresponding to 1/1000 excess risk for the REL, it was not apparent to us. An REL around 1 ppb finds convergent support from other analyses. We have previously written a peer-	The authors largely concur; the choice of 0.005 ppm was not determined by smokers' risk but in response to all the risk estimates using different approaches, and in consideration of what the appropriate excess risk maximum should be for this type of impairment. Lowest unoccupied molecular orbital (LUMO) is relevant but it is not sufficient to conclude by LUMO itself that diacetyl has toxicity comparable to toluene diisocyanate (TDI). See also response to comment 5086 in the peer review comment response document.

		reviewed article recommending an exposure limit around or below 1 ppb (attached - Egilman 2011), based on a qualitative structure activity relationship (QSAR) analysis, a BMD analysis of (limited) animal data, and evidence of worker disease at "low" exposure levels. Although we understand the criteria document has been in production for some time, we feel this article should have been considered in the process of developing the REL, as it contains novel data and analyses. For example, the QSAR analysis (which we have previously submitted to the docket), conducted by Kendall Wallace PhD, of ToxDx, found that diacetyl and 2,3-pentanedione have lowest unoccupied molecular orbital (LUMO) energy values that are comparable to diisocyanates (specifically TOI and NDI). These comparable, negative LUMO energy values suggest similar biological reactivity and toxicity. The American Conference of Governmental Industrial Hygienists (ACGIH) sets the TOI exposure limit at 5 ppb (similarly, the NIOSH REL for NDI of 5 ppb). However ACGIH noted that FEV1 reductions occur at TDI exposures as low as 2 ppb, and has recommended reducing the exposure limit to 1 ppb (see http:/www.acgih.org/tiv/03_TLV-CS-Update_AIHce06.pdf). There is clear evidence that 5 ppb is too high to protect workers from TDI exposures, and we feel it would be a grave error to repeat this mistake with diacetyl. Further, although we understand the technical limitations in detecting 2,3-pentanedione, the very similar LUMO energies of diacetyl and 2,3-pentanedione support the assertion that these two chemicals should have the same RELs. We feel it is unwise and short-sighted to base an REL on detection limits, when evidence indicates the detection limit is too high for a TWA exposure. Rather, the REL for 2,3-pentanedione	

		should be set at the same level as diacetyl (we recommend 1 ppb), with notation that the detection limit is above the REL (therefore any detectible exposures are too high). As the REL stands, if future technologies lower the detection limit we will be left with a completely arbitrary REL that is known to be too high to protect workers. In sum, all the analyses in our article, and all the BMD analyses conducted by NIOSH on the worker exposures indicate that the diacetyl REL should be set below 5 ppb. We strongly recommend an REL of 1 ppb based on all these analyses. Further, the REL for 2,3-pentanedione should also be set at this level (1 ppb), despite the technical issues relating to detection limits.	
RA-10	David Egilman, MD, MPH, Brown University and Hank Schilling- Never Again Consulting	3. Denial of consumer risk with no testing and no data As summarized in our presentation slides given at the public meeting (attached), both NIOSH and the FDA have denied that butter flavorings pose a risk to popcorn consumers. This reassurance was given without any data, any testing, and in the face of at least one case report of BO in a consumer of butter-flavored microwave popcorn. We feel such baseless reassurances are reckless and dangerous to public health. Contrary to such claims of "no risk to consumers," we have conducted analyses indicating that consumer exposures can readily exceed NIOSH's diacetyl STEL, and can also readily exceed the REL (see attached powerpoint). This is further supported by evidence of lung disease in QA workers at popcorn manufacturing plants (see Egilman et al. 2011, attached).	See response to comment EA-17. Further, it is beyond the purview of this document to attempt to address consumer issues.
RA-11	David Egilman, MD, MPH, Brown University and Hank Schilling- Never Again Consulting	4. Other issues/corrections As indicated at the public meeting, the odor threshold in air given in Table 1.1 (page 16) is incorrect. It should be 25 ppb based on the Iliovo Sugar Limited 2009 MSOS, and 2.8 to 5.6 ppb based on Blank et al. 1992 (see attached powerpoint).	Table 1.1 has been revised to include these and other threshold values.

		This is important because it indicates whether diacetyl has an odor warning property or not. The odor threshold in water is similarly incorrectly converted - it should be 14 ppb based on Oiaz et al 2004, or 1.4 ppm based on Lawless et al. 1993.	
RA-12	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Chapter 5 - Quantitative Risk Assessment Based on Worker Data In Section 5.3, NIOSH makes a conjecture about a susceptible portion of the exposed population leaving the studied workforce. Further explanation of this factor would be beneficial, including an explanation of any epidemiological or toxicological evidence for this effect, beyond the fit of the mathematical model.	The document was revised as suggested.
RA-13	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Chapter 7 - Basis of Recommended Standards The Criteria Document states that the REL for 2,3-pentanedione should be equivalent to the REL for diacetyl, but that a higher REL was selected due to limitations of the sampling and analytical method. The use of technological feasibility to establish a REL that exceeds the health-based recommendation is inconsistent with previous practice. Is it NIOSH's intention to change the REL if more sensitive methods are developed? It would be more appropriate to propose a health-based REL, and acknowledge that airborne vapor concentrations cannot be measured at that level. This would encourage method development. Also, the REL is used to develop maximum use concentrations for respirators, and there is no difficulty in measuring 2,3 pentanedione at those concentrations. We believe this section must emphasize that the 2,3-pentanedione REL should be changed to a more appropriate health-based number when more sensitive methods become available.	Current NIOSH policy has analytic feasibility as a criterion for an REL. If a more sensitive method for 2,3-pentanedione is developed prior to finishing the criteria document, that REL will be lowered, as suggested by the reviewer. The second paragraph of Chapter 7 has been expanded to address this issue. In section 7.5.2 the document states that the "REL for 2,3-pentanedione will result in a residual risk of lung disease similar to diacetyl, but may be higher. It does not imply that 2,3-pentanedione is safer than diacetyl. Because the REL is established at the reliable quantitation level, no AL is established for 2,3-pentanedione." It has not been determined if a revised REL will be developed when the analytical method can reliably quantify at lower concentrations.

RA-14	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Cal/OSHA and CDPH also recommend the following issues be given consideration in this section	No response necessary
RA-14a	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Provide a reference for NIOSH's selection of a short-term exposure limit (STEL) that is 5 times the TWA value. Is there a reason why a multiplier of 5 was selected?	As detailed in section 7.5, the selection of a STEL that is five times the REL is based upon past precautionary practice [Federal Register 1997]. We have added this reference to the document. NIOSH also states in section 7.5: On the basis of general industrial hygiene principles, the STEL, which is five times the REL, would serve to reduce peak exposures and tend to reduce overall worker exposures to diacetyl. In the absence of a STEL in workplaces complying with the NIOSH REL for diacetyl of 5 ppb TWA, workers could theoretically be exposed to 2,400 ppb diacetyl for 1 minute or 480 ppb for 5 minutes in an 8-hour day with no additional exposure the remaining part of their 8-hour shift. The STEL for diacetyl of 25 ppb would limit those exposures to a possible peak of 375 ppb for 1 minute and 75 ppb for 5 minutes.
RA-14b	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Provide a clear acknowledgment that the RELs are based on risk assessments derived from measurements of flavoring chemicals in the vapor phase only, which may inadequately represent the risk in workplaces where both dust and vapor exposures are present. Give guidance on the implications of this problem.	We have adjusted the text in Appendices 3 and 4 and in the executive summary to make clear that only vapor forms of diacetyl were analyzed in this risk assessment. Additionally, a phrase was added to the opening paragraph of Chapter 9, Medical Monitoring and Surveillance of Exposed Workers, indicating that unmeasured exposure might occur to powdered flavoring chemicals.

RA-14c	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Since the REL is based on full-shift, 40-hr/week exposure, provide guidance on how employers should adjust the REL to account for alternative work schedules (e.g., 10-hr shifts, 6-day work weeks).	NIOSH has established RELs for full work-shift exposures as a means of preventing chronic health effects. These RELs have been expressed as a TWA concentration for up to either an 8-hr or 10-hr work shift during a 40-hr workweek. In NIOSH testimony at the OSHA PEL update process in 1988, NIOSH [1988] commented on the mathematical adjustment of a NIOSH 10-hr TWA REL to an 8-hr TWA exposure limit (i.e., converting a 10-hr TWA of 100 ppm (1,000 ppm hr) to an 8-hr TWA of 125 ppm (1,000 ppm hr). NIOSH stated that it would be contrary to the original intent and that such a conversion would be opposed. The conclusion was that, so long as the work schedule did not exceed 10 hours per day or 40 hours per week, there was not sufficient precision in the selection of exposure limits to justify the precision implied by any mathematical adjustment. Therefore, the same TWA REL was intended to be applied to 8-hr and 10-hr work days in a 40-hr work week. Different approaches have been proposed for adjusting a conventional full-shift TWA occupational exposure limits (OELs) for unusual work schedules (e.g., extended work shifts). Some approaches have been based on simple adjustments to account for less time for elimination of agents from the body between exposures, while other approaches are based on more detailed knowledge of the pharmacokinetic properties of the substance (e.g., biological half-life) or information on dose-rate effects of the substance.

			OSHA does not adjust its PELs for work shifts longer than 8 hours, except for lead. Rather, they attempt to assess the highest TWA exposure for a continuous 8-hr period during the work shift [OSHA 2011]. ACGIH does not make a specific recommendation, but provides a general discussion of the various models to adjust for unusual work schedules [ACGIH 2011].
RA-14d	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Section 7.5.1 on the proposed Action Level should include an explanation of the basis for the AL being proposed.	The action level is historically 50% the REL. For the case of diacetyl, 50 % of the REL would be 2.5 ppb, but the lowest concentration that can be measured is 2.6 ppb. For this reason, the AL was set at 2.6 ppb.
RA-14e	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	Section 7.8 on the hazards of diacetyl substitutes should include a complete listing of substitutes NIOSH knows of and is concerned about (or refer to another section or table where they are listed). The list should include diacetyl trimer.	Because the list of compounds used in place of diacetyl or 2,3-pentanedione is both extensive and ever changing, and is also application specific, it is not practical to try to include such a list in this document. NIOSH has documented its concern on substances structurally similar to diacetyl and 2,3-penanedione. NIOSH believes information provided in section 7.5 is more helpful than a static list.
RA-15	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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 I (Forced Expiratory Volume in one second ("FEVl") below normal) as the critical health effect metric. This definition is not specific fo r diacetyl exposure, and thus creates false positives.	Regression analysis estimates a baseline (or background level, or rate) corresponding to nonattributable cases. Some further analysis of smoking has been done. Unless pre-existing asthma has influenced job placement, the estimates of diminished lung function should be valid; if pre-existing asthma has resulted in workers taking jobs with lower exposures, the regression estimates will possibly underestimate diacetyl effects in the general population. See

			also responses to reviewers' comments RA-52 and 5130.
RA-16	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	*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.	Chapter 6 has been rewritten.
RA-17	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	*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.	See response to comment 5086 in the peer review comment response document.
RA-18	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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.	It is not possible to assess the validity of this comment without a list of the other chemicals that the commenter considers to be “of comparable reactivity.”
RA-19	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	E) The proposed REL is so low that naturally occurring diacetyl in many foods will likely result in exceedances of the proposed standard.	See responses to comments 5130 in the peer review comment response documents and G-18 in this document.
RA-20	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	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.	If this comment is directed at the risk assessment performed using data from the NIOSH index plant (Facility G) [NIOSH 2006], underestimating exposures prior to 2001 would have a modest effect because the mean duration of exposure was only 2.6 yr, which for many subjects would have occurred after 2001. We believe that we have overestimated exposures prior to 1994 due to product changes.
RA-21	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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	Chapter 6 has been rewritten.

		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 peri bronchiolar regions, is curious and results in a lower benchmark dose estimate for this endpoint.	
RA-22	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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 I 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 311 0 (30%) would be	Risk estimates are based on the point estimate of the exposure-response parameter. See also response to reviewers' comments RA-25 and RA-45 in this document, and 5086 in the peer review comment response document.

		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 I in 1 000 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 at. 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.	

RA-23	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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 noncarcinogens (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	NIOSH has an established policy of using 1/1,000 risk level for carcinogens or other substances that have debilitating effects such as diacetyl. The public commenter is mistaken on the rationale on the NIOSH REL in the carbon nanotubes document. Within both the draft document and the final document published in 2014, the REL is based on analytical feasibility, i.e., the LOQ of the measurement method.
RA-24	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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 13 1 of the draft criteria document it is stated that 13 cases, where case definition was FEV1 <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	We have a new interpretation of the susceptibility question in the NIOSH index plant (Facility G) [NIOSH 2006] population that no longer requires a special estimate of the risk in the case of short-term employment and so we are no longer making the “high-risk” calculation cited. This earlier calculation contributed no more than one third of the overall risk estimate. This is fully explained in the revised criteria document. The linear extrapolation utilized covers a rather mild range of exposure level, by a factor of only 1,020 below the observed exposure range. The choice of linear extrapolation for non-cancer endpoints was examined quite thoroughly in the recent National Academy of Sciences review [National Research Council 2009] and provides strong support for this application using pulmonary function outcomes in risk

		level, and that there is no zero-effect threshold. Indeed the lack of evidence of actual 80 resulting from these low exposures suggests that the dose/response relationship is non-linear and/or that there is a nontrivial 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. **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, 20096 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 f unction deficits. Maier, et ai, 20 I 0 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, 20097 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).	assessment. As is widely acknowledged in statistical modeling, the observation of a no observed adverse effect level (NOAEL) is not a valid basis for defining a threshold because that level is entirely dependent on the statistical power of the investigation. We do not agree that there is sufficient long-term observation and mechanistic understanding to conclude that “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” (sic). As explained elsewhere in these comments, the Environmental Protection Agency’s (EPA) benchmark dose (BMD) software was developed for analyzing animal studies and does not accommodate confounding risk factors in its modeling procedure.

RA-25	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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 I 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 I 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 [See Hawk letter for Tables] 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.	Preventing rapidly fatal results requires a much less stringent standard than preventing impairment over a working lifetime of exposure. There is some consistency and precedent, with the interpretation and analysis of the available diacetyl data and other RELs and PELs. The OSHA PELs for acrolein, phosgene and TDI were derived from industry consensus standards based on animal models or on acute irritancy, imminent fatal hazard or sensitization, not chronic long-term human effects. Thus they regulate above a 1/1,000 risk. A PEL for TDI proposed by OSHA in 1989, at 0.005 ppm, was vacated after industry challenge in court in 1992. If actually regulated for 1/1,000 excess lifetime risk of chronic respiratory disease (or cancer), the PELs for acrolein, phosgene, and TDI would be lower than they are today. (The current threshold limit value for TDI is 0.005 ppm.)

		The RD50 for diacetyl in humans was estimated to be 29,000 ppb,[8] which is intermediate between the nonreactive chemicals in Table I and the reactive chemicals in Table 2. [See Hawk letter for Tables] 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. [See Hawk letter for Tables] 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. [See Hawk letter for Tables] 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.	
RA-26	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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	Concerns have been raised in several public comments about affected industries having insignificant or "naturally occurring" diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxins, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.

		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. 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.	

RA-27	Robert E. Hawk on behalf of Weaver Popcorn Company, Inc.	**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 FEV1) 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 noncancer 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.	Please see RA-15-RA-26 for specific responses to this comment.

		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. 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.	
RA-28	Dana M. Hollins, MPH, ChemRisk, LLC	***3) The animal studies of Morgan et al are an appropriate basis for establishing an OEL.*** Maier et al. (2010) evaluated the available health effects data on microwave popcorn and food flavoring manufacturing workers and concluded that the results would not support the development of a valid threshold. Specifically, of the worker studies, they concluded that Lockey et al. (2009) was the most robust data set and noted that the Lockey et al. (2009) findings appeared to suggest a threshold for airway obstruction of ≥ 0.8 ppm-years. However, Maier et al. (2010) concluded that the Lockey et al. (2009) investigation suffered from too many uncertainties, including: 1) the diacetyl measurements underestimated the actual airborne concentrations due to humidity complications, 2) the airborne measurements likely underestimated historical	The NIOSH REL for diacetyl is not based on analysis of the animal data, but rather on analysis of the health effects observed in workers who were occupationally exposed to diacetyl. When adequate human data are available for dose-response analysis, as in the case of diacetyl, the epidemiologically-based REL estimate takes precedence over one based on limited animal data.

		exposures, 3) the lack of controlling for the numerous other compounds to which the workers were exposed, 4) difficulty in controlling for exposures that occurred in previous employments, 5) difficulty in controlling for non-occupational risk factors, and, 6) as I mentioned earlier, the magnitude of the changes in the PFT values were small according to the definitions used by ATS and NIOSH (and likely of no biological significance). Hence, a threshold of ≥ 0.8 ppm-years would likely be an overly conservative estimate of a threshold for diacetyl-related obstructive effects. I have noted several other issues associated with the Lockey et al. (2009) study above, most of which concern the lack of an observed diacetyl exposure-response relationship. For those reasons alone I do not believe that the results from the Lockey et al. (2009) study serve as a valid basis for which a cumulative-exposure threshold for diacetyl could be established. Maier et al. (20 I 0) also evaluated the results from the available animal studies and concluded that the subchronic mouse study conducted by Morgan et al. (2008) provided sufficient data for the derivation of a diacetyl exposure threshold. As detailed in their analysis, they conducted what is commonly referred to as a "benchmark concentration" analysis using "minimal to mild" peribronchial lymphocytic inflammation (PLI) as the critical adverse effect endpoint. This yielded a human equivalent concentration for occupational exposure of 2 ppm; the 2 ppm value was then adjusted by an aggregate uncertainty factor of 100 to arrive at the proposed occupational exposure limit of 0.2 ppm. It is important to note that this threshold is based on minimal effects in the URT; any threshold based on obstruction or actual *bronchiolitis obliterans* would arguable be higher. Further, it is worth noting that some of the "minimal to mild" PLI effects considered to be	

		"significant" by Maier et al. (2010) may have in fact not been significant at all. Specifically, Morgan et al. (2008) did not provide any measures of statistical significance in their effects table (Table 6), and it is unclear whether any effects observed in the 25 ppm exposure group, and possibly even the 50 ppm exposure group, were greater than in the controls. Further, it could be argued that 25 ppm is a NOAEL for PLI, rather than a LOAEL, given the fact that 3/5 *mice in the control group* experienced PLI effects 6 weeks post-exposure, with a frequency and severity *greater than those* in the 25 ppm group at both 6 weeks and 12 weeks. Clearly, the PLI effects at 25 ppm are probably not treatment-related. Finally, if one assumes that a severity score of 2.0 ("mild") or greater is required to qualify as a true adverse effect (as opposed to the "minimal" scores of 1.0 included by Maier et al. (20 I 0), which appear to be indistinguishable from background in the Morgan study), the LOAEL is actually 100 ppm. Along these lines, I am not aware of any occupational standard, set by any regulatory agency in the world, that is based on only "minimal" URT effects that actually occur with *greater* severity and frequency in the unexposed population. In short, the modeling exercise employed by Maier et al. (2010) is a valid but very conservative exercise, and other just as reasonable and valid approaches would yield much higher thresholds. Egilman et al. (2011) proposed a "safe" occupational limit of "around or below 1 ppb" (equivalent to a 45-year occupational exposure of 0.045 ppm-years or less), based on "evidence from multiple epidemiology studies." The authors also suggest that 1 ppb, or even levels below 1 ppb, may still pose a risk of B0 to the consumer. The concept of a 1 ppb (or less) threshold for B0 is clearly not valid. For example, according to Egilman et al (2011), the odor threshold for diacetyl is 1.5 ppb. by extension, a ≤ 1 ppb threshold	

		would infer that an individual who sniffed a glass of California chardonnay might end up needing a lung transplant. Similarly, Rothweiler et al. (1992) characterized the "long term" emissions from carpets and water-based adhesive in a residential setting, and reported indoor diacetyl concentrations of 9 ppb and 15 ppb for carpet with polyurethane and latex backings, respectively, four days following the carpet installation. According to the threshold proposed by Egilman et al. (2011), individuals living in newly carpeted settings may be at risk of developing 80. Further, airborne diacetyl levels in the offices and warehouses of the popcorn and flavorings facilities routinely exceeded I ppb by several orders of magnitude yet clearly these workers are not at risk of developing 80. In summary, based on the weight of the scientific evidence, the 0.2 ppm threshold is a reasonable, and likely conservative, cumulative exposure threshold to use in the characterization of health risks to workers exposed to diacetyl.	

RA-29	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	**Chapter 3 - Effects of Exposure** This section needs emphasis on the fact that the health risks associated with combined powder and vapor exposure as opposed to vapor exposure alone are not known.	Chapter 5 has been extensively rewritten to address these and other comments, and tables have been improved, which we believe helps to make the content more easily understood. The progression from statistical models to risk assessment procedures has been made more explicit, and the individual steps in the two procedures are presented in more detail. Five peer review comments questioned the use of data from one plant to define the exposed population. The analyses upon which the risk assessment is based were entirely focused on diacetyl vapor exposures. There were no useful, comprehensive air sampling data for diacetyl in any other form in populations with respiratory outcomes measured, and the historical contributions of powdered or encapsulated forms in the studied workplaces is unknown; diacetyl exposure in particulate form has not been investigated in any detail. Whether particulate forms are less (or more) toxic is not known but a valid question for future research. The choice of plants to analyze for the risk assessment was entirely determined by the quality of information available from many candidate sites. The number of plants selected has little inherent significance for generalizability on the effects of diacetyl as vapor, provided that is the dominant form of exposure. Generally more plants implies greater statistical power but with the possible cost of more exposure misclassification due to diminishing quality of retrospective exposure assessments or work history detail. The final decision on using the

			NIOSH index plant (Facility G) [NIOSH 2006] was based on data quality but also on (a) the relative confidence that exposure levels prior to the health hazard evaluation had not changed materially, and (b) the observed heterogeneity of exposure response at two other candidate plants at least one of which had important exposure history lacking.
RA-33	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**5. The <LOQ range, which currently may exceed the REL, is likely associated with diacetyl that is known to occur naturally in many foods Regulating to such a low level would cause consumer confusion and concern, as naturally occurring butter flavor components could very likely exceed the proposed REL's. This is not justified by the available data since there is no credible evidence of a risk to consumers.** As stated in the criteria document (page 56), of three cafeterias surveyed, "neither diacetyl nor acetoin was found at or above the minimum detectable concentration (0.02ppm)." Since	Concerns have been raised in several public comments about impacted industries having insignificant or "naturally occurring" diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxins, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or

		0.02ppm/20ppb would be above the newly proposed REL, this begs the question as to what the customer exposure in those cafeterias might be and might they exceed the level NIOSH is proposing as safe. This has the potential to cause consumer confusion when, in fact, there is no evidence that low levels of diacetyl represent a consumer hazard. Furthermore, there remains no peer reviewed published literature reports that demonstrate any risk to consumers. In fact, in response to a question about consumer risk, NIOSH posted on is "Science Blog" in 2008 the following statement: "Unlike workers, so far there have not been peer-reviewed scientific studies showing that consumers using products such as microwave popcorn that contain butter flavoring chemicals are at increased risk for lung disease. Nor is there any evidence that cooking with butter is associated with increased risk for lung disease." Further, we know from the comments submitted in the previous Federal rulemaking Small Business Regulatory Enforcement Fairness Act (SBREFA) process and in the California rulemaking that all of the following food categories either contain diacetyl naturally or it is formed naturally as part of the manufacturing process: butter, cheese, milk, yogurt, tomatoes, citrus fruits, juices, vinegar, black tea, coffee, beer, wine, whiskey, cognac, guava to name a few. Many of these industries have been operating for multiple decades, if not approaching a century, without apparent evidence of concerning lung decrement, including the unusual condition of bronchiolitis obliterans. This also would indicate that there are a lot of food source that potentially offer low- level exposure to the consumer, yet in that realm, as noted above, there are no credible data to support a concern.	not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.

		Based upon this information, it is a disservice to public health in general to recommend an excessively conservative REL that is not supported by the available data and could have impact on millions of consumers and workers for which, by NIOSH own statements, there is no data to support a risk.	
RA-34	Nancy J.Rachman, Ph.D on behalf of the Grocery Manufacturers Association	**7. The risk assessment docs not seem relevant to the food industry. The lack of cases of significant lung decrement and/or bronchiolitis obliterans versus what would be predicted by NIOSH's risk modeling supports the risk assessment is faulty.** As noted in Comment #2 above, cases of significant lung decrement and/or bronchiolitis obliterans have not been observed in the food industry as a whole despite widespread and long-term exposure to low, naturally-occurring levels of diacetyl for decades or even centuries. This apparent disconnect may be explained by one or more of the following: NIOSH's estimates of cumulative exposure used in the risk assessment are significantly underestimated, especially for the higher-exposed workers, such that the risk is significantly overestimated. By its own admission, the health effects data upon which the draft REL is based may be unreliable. NIOSH asserts in the draft criteria document that, "Spirometry testing was performed following ATS [American Thoracic Society 1 guidelines" (p. 118); however, in the actual HHE report, NIOSH acknowledges that, "Most tests could not be assessed with regard to quality because a sufficient number of force expiratory maneuvers were not recorded during the test. A minimum of three satisfactory maneuvers are necessary to comply with A TS criteria for standardization of spirometry ... Without high quality data, interpretation or lung function changes over time may not be valid (i.e., changes in test values may be due to test performance and not actual changes in lung function)" (p. 11 of HHE	In numerous plants in the food and flavoring industry, cases consistent with bronchiolitis obliterans and significant lung decrement have been missed because no surveillance was available for an unrecognized hazard; therefore, the cause of individual cases could not be ascertained without an epidemiologic approach. In none of the five microwave popcorn facilities, nor in a coffee facility, nor in most flavoring facilities, were cases initially recognized as occupational disease. The absence of recognized cases in food production does not indicate absence of risk. The commenter quotes the NIOSH 2006 report [NIOSH 2006], which he/she incorrectly identifies as HHE Report 2000-0401-2991. The spirometry measurements used in the risk assessment were all conducted by NIOSH and were of high quality, meeting ATS standards. In the NIOSH 2006 report, NIOSH reports review of company-supported measurements from June 2003 through July 2005 (taken almost entirely after NIOSH's involvement through August 2003) and found them to be inadequate in quality. NIOSH did not use the unreliable company measurements in its risk assessment. It is well known that one does not establish a threshold simply by not observing a significant excess below some

		Report 2000-0401-2991). NIOSH's proposed REL is intended to equate to less than one-in-one thousand risk of lung function decrement; however, this level is far outside of the observable range and is dependent on low-dose extrapolation that ignores the possibility of a threshold suggested and supported by other publically available data. For example, Lockey et al. (2009) did not observe lung function decrements below a cumulative exposure of 0.8 ppm-years. As noted in Chapter 6 of the draft criteria document (Quantitative Risk Assessment Based on Animal Data), Toxicology Excellence in Risk Assessment (TERA) conducted a quantitative risk assessment based on animal data as the basis of a recommended occupational exposure limit (OEL) of 0.2 ppm. This analysis has since been published by Maier et al. 2010. NIOSH conducted a similar analysis, relying on the same study (Morgan et al. 2008) and making identical or similar assumptions. The primary difference between the two analyses is the target risk level. NIOSH again targeted a theoretical risk level or less than one in one thousand, which required extrapolating far outside the observable range. Conversely, Maier et al (2010) followed established EPA methods for benchmark dose modeling (utilizing EPA's Benchmark Dose Modeling software), identifying a concentration predicted to result in effects in 10 percent of the population, and then applying an uncertainty factor. The rationale for the conservative approach taken by NIOSH requiring considerable extrapolation of potentially unreliable data is not clear and is not justified based upon other peer reviewed investigations of this issue (Maier et al., 2010 and Lockey et al., 2009).	specified level. This becomes a statistical power limitation. In the NIOSH risk assessment, the 1/1,000 level of excess risk corresponds to diacetyl levels (over 45 yrs) that are not far removed from the observed values. As explained in the discussion section of Chapter 5, 17% of NIOSH index plant (Facility G) [NIOSH 2006], workers had career-average exposures below 0.01 ppm, which is within a factor of 2 of the proposed REL, and there is good reason to assume linearity even below this level just based on diversity of response in the population. The standard EPA approach applies uncertainty factors to a level corresponding to 100/1,000 adverse effect prevalence, a level far in excess of acceptable risk even with a 10-fold reduction based on uncertainty factors, and especially for frank peribronchial lymphocytic inflammatory changes observed in animals observed over only 12 weeks. The NIOSH risk assessment illustrates the importance of having human data available. No change in the document has been made in response to this comment.

RA-35	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Comment 2: The NIOSH proposed STEL of 25 ppb for diacetvl is unjustifled.** There is no evidence that short-term exposures to diacetyl in the low ppm range can cause harm to humans. NIOSH's rationale that without a STEL a worker might be exposed to diacetyl for 2400 ppb for one minute and to zero for the remainder of the day is neither a realistic scenario nor an intrinsic problem. NIOSH asserts that a STEL would limit this scenario to a peak exposure of 375 ppb, without any basis for determining that exposure to 2400 ppb for one minute is hazardous and to 375 ppb for one minute is nonhazardous. While NIOSH may have a concern that peak exposures may have greater toxicity than the same total dose spread out over a longer period of time (Ubbink and Schoonman 2002), no evidence supporting the decision to act on this concern has been presented in the criteria document (NIOSH 2011b).	As detailed in section 7.5, the selection of a STEL that is five times the REL is based upon past precautionary practice [Federal Register 1997]. We have added this reference to the document. NIOSH also states in section 7.5: On the basis of general industrial hygiene principles, the STEL, which is five times the REL, would serve to reduce peak exposures and tend to reduce overall worker exposures to diacetyl. In the absence of a STEL in workplaces complying with the NIOSH REL for diacetyl of 5 ppb TWA, workers could theoretically be exposed to 2,400 ppb diacetyl for 1 minute or 480 ppb for 5 minutes in an 8-hour day with no additional exposure the remaining part of their 8-hour shift. The STEL for diacetyl of 25 ppb would limit those exposures to a possible peak of 375 ppb for 1 minute and 75 ppb for 5 minutes.
RA-36	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Comment 11: The benchmark dose approach used by NIOSH is not appropriate.** In Its proposed rule, NIOSH has utilized a benchmark dose approach for setting the recommended worker exposure standard for diacetyl. The benchmark dose model develops for a given response rate a central value benchmark dose (BMD) and a benchmark dose limit (MBDL), which is an equivalent dose value at the 95% lower confidence limit below the central value for the dose equivalent to the given benchmark response rate. This method provides much more restrictive benchmarks for conducting a quantitative risk assessment as opposed to using the more conventional NOAELs and LOAELs as the point of departure for the risk assessment. In its benchmark dose technical guidance document (USEPA 2000), the U.S. Environmental Protection Agency states that: " ...	It is difficult to conceive of an exposure-response relationship for diacetyl and respiratory capacity that would not be monotonic. In the low dose region (e.g., < 0.2 ppm) it would not even be a testable hypothesis in the populations available for study. By usual occupational epidemiological standards, aside from the selection/susceptibility issue, this is not a particularly complex or confounded study and has rather extensive risk factor information. The detailed work history and retrospective exposure assessment at NIOSH index plant (Facility G) [NIOSH 2006], permits a diverse population to be pooled and analyzed. The four separate plants examined

		However, it is likely that there will continue to be endpoints that are not amenable to modeling [by the benchmark dose procedure] and for which a NOAEL/LOAEL approach must be used ... "Furthermore, a requirement for the BMD approach (USEPA 2000) is: ". .. the minimum data set for calculating a BMD should at least show a significant (and monotonic) dose-related trend in the selected endpaint(s) ... "It is important to note that the data sets used by NIOSH for their benchmark dose modeling do not adequately meet this basic and fundamental requirement. Further, the data sets for each of the four sites combine older workers with historical exposures and younger workers exposed only after PPE and engineering controls have been in place. This complexity of confounding factors makes it difficult to combine the response rates and severities of these two cohorts in a meaningful way, and ultimately makes a combined statistical analysis meaningless. While benchmark dose modeling may be useful for individual risk assessments, it is unclear whether this is an advisable method for establishing recommended standards in this case. Using a BMD approach for developing recommended occupational exposure standards for diacetyl and 2,3-pentanedione drives the proposed standards to overly-conservative levels and puts these recommended standards at odds with those developed by NIOSH for similar chemicals. The statistical analysis and adjustments used by NIOSH makes for a rigorous (but flawed) statistical analysis that yields a benchmark dose that is so skewed that it has no real meaning in terms of toxicologically-significant levels. For these reasons, and due to the limitations, complexities, confounding factors, and inconsistent dose-response curves from the existing data sets available for worker exposures to diacetyl, it is recommended that a more traditional NOAEL/LOAEL approach be used in	were not pooled because there were major concerns about uncharacterized historical exposures. Had they been pooled, the proposed REL would be lower. See also response to comment 5086.

		establishing recommended occupational exposure standards for diacetyl and 2,3-pentanedione.	
RA-37	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Comment 12: The proposed RELs for diacetyl and 2. 3-pentanediane are premature**. Attempts have failed to separate the hazards posed by diacetyl and 2, 3-pentanedione from those of other chemicals with which diacetyl and 2, 3-pentanedione are found in the workplace. NIOSH has conducted numerous Health Hazard Evaluations (HHEs) of manufacturing facilities with likely cases of BO and/or likely exposures to butter flavoring diacetyl. Despite air sampling for a wide range of volatile and potentially hazardous ingredients in these facilities, NIOSH has been unable to identify the relative hazard posed by each ingredient or combination of Ingredients. The following explanation, from NIOSH's 2004 HHE Report on American Pop Corn plant, presents a frank discussion of this Issue (Kanwal et al. 2004): ”..... NIOSH measured the air levels of diacetyl and acetoin, two cammon ingredients in butter flavoring, as indicators of exposure to butter flavoring vapors. Animal experiments at NIOSH indicate that diacetyl is one of the chemicals in butter flavoring that can lead to airway injury. The other chemical components that may contribute to toxicity, and the levels of exposure that are considered safe, are still not known. Recommended air exposure limits have nat been established for most chemicals used in flavorings ...." There is no doubt that occupational illness has been linked to certain food manufacturing operations; however, the key question of "what chemical component(s) is/are causing disease?" remains unanswered. NIOSH cites a series of studies by van Rooy and Frits (e.g., Frits et al. 2007) as important in establishing a causal link between diacetyl exposure and BO. Their investigation of workers at a chemical plant in	In the cited study, three of 102 workers was a significant outcome, particularly with bronchiolitis obliterans as the endpoint. See response to reviewers' comments RA-52 and RA-46 in this document, and 5135 in the peer review comment response document.

		the Netherlands that produced diacetyl found BO in only three of 102 workers. Air concentrations ranged from 1.8 to 351 mg/m^3 (0.51 to 100 ppm) for diacetyl and from 0.4 to 29 mg/m^3 (0.22 to 16 ppm) for acetaldehyde. As NIOSH points out: " .. .During production of diacetyl, workers were also potentially exposed ta acetoin, acetaldehyde, and acetic acid .... the investigators were not able ta demanstrate an exposure-response relationship between relative cumulative exposure to diacetyl and FEV1 .... "The study authors were careful not to overstate the findings of their study by noting that: " ... Our study suggests a causal role of diacetyl. However, we cannot rule out a possible contribution of acetoin or even acetaldehyde, either as causative or contributing agents ... "In the criteria document, NIOSH states (NIOSH 2011b, p.23) that: " ... Many work environments have mixed exposures, with multiple chemical agents present. Although the primary focus of this criteria document is diacetyl and 2,3-pentanedione, other compounds can also be of concern. Depending upon the processes employed in a workplace, sampling should be conducted for agents of concern to maintain safe work environments ... "The fact that NIOSH has collected hundreds of samples showing the presence of diacetyl in workplaces where workers have contracted lung disease does not prove a causal relationship. NIOSH has sampled for diacetyl as a surrogate for the dozens of other chemicals in butter and other flavorings. In one plant (Kreiss et al. 2011), NIOSH discovered that workers were exposed to 24 of the 34 food additives listed by Flavor and Extract Manufacturers Association (FEMA) as "high priority" substances; that is, "flavoring substances that may have the potential to pose respiratory hazards in flavoring-manufacturing workplaces (OSHA 2010)." In a popcorn plant, NIOSH found more than 100 different volatile	

		organic compounds in the air of the mixing room (Kreiss et al. 2002). Until epidemiology studies can confirm the theory that occupational exposure to diacetyl by itself causes BO, the promulgation of the proposed recommended exposure limits (RELs) for diacetyl and 2,3-pentanedione is premature.	
RA-38	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	Comment 13: NlOSH's expansion of the scope to include all flavoring agents is not justified. Per review of NIOSH's Criteria Document's requirements for employers to implement exposure monitoring, medical monitoring, respiratory protection programs, engineering controls and other administrative controls, NIOSH's intent in the document Is to regulate exposure to ALL flavoring agents that may pose a health hazard. For example: Ÿ " .... A safety and health program designed to protect workers from the adverse effects of exposure to diacetyl, 2,3-pentanedione, and other flavoring chemicals should include mechanisms to identify all risk factors for exposure to flavoring substances ... ." (NIOSH 2011b, p. 281) Ÿ " .. ..Because flavorings can consist of many chemicals in addition to diacetyl and 2,3-pentanedione, deciding what to sample often requires preliminary knowledge of the specific flavoring chemicals being produced or used, or that are present in flavorings ar other food ingredients used in the workplace, and the known exposure hazards posed by each ..." (NIOSH 2011b, p. 284) Ÿ " .... AII workers (permanent, temporary and contract workers) who regularly work in or enter areas where diacetyl and	The purpose of this criteria document is to reduce or eliminate significant risk of health impairment from exposure to diacetyl and 2,3-pentanedione and prevent flavorings-related lung disease. There are recommendations for flavoring ingredients to control and reduce exposure which can be applied to all flavoring ingredients.

		similar flavor ingredients (or products that contain these ingredients) may benefit by being included in the medical monitoring program .... " (NIOSH 2011b, p. 260) Ÿ " ... An analysis should be performed on each operation involving diacetyl, 2,3-pentanediane, or other food flavoring compounds to assess the potential exposures and to establish specific guidance about when to use skin, eye, and face protection .. ." (NIOSH 2011b, p. 244). p This vast expansion in scope is not supported by the title of the Criteria Document or data presented therein. NIOSH has not even attempted to establish a scope, justification or scientific basis for such an expansion. This regulatory short-cut is clearly not warranted and would have vast repercussions throughout the entire food production and service industry. Literally thousands of flavoring chemicals are in use currently. Of these, only 46 have OSHA PELs (NIOSH 2011b, p.14). Meaningful implementation of any new requirements on flavorings would require that NIOSH identify each chemical of interest, and develop a recommended exposure limit (REL) for each chemical that NIOSH would wish to include. Justification is clearly lacking with regard to why exposures to flavoring agents in general, and diacetyl and 2,3-pentanedione specifically, would be elevated to priority status above other workplace chemical exposures	

RA-39	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	*39* **Comment 14: NIOSH's call for development of substitutes at this time is ill-advised**. The recommendation by NIOSH that substitutes be developed for diacetyl and 2,3-pentanedione is unwarranted because the available science as selectively presented by NIOSH does not provide adequate justification for regulating the current worker population's exposures to diacetyl and 2,3-pentanedione, per the above comments. Further, the encouragement of substitutes at this time may result in chemicals entering the flavoring marketplace that may be associated with poorer performance and perhaps even greater toxicity. In fact, we know even less about the hazards of some of the proposed substitutes for diacetyl than we do about diacetyl and 2,3-pentanedione. It may be decades before any proposed substitutes can be adequately tested to provide a level of assurance of safety.	We agree with the commenter. Because the current knowledge on toxicity of available substitutes for diacetyl and 2,3-pentanedione is limited, and exposure to substitutes may also need to be controlled, elimination and substitution may not provide feasible control strategies. We do not discuss these control strategies in detail in the revised criteria document in detail because the call for substitutes for diacetyl and 2,3-pentanedione is ill advised, and demonstrating the comparative toxicity of possible substitutes will take years if ever undertaken at all. In the wake of NIOSH findings of the toxicity of diacetyl in experimental animals and in flavoring-exposed workers, many clients of flavoring manufacturers called for flavoring products without or with less diacetyl in order to avoid regulation by CalOSHA which began in December 2010 but was anticipated during advisory committee deliberations starting in about 2006. The use of 2,3-pentanedione as a substitute for diacetyl began by the mid-2000s and was discovered by NIOSH in a 2007 food production health hazard evaluation in which the employer had no idea about the substitution, and material data safety sheets from several flavoring suppliers did not disclose that 2,3-pentanedione was part of the flavoring contents. We now know that 2,3-pentanedione and diacetyl have comparable toxicity in experimental animals. Rather than substituting chemicals with unknown toxicity for diacetyl, it would be preferable to use diacetyl in a safe way, protecting workers

			from exposures greater than the draft REL and STEL with engineering controls and respiratory protection. There is no health protection advantage to using 2,3-pentanedione as a substitute for diacetyl, and the higher draft REL and STEL for 2,3-pentanedione are purely a consequence of there being no analytic method to support lower values. It is plausible that the alpha-diketone group common to many of the proposed substitutes is responsible for both flavor properties in common and toxicity, such that none of the proposed substitutes can be presumed to be safer than diacetyl.
RA-40	Jason T. Capriotti, CIH, CSP, Industrial Hygiene Solutions, LLC	**2. Chapter 7: Basis of the Recommended Standards for Diacetyl and 2,3 Pentanedione** Re-evaluate the QRA and propose a REL to a "safe" level that does not impact consumers. Propose a REL that does not creep into ambient naturally occurring diacetyl levels commonly found in industries that use strawberries, beer, wine, dairy products, tomatoes, coffee, baked goods, roast chicken, and margarine. This is only fair because, at the current time, there is no evidence of disease in these industries	Concerns have been raised in several public comments about affected industries having insignificant or “naturally occurring” diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxin, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.

RA-41	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	**<u>Naturally Occurring Diacetyl and the Proposed RELs</u>** Diacetyl occurs naturally in a wide variety of foods including some fruits and vegetables, dairy products such as milk, butter, cheese and yogurt, and fermented beverages such as beer, wine, and some distilled spirits (Nijssen et aI., 2011). It is important that throughout the Criteria Document there is a clear recognition that there have been no reported health effects in workers in any industries where exposure to diacetyl is solely from the naturally occurring substance - there are no reports of illness among workers in the wine, dairy, beer, or distilled spirits production industries. It is also important to be clear on which foods may contain flavors and which may not. For example, while standard wine may contain naturally occurring diacetyl because of malolactic fermentation, it cannot by law contain added flavors. FEMA requests that NIOSH make it clear throughout the Criteria Document that any recommended exposure limits (RELs) for diacetyl or 2,3-pentanedione do not apply to facilities where exposure to either of these substances may occur solely through exposure to naturally occurring diacetyl or 2,3-pentanedione in foods and beverages. Therefore, wine, beer, and distilled spirits production facilities, and dairy-related facilities not engaged in the production of flavoring materials such as butter starter distillate, would be subject to the RELs only if neat diacetyl or 2,3-pentanedione was present in these facilities, or compounded flavors are present containing these substances.	Concerns have been raised in several public comments about affected industries having insignificant or “naturally occurring” diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxin, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to concentrations of these chemicals above the REL should be prevented.

RA-42	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	"Causation" and Diacetyl and 2.3-Pentanedione FEMA has consistently advocated for the application of sound science in addressing respiratory health and safety issues in flavor manufacturing. Throughout the Criteria Document NIOSH has assumed that causation has been established with a high degree of scientific certainty - that exposure to diacetyl causes bronchiolitis obliterans. This assumption, in addition to not being scientifically appropriate, risks creating a false sense of certainty in what is an extremely complex situation. In the face of significant uncertainty related to causation, which remains today, FEMA has recommended for more than ten years that flavor manufacturers focus on the key elements of exposure control for many flavoring substances including diacetyl, medical surveillance when appropriate, and hazard communication (e.g. FEMA, 2004). It is clear that the current scientific information on the toxic potential of diacetyl does not allow a conclusion that diacetyl causes bronchiolitis obliterans (or related illnesses) according to the well-recognized criteria established by Hill (1965). Consistent with Hill's conclusions, the relationship between diacetyl and bronchiolitis obliterans is most properly considered an association. Hill identified nine criteria to establish causation: 1. The existence of a temporal relationship 2. A strong statistical correlation 3. A dose-response relationship 4. Consistent replication of the observed effect 5. Plausibility of the connection between cause and effect 6. The consideration and rejection of alternate explanations 7. Appropriate experimental support for a causal relationship 8. Support for a causal relationship by the specificity of the cause and effect 9. The coherence of the causal relationship - compatibility of existing theory and knowledge It is clear that the available information on diacetyl meets few, if any, of Hill's criteria for causation. The complexity of	The Hill criteria are very well supported in the case of diacetyl, as discussed in Chapters 4 and 6. See also responses to comments RA-46 and RA-52.

		determining the causes of bronchiolitis obliterans and related respiratory illnesses was acknowledged by King and Kinder (2008) in the definitive reference on these illnesses in which they listed "volatile flavoring agents" as possibly resulting in "inhalation injury" and "clinical syndromes *associated* with bronchiolitis." (emphasis added). A major issue in establishing that diacetyl causes bronchiolitis obliterans is the absence of an appropriate animal model for the illness because rodents are "obligate nose breathers" and therefore are not able to simulate human exposure to gases and vapors. The absence of an appropriate animal model for bronchiolitis obliterans (and related illnesses) has severely hindered research that could advance our understanding of the role that diacetyl may play in the development of these illnesses in workers in microwave popcorn and flavor manufacturing facilities. Intra-tracheal instillation in rodents, a highly artificial route of exposure, has resulted in the production of some interesting data (e.g. Flake et al., 2010) that have yet to be verified as relevant to human exposure. It seems clear that the appropriate characterization of the relationship between diacetyl and bronchiolitis obliterans is that an association exists but that causation has not been established. With respect to 2,3-pentanedione, we are unaware of any instances of human illness that have been associated with exposure to this substance. 2,3-Pentanedione shares similarities of chemical structure with diacetyl which indicates that appropriate precautions be taken with this substance as should be taken with diacetyl. FEMA requests that NIOSH revise the Criteria Document to describe the relationship between diacetyl and respiratory illness, including bronchiolitis obliterans, as an association and not as a causative relationship. FEMA also requests that NIOSH revise the Criteria Document throughout to make it clear that there are no known	

		cases of respiratory illness associated with exposure to 2,3-pentanedione. As noted previously, FEMA recognizes and fully supports sound workplace safety practices regarding potential exposure to these substances and has long called for an active workplace safety approach in the face of significant uncertainty (FEMA, 2004).	
RA-43a	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 1 – Introduction In Section 1.5, the Criteria Document lists examples of "flavored food products" and includes beer and wine in this list. Standard wine is not permitted to contain added flavors nor is beer unless it is clearly labeled as containing flavors. Standard wine may contain naturally occurring diacetyl through the natural process of malolactic fermentation but it may not contain added flavors. FEMA requests that NIOSH clarify this sentence by deleting reference to wine and beer. FEMA also requests that NIOSH include information explaining the distinction between diacetyl which may be present in foods naturally (i.e. through natural occurrence or through natural fermentation processes and not through addition) and diacetyl present in foods through intentional addition to provide flavor. FEMA also notes that diacetyl is endogenous in humans through normal metabolism.	In section 1.5, beer and wine have been deleted from the list of examples. No distinction is made between natural and added diacetyl.
RA-43b	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 1 – Introduction In Section 1.3 of this chapter, NIOSH states in the context of information on diacetyl that "Occupational exposures in the flavoring and food production industry (sic) have been associated (emphasis added) with respiratory disease . . ." Several sentences later in the same paragraph NIOSH states "Although a causative relationship between diacetyl and respiratory disease has been observed . . ." (emphasis added). With reference to FEMA's comments above on	It is our contention that the Hill criteria have been met.

		causation, FEMA requests that NIOSH revise this and all other statements in the Criteria Document to accurately reflect the current state of scientific knowledge that there is an association between inhalation exposure to diacetyl and respiratory illness but that causation consistent with the Hill criteria has not been established.	
RA-44	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 5 - Quantitative Risk Assessment Based on Worker Data It appears that NIOSH has based many of its conclusions and recommendations on data from the "sentinel" microwave popcorn manufacturing facility in Jasper, Missouri (NIOSH, 2006). Such significant reliance on a single data set isn't scientifically appropriate. It is a challenge to address the broad use of flavoring substances in manufacturing an extremely diverse set of flavors and foods together with the large number and diversity of facilities producing flavors and foods. However, limiting the quantitative risk assessment described in the Criteria Document to one facility, the sentinel plant, means that the risk assessment has limited relevance to flavor manufacturing. We request that NIOSH explain the relevance of the quantitative risk assessment presented in Chapter 5 to flavor manufacturing facilities. Several years after completing its work at the Gilster Mary Lee facility (NIOSH, 2006), NIOSH recognized that the analytical method used to characterize breathing zone and area samples (NIOSH Method 2557) was subject to perturbation by ambient humidity (Cox-Ganser et a!., 2011). NIOSH proposed a correction methodology for the published data noting that "underestimation of worker exposure may lead to overestimation of respiratory health risk in quantitative exposure-effect analyses." (Cox-Ganser et aI., 2011). However, for reasons that are not clear, NIOSH chose not to apply its correction methodology to samples identified as being below the limit of detection (LOD) stating "It is not possible to know if the workplace	See response to reviewers' comments EA-3 in this document and 5130 in the peer review comment response document.

		diacetyl concentration was indeed below the LOD or if losses due tohumidity and days from sampling to extraction in the laboratory caused the sample value to be below the LOD." (Cox-Ganser et a!., 2011). Failure to correct and include the LOD samples in the overall collection of data points introduces a significant amount of uncertainty and affects the confidence to be placed on resulting exposure data. For example, 40 percent of the personal samples and 42 percent of the area samples collected at the Gilster Mary Lee facility were reported to be below the LOD. Furthermore, 251 sample results using the initial uncorrected method were below the LOD as noted by NIOSH in the exposure assessment in the Criteria Document. If the analytical results for these samples were corrected and used by NIOSH the risk assessment may have yielded a much different outcome resulting in a higher and more reasonably achievable REL for diacetyl- FEMA requests that NIOSH perform this analysis and report the results in the Criteria Document.	
RA-45	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 6 - Quantitative Risk Assessment Based on Animal Data In Section 6.1.4.1, "Comparison with other animal-based risk assessments," NIOSH discusses the work on the non-profit organization Toxicology Excellence for Risk Assessment (TERA) and cites a preliminary TERA analysis submitted to OSHA in 2008 as "IDFA, 200B." This preliminary analysis was expanded, completed, and published in 2010 (Maier et a!., 2010). The Maier et al. publication is of critical importance to both the risk assessments in the Criteria Document based on animal and human data and is not discussed or cited in the Criteria Document. An important aspect of the Maier et al. report is the report's thorough evaluation and consideration of the available information and especially its use of the information and analysis of the report by Lockey et al. (2009) who	A risk assessment based on the plant discussed in the Lockey publication [Lockey et al. 2009] would produce an even lower REL (see draft criteria document Table 5.30). The Toxicology Excellence for Risk Assessment (TERA) animal-based analysis uses short-term exposure (6-week, 12-week), extrapolation from very high exposures (> 25 ppm) and an inappropriate benchmark response rate, corresponding to high excess risk 100/1,000. The TERA animal-based risk assessment by Maier et al. [2010] reviewed the available human epidemiological literature on diacetyl and concluded that the published findings were insufficient for a risk assessment. Eleven peer reviewers and seven public

		reported on findings from a microwave popcorn production facility other than the sentinel microwave popcorn plant (NIOSH, 2006) so heavily relied on by NIOSH for its risk assessments. FEMA requests that NIOSH, in both Chapters 5 and 6 on its risk assessments, and in Chapter 7 on the basis of its REL for diacetyl compare the results of its risk assessments yielding an REL of 5 ppb (8hr. TWA) for diacetyl with the OEL of 0.2 ppm recommended by Maier et al (2010) and thoroughly explain its rationale for the substantial difference.	commenters addressed the issue of animal data, with six recommending the animal data not be used, one suggesting that it is sufficient for the purposed intended, and two specifically addressing the TERA assessment. Comments on conclusions by Meier were divided. On principle, NIOSH prefers to base policy decisions on human findings when sufficient data exist. Upon review of the available population data, including data collected for NIOSH health hazard evaluations, NIOSH investigators concluded that the data from one health hazard evaluation was indeed a valid and promising basis for further investigation of the diacetyl exposure response and for derivation of the required estimates of risk. The grounds for this decision have been spelled out in some detail in the draft and revised criteria documents. Additionally, there are features of the TERA risk assessment that limit its usefulness in the context of NIOSH policy. In our judgment, an analysis based on lung function in workers exposed to diacetyl takes precedence over a recommendation derived from such limited animal data.

RA-46	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Chapter 7 - Basis of the Recommended Standards for Diacetyl and 2.3-Pentanedione As noted previously, it is scientifically inappropriate to conclude that diacetyl causes bronchiolitis obliterans. FEMA has significant concerns related to the extremely low recommended exposure limits (RELs) proposed for diacetyl and 2,3-pentanedione and whether these RELs are reasonably achievable. With respect to 2,3-pentanedione, we are unaware of any instances of human illness that have been associated with exposure to this substance. 2,3-Pentanedione shares similarities of chemical structure with diacetyl which indicate that appropriate precautions should be taken with this substance. However, it appears premature to propose a REL for this substance.	Some reviewers commented that there is no (or little, or not significant) evidence to link exposure of diacetyl or 2,3-pentanedione to various issues discussed in the criteria document. Two peer reviewers questioned the link between animal data and human response and the significance of the data presented. Nine public comments suggested there was no evidence to link exposure to bronchiolitis obliterans, pulmonary disease, abnormal spirometry, or other respiratory problems. "No evidence" must be considered in relation to whether any effort has been made to ascertain excess risk. For example, have there been surveillance studies of consumers' respiratory status or population-based case series; case-control studies of incident bronchiolitis obliterans; or special case identification procedures in large provider systems to detect emerging bronchiolitis obliterans cases that otherwise might be misdiagnosed as complicated bronchitis/emphysema? No data have been reported in these subjects. Does "no evidence" mean some employers have been doing medical surveillance for loss of breathing capacity in current workforces, on employees leaving employment, on former employees, on retirees? If so, this data should be shared and reported. What is the statistical power of these efforts? If not, there are no grounds for claiming "no evidence." For workforces exposed to low levels of diacetyl (e.g., < 0.05ppm), very large long-term studies would be required to detect cumulative deficits corresponding to

			significant lifetime risks of impairment. The Lockey study [2009] at four plants is not sufficient grounds for complacency because employee selection out of exposure was not addressed, the workers were followed for only one year, and the exposures studied were quite low (coming in most cases after 2005). Three out of four plants had median corrected exposures below 0.03 ppm in nonmixers, and below 0.7 ppm in mixers [White 2011]. Here again, "no evidence" could mean some employers have been doing medical surveillance for loss of breathing capacity on current workforces, or surveillance on employees former employees or retirees. No data have been published on any of these issues. Given that industry exposure levels for diacetyl have been declining, one would not expect to observe new cases of bronchiolitis obliterans related to current exposures, except possibly in the future. The important question is whether cumulative decrements in pulmonary function are still occurring.

RA-47	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	With respect to diacetyl, the proposed REL of 5 ppb (8 hr. TWA) is exceedingly low and it is highly unlikely that the majority of flavor manufacturers will be able to comply with this limit without the use of respirators that, according to NIOSH, is the least desirable method of exposure control. The low proposed REL is unlikely to be reasonably achievable for the majority of flavor manufacturers. The proposed REL of 5 ppb is approximately 10-fold lower than the estimated daily exposure to diacetyl from smoking about one-half of a pack of cigarettes per day. If converted to a daily dose the proposed REL of 5 ppb may be expressed as 0.005 mg/kg/day. The mean diacetyl content in cigarette smoke is 0.336 mg/cigarette (Fujioka and Shibamoto, 2006) meaning that smoking one-half of a pack of cigarettes per day for 15 years results in a daily dose of 0.048 mg/kg/day, more than ten times greater than the proposed REL for diacetyl. There is no evidence that cigarette smoking is associated with the development of bronchiolitis obliterans. Maier et al. (2010) developed an occupational exposure limit (OEL) for diacetyl of 0.2 ppm (8 hr. TWA) based on many of the same data as used by NIOSH in developing its REL. It appears that the significant difference in the two proposed exposure limits is due to NIOSH's over-reliance on the data from a single microwave popcorn manufacturing facility, the Gilster Mary Lee facility (NIOSH, 2006). Maier et al. relied on a broader data set including significant information in Lockey et al. (2009).As described above, it is important to note that the Maier et al. report is not referenced in the Criteria Document. The Criteria Document references only a preliminary report as "IDFA, 2008" suggesting that NIOSH did not evaluate or use information from Maier et al., 2010. FEMA requests, as explained above, that NIOSH review the information	Chapter 3 has a section on the Hill criteria for causation in which NIOSH describes how each criterion for causation has been met for an epidemiologic association to be interpreted as causal. We have not changed the document in response to this comment. We are not distinguishing between exposure to diacetyl present in foods and diacetyl added to foods, because its potential toxicity is not affected by source. Regarding the Maier [2010] data, the TERA analysis uses short-term exposure (6-, 12- wk), extrapolation from very high exposures (> 25 ppm) and an inappropriate benchmark response rate, corresponding to high excess risk 100/1,000. The TERA animal-based risk assessment by Maier et al. [2010] reviewed the available human epidemiological literature on diacetyl and concluded that the published findings were insufficient for a risk assessment. Eleven peer reviewers and seven public commenters addressed the issue of animal data, with six recommending the animal data not be used, one suggesting that it is sufficient for the purposed intended, and two specifically addressing the TERA assessment. Comments on conclusions by Meier were divided. On principle, NIOSH prefers to base policy decisions on human findings when sufficient data exist. Upon review of the available population data, including data collected for NIOSH health hazard evaluations, NIOSH investigators concluded that the data from one health hazard evaluation was indeed a valid and promising basis for further investigation of the diacetyl

		from Maier et al. (2010) and use it as requested in the Criteria Document.	exposure response and for derivation of the required estimates of risk. The grounds for this decision have been spelled out in some detail in the draft and revised criteria documents. Additionally, there are features of the TERA risk assessment that limit its usefulness in the context of NIOSH policy. A benchmark response of 5% or 10%, corresponding to 50 and 100/1,000 excess risk, in a relatively short-term (6-, 12-week) animal study of lung pathophysiology is unacceptable for respiratory impairment in humans potentially leading to disabling or fatal disease.
RA-48	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	FEMA also requests that NIOSH make it clear that the proposed RELs do not apply to facilities in which the only potential exposures are to naturally occurring diacetyl such as facilities involved in the production of wine and beer where no neat diacetyl or diacetyl-containing flavors are present. The RELs should also not apply to dairy-related facilities unless those facilities are engaged in the production of dairy-based concentrated flavoring products such as butter starter distillate.	Concerns have been raised in several public comments about affected industries having insignificant or "naturally occurring" diacetyl exposures. Other naturally occurring chemicals (e.g., aflatoxins, endotoxins, asbestos) also require the use of controls to limit exposure. The RELs for diacetyl and 2,3-pentanedione do not consider the source of these chemicals because the hazard of exposure to these chemicals does not depend on the source (i.e., naturally occurring or not). While wine, beer, or other food products, labeled or not, may contain naturally occurring diacetyl or 2,3-pentanedione, worker exposures to

			concentrations of these chemicals above the REL should be prevented.
RA-49	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	The Recommended Exposure Limit (REL) for 2.3-Pentanedione Sensient Flavors echoes the comments of FEMA on this subject. There is simply no empirical scientific evidence cited in the Criteria Document that indicates 2,3-Pentanedione exposure causes bronchiolitis obliterans, or any other respiratory disease. Sensient Flavors believes that all references to 2,3-Pentanedione and all standards being recommended for exposure to that chemical, should be removed from the Criteria Document.	The published animal data indicate that 2,3-pentanedione toxicity is comparable or exceeds diacetyl toxicity. Thus prudence suggests that both should be regulated to the same degree. No change in document made.
RA-50	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	The Criteria Document's "Action Levels" and "Short Term Exposure Levels" FEMA has discussed and offered a critique of the proposed RELs for both diacetyl and 2,3-Pentanedione. In Sensient Flavor's view, that same discussion and analysis apply to the action levels and short term exposure levels for these chemicals that have been proposed by NIOSH. To the extent FEMA's critique causes NIOSH to re-evaluate and adjust these RELs, the action levels and short term exposure levels should be similarly modified.	See responses to reviewers' comments RA-52, RA-46, and G-18.

RA-51	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Restrictive versus Obstructive Lung Abnormalities The proposition advanced in the Criteria Document that restrictive, rather than obstructive, lung function abnormality is related to diacetyl exposure is speculative and not proven. The Criteria Document references just three alleged instances, on Pages 69, 76 and 77, of restrictive lung functions. The first reference is to a Wisconsin flavor manufacturer, where diacetyl in starter distillate is just one component of many, including bacteria, in use in the manufacturing process. Two of fifteen employees potentially exposed to flavorin grelated chemicals were evaluated by NIOSH as having restrictive abnormalities. There is no evidence presented that diacetyl or any other flavoring chemical, is the causative agent. The second reference is to an Indiana flavoring manufacturer, where NIOSH claims diacetyl is used nearly daily but acknowledges that chemical exposures are diverse. Areas within this plant that are incorrectly identified as having higher potential for diacetyl exposure include extract/distillation and dry blend. In fact, this manufacturer monitored the dry blend area and found diacetyl levels below 2 ppb; there is no use of diacetyl in the extract/distillation area, so there are no data for this location. It appears that NIOSH chose to include these areas in the analysis to bolster the hypothesis that diacetyl is a causative agent in the development of restrictive lung function. But the opposite appears to be true: if employees working in these two areas have restrictive lung function, it could not have been caused by diacetyl because the chemical was not present. Significantly, the Health Hazard Evaluation (HHE) that was generated as a result of NIOSH's evaluation of this facility conceded that it could not be concluded that diacetyl was the cause of the purported respiratory issues experienced by these workers. The third instance of alleged restrictive lung	The commenter requests that references to restrictive lung disease be removed from the criteria document. Since the draft criteria document, the evidence regarding restrictive lung disease in flavoring-exposed workers has been summarized in Kreiss [2012], and this information has been added to Chapter 3. While the causative exposure(s) are not yet clear, restrictive disease is part of the spectrum of three published case series of biopsy-documented constrictive bronchiolitis. Hence, we have chosen to retain and amplify the current information about restriction in the criteria document. The commenter (who represents the Indiana company with the excess of spirometric restriction) says that NIOSH incorrectly classified two areas (among five) as having higher potential for flavoring exposure because neither extract and distillation nor dry blend had diacetyl exposure. The impact of possible misclassification of exposure in extract and distillation is negligible because no employees currently work in this area, and only one worker was said to have worked in the past in this area. The commenter is incorrect in stating that dry blend had no diacetyl measurements above 2 ppb. In the report [NIOSH 2011b], company-supplied area measurements for dry blend ranged from 1 to 799 ppb, and personal measurements ranged from 2 to 219 ppb. NIOSH did not allege that diacetyl was the cause of spirometric restriction and exposure category-related decline in FEV_1 in this report because company measurements were

		function in employees references a bakery mix plant where diacetyl could not be detected through air testing. Instead, 2,3-Pentanedione was detected. NIOSH makes no attempt to correlate employee exposure to work station or the handling of 2,3-Pentanedione. Based upon the problems and limitations associated with the science in this area, Sensient Flavors believes that all references to diacetyl and 2,3-Pentanedione causing and/or being associated with restrictive lung function abnormalities should be removed from the Criteria Document.	inadequate to assess quantitative exposure-response relationships. The impact of exposure misclassification would be to underestimate associations between health outcomes and exposures, and not, as the commenter alleges, “bolster the hypothesis that diacetyl is a causative agent.”
RA-52	John B. Hallagan on behalf of the Flavor and Extract Manufacturers Association	Possible Synergistic Effects The Criteria Document acknowledges possible synergistic effects from flavoring chemicals other than diacetyl or 2,3-Pentanedione that may contribute to lung abnormalities. When this question was raised at the public hearing, NIOSH replied that, since such flavoring chemicals were often used simultaneously, diacetyl would serve as a surrogate with an exposure level to represent all associated compounds. But this approach avoids establishing a causal effect between diacetyl, other chemicals simultaneously in use, and lung abnormalities. Worse, if it were scientifically proven that another flavoring compound has more deleterious effects, the more dangerous chemical could be used in higher amounts to replace diacetyl, thus resulting in greater risk to employees. p On page 10, line 5 the Criteria Document indicates that the standard sought to be set is "necessary to... prevent flavorings-related lung disease." Since synergistic effects have not been evaluated, it is impossible for a single REL to accomplish this stated goal. Further, even if diacetyl is harmful, limiting the use of diacetyl may or may not result in disease prevention.	Taken together, the human and animal studies provide a compelling case for the respiratory toxicity of alpha-diketones of which diacetyl is the most thoroughly studied. The clinical experience and worker population studies have revealed a clear association between diacetyl exposure and diminishing respiratory capacity that evidently in some cases has led to cases of bronchiolitis obliterans. Other exposures in the studied environments are not plausible causes. The expanding animal research on diacetyl clearly describes pathological changes specific to this compound that provide an ample mechanistic basis for anticipating respiratory disease in humans. In Chapter 5 of the criteria document, a risk assessment is presented that begins with the premise that diacetyl causes irreversible respiratory damage. The analyses presented are designed specifically to describe that causal relationship for the purpose of predicting risk in working populations, not to prove that a causal relationship exists. Thus statistical significance is less important than

			insights provided into the nature of the relationship between diacetyl and diminishing respiratory capacity. Other potentially reactive or toxic compounds can be present in association with diacetyl in flavoring applications, such as acetoin or acetaldehyde. A National Toxicology Program (NTP) 90-day study on acetoin is in progress [National Toxicology Program 2013b], but the chosen maximum exposure level (generally representing the maximum tolerated dose) is 800 ppm whereas in the NTP 90-day diacetyl study the maximum exposure level is 100 ppm [National Toxicology Program 2013a]. This implies a considerably lower level of toxicity for acetoin. Furthermore, in microwave production jobs at Plant G, the mean diacetyl concentration over all sampling surveys, combining both area and personal samples, was 3.4 ppm compared with 0.28 ppm for acetoin determinations from the same air samples. Thus acetoin is an unlikely candidate for the observed respiratory effects. Acetaldehyde is less consistently associated with diacetyl and is often below the limit of detection. The glues, inks, salts, oils, and other volatile chemicals present in popcorn plants are widely used in industry and there has been no outbreak comparable to diacetyl in those sectors, often with far greater numbers of exposed workers. The flavoring manufacturing operations do not share most of those generic packaging exposures but have had bronchiolitis obliterans cases identified.

RA-53	Jacqueline Nowell on behalf of the United Food and Commercial Workers Union, CLC	**RELs, STELS and AL** NIOSH has conducted an extensive review and quantitative assessment of human exposures for these recommended levels. Based on the science to date on these chemicals, the UFCW supports the recommended exposure limit, the action level and the short-term exposure limit for diacetyl proposed in the criteria document. As outlined in their recommendation for exposure limits to 2,3-pentanedione and based on the limitations of the analytical method, the UFCW also supports the EL and STEL recommended in the criteria document	No response required.
RA-54	Daniel Smigal on behalf of the United States Department of Agriculture, Food Safety and Inspection Service	FSIS is concerned that the proposed diacetyl and 2,3-pentanedione RELs and STELs do not explicitly consider the dermal and irritant effects of these compounds. Our experience with diacetyl exposure in a poultry slaughter establishment suggested that dermatitis and intolerable eye and sinus irritation were noted in the absence of any lower respiratory symptoms. NIOSH believes that setting OELs that are protective against precursors to bronchiolitis obliterans (BO) will inherently protect against dermal and irritant effects, but no objective evidence is presented to support this assumption. The potential for differences in personal protective equipment (PPE) use in various exposure settings makes it inappropriate to draw firm inferences about irritant effects based purely on observations in popcorn and flavorings manufacturing. For example, the visual demands of poultry inspection tasks preclude the use of	While the odor threshold for diacetyl may be below the proposed REL, there have been no published data that indicate respiratory or other irritation airborne levels near the proposed REL. Similarly there is no evidence that diacetyl acts as a skin irritant or produces dermatitis or other dermal symptoms at these levels.

		chemical protective eyewear in most instances, although the use of eye protection was documented in at least some of NIOSH's diacetyl-related HHEs. Additionally, the use of protective eyewear or full-faced respirators was not fully described in all HHE reports, making the assumption that the proposed REL and STEL protect against irritation tenuous at best. Explicit consideration should be given to dermal and irritant effects in the development of OELs, to ensure that an appropriate level of protection is achieved.	
RA-55	Mary C.Townsend, Dr. P.H., M.C. Townsend Associates, LLC	1. FEV1 s are distributed with constant variability around the predicted values as people age, so that a worker who remains at a constant position relative to his predicted value (e.g., 1 L below it) will have an FEV1 %pred that gets smaller as he ages since the denominator of this index gets smaller. Therefore, for risk analysis, FEV1 % of pred does not fully remove the effect of age, and if you have independent variables that are time-related, use of %pred may exaggerate the impact of those variables if the age range is big. If all workers are about the same age, the impact will be negligible. I would recommend using deviation from the NHANES FEV1 predicted value as your dependent variable, which will remove the effects of age as well as height, sex, and ethnicity so that you don't need to consider those variables in your model. I would think that at least verifying the conclusions of your analyses using this alternative approach is a good idea.	The cross-sectional survey does not follow the same worker but rather examines diminishing % of predicted as a function of cumulative exposure across the surveyed population. For individuals with a fixed 1-liter loss, increasing age would exhibit an increasing loss in terms of % predicted. We believe other specifications for the regression analysis would not produce substantial differences in the ultimate risk assessment.
RA-56	Mary C.Townsend, Dr. P.H., M.C. Townsend Associates, LLC	If you have a number of non-smokers, I would perform the risk analysis for that group alone and then for all smoking statuses combined using a dummy variable for smoking status. The thing that has struck me about diacetyl exposure-related cases is that a high number of them have occurred in non-smokers - this is unusual in the occupational setting and means that you don't need	The risk analyses controlled for cigarette smoking, thereby meeting the commenter's request. As was clear in Kreiss et al. [2002], nonsmokers had much higher increased risk of spirometric obstruction compared to smokers. However, smokers also had risk compared to smokers in the general population. In regression models of

		to worry about any part of the effect In those workers being caused by the big personal exposure - smoking.	diminishing pulmonary function and in the calculation of excess lifetime risk, smokers had lower values of risk; however, because regulation is not specific to personal risk factors, the risk estimates presented for the REL did not distinguish smokers and nonsmokers.
RA-57	Mary C.Townsend, Dr. P.H., M.C. Townsend Associates, LLC	The end-of test criteria will impact the ratios (falsely making them too large and "non-obstructed" since the FVC will be under-recorded.) None of these concerns are present when NIOSH's teams of well-trained techs go out to do spirometry using their well-maintained volume spirometers - however, it would be wise to investigate all of these issues if you plan to put much weight on non-NIOSH measurements. Since the need for accuracy is great in performing these risk analyses and you have the luxury of having many tests performed by NIOSH teams, I also would not use results from non-NIOSH testing unless I was able to review the graphs generated by non-NIOSH sources.	The spirometry tests used in risk assessment were all conducted by NIOSH technicians. No change was made in the document based on this comment.
Tox-1	David Egilman, MD, MPH, Brown University	At the diacetyl hearing, I discussed Morgan's study of 2,3 pentanedione which should be considered at least as peer reviewed as the MSDS sheets that NIOSH cites for key information on diacetyl and pentanedione. Poster Board 914. Lung Function and Pathogenesis of Bronchiolitis Obliterans in Rats Exposed to 2,3-Pentandedione D.L. Morgan; H.C. Price; C.L. Johnson; M.P. Jokinen; W.M Gwinn; G.P. Flake http://www.niehs.nih.gov/news/events/pastmtg/2011/sot/sot2011.cfm In fact Dr. Howard has cited this in official NIOSH notices. http://edocket.access.gpo.gov/2011/2011-274.htm cited as: Morgan, D.L., Kirby, P.J., Price, H.C., Bosquet, R.W., Taylor, G.J., Gage, N., and Flake, G.P. (2010). Inhalation toxicity of acetyl proprionyl in rats and mice. The Toxicologist: Supplement to Toxicological Sciences	Chapter 4 of the final criteria document has been revised to describe the most current literature pertaining to 2,3-pentanedione. Please see Hubbs et al. [2012], Morgan et al. [2012], and Morgan et al. [2016]. Unfortunately, there are no peer-reviewed studies that have investigated the hypotheses regarding carcinogenicity of diacetyl, and BASF's study was not peer reviewed, so no additional changes would fall within NIOSH guidelines for the criteria document.

		114(1), 316. I have attached this poster. This study shows that pentanedione is more toxic than diacetyl. [See Egilman attachment for references] Finally Ezrailson published a letter (below) that indicated that due to its chemical structure diacetyl could be a carcinogen: **To the Editor: Kreiss et al. (Aug. 1 issue) 1 report a high incidence of bronchiolitis obliterans at a microwave-popcorn factory. The chemical diacetyl (2,3-butanedione) was singled out as a possible causal agent of this deadly condition and other medical problems found in workers in this plant. As a chemist, biochemist, and toxicologist, I would like to point out that 2,3-butanedione is in chemical equilibrium with 1,3-butane-diene-2,3-diol (Figure 1 Chemicals 2,3-Butanedione and 1,3-Butane-Diene-2,3-Diol, and Their Expected Product, 1,3-Butane-Diepoxide-2,3-Diol.). This phenomenon, which is well known in organic chemistry, is called ketoenol tautomerism. This isomer is expected to be very reactive with oxygen both at room temperature and on heating. Thus, 1,3-butane-diepoxide-2,3-diol would be expected as a product. Although the parent compound is known to be reactive with arginine, the diepoxide is of particular interest, since butadiene diepoxide is a known human carcinogen. The appropriate government agencies must investigate and evaluate whether diacetyl should be banned from food products. [See Egilman letter for Figure] Edward G. Exrailson, Ph.D. 2308 West Settler's Way, The Woodlands, TX 77380** Edez1@prodigy.net Letters to NEJM are peer reviewed prior to publication by the editors and often by others and reviewed by the authors of the paper to which they refer. Finally I attach BASF's 1993 diacetyl toxicology study which is cited in many corporate MSDS sheets. This provides LC 50 data and pathologic evidence of lung disease in one rat. If NIOSH can cite MSD sheets as you do then NIOSH should	

		be able to use this LC 50 data. [See Egilman attachment for references]	
Tox-2	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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).	The actual sentence, found in section 3.7 of the document, refers to Chapter 4 and reads, "Biologic plausibility is supported by the evidence of diacetyl toxicity identified in several animal exposure studies and other nonhuman research (see Chapter 4)." It was the intent of this sentence to refer the readers to Chapter 4, which describes the airway epithelial toxicity, computational fluid dynamic-physiologically based pharmacokinetic models that explain species differences in sites of diacetyl uptake in the respiratory tract, and the recent development of an animal bronchiolitis obliterans model that uses diacetyl. To clarify that the intent is to refer the reader to Chapter 4, we modified the sentence to say, "Biologic plausibility is supported by studies of diacetyl toxicity summarized in Chapter 4." While this change is important and improves the criteria document, the final phrase in the comment, "no rodent has been shown to developed bronchiolitis obliterans" is not true as noted on page 104 of the criteria document and as noted by Ungers and Mink in their second comment below.
Tox-3	Leslie J. Ungers, MS, CIH, Ungers and Associates and Frank L. Mink, Ph.D, MAI	**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	In the Morgan et al. [2008] and Palmer et al. [2011] papers, vehicle controls were used that did not develop bronchiolitis obliterans. It is true that aspiration of some additional agents with structural similarities to diacetyl, including acetoin and 2,3-pentanedione can cause bronchiolitis obliterans-like lesions in

		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	rats [Flake et al. 2010], but aspiration as an exposure technique does not cause bronchiolitis obliterans-like lesions in rats [Morgan et al. 2008; Palmer et al. 2011; Rao et al. 2003]. The reports of the induction of bronchiolitis obliterans-like changes in the deep lung of laboratory animals following aspiration of diacetyl are important because (a) no prior animal model of bronchiolitis obliterans existed (as noted by Ungers and Mink in their previous comment), and (b) it is a technique that bypasses the rodent nose, which computation fluid dynamic-physiologically based pharmacokinetic models have demonstrated to absorb more diacetyl than will be absorbed in the upper airways of workers. To respond to the comment, the following has been inserted on page 104, line 5 prior to the last two sentence of the paragraph: "The reports of the induction of bronchiolitis obliterans and bronchiolitis obliterans-like changes in the deep lung of laboratory animals following aspiration of diacetyl are important because (a) no prior animal model of bronchiolitis obliterans existed, and (b) it is a technique that bypasses the rodent nose, which computation fluid dynamic-physiologically based pharmacokinetic models have demonstrated to absorb more diacetyl than will be absorbed in the upper airways of workers (see section 4.2.6)."
Tox-4	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH,	We would like the Criteria Document to address these questions, or to at least make clear in this section that these remain questions for further research: 1) Apart from the added amount of diacetyl that may be present	To provide the requested information, the following paragraph was added at the end of section 4.2.3: "Although powdered butter flavoring can produce fewer vapors than

	California Department of Public Health	on surfaces or encapsulated in powdered flavors (and presumably is not captured in vapor monitoring), does the deposition of particles directly into sensitive regions of the lung impart added toxicity?	liquid butter flavorings, the powders have a major respirable component [Boylstein et al. 2006; Rigler and Longo 2010]. If powdered butter flavorings are substituted for liquid butter flavorings, diacetyl and 2,3-pentanedione vapor concentrations may well be below exposure limits. In particular, encapsulated flavoring powders are designed to contain diacetyl or 2,3-pentanedione vapors. However, inhalable particulates can be deposited in the nose, conducting airways, and deep lung and dissolve in the mucous layer. No peer-reviewed studies are available that investigate the potential for encapsulated flavorings to release diacetyl and/or 2,3-pentanedione directly to the target cells lining airways. However, a recent study indicates that more than a quarter of particulates in flavoring powders are less than 10 µm in diameter. Therefore, powders have the potential to reach the intrapulmonary airways [Rigler and Longo 2010]. NIOSH has recently funded a study that is addressing the toxicity of inhaled butter flavoring powders to address the research gaps. As requested, we added the following two questions to the research needs listed in Chapter 11. (a) Apart from the added amount of diacetyl that may be present on surfaces or encapsulated in powdered flavors (and presumably is not captured in vapor monitoring), does the deposition of particles directly into sensitive regions of the lung impart added toxicity? (b) What is the relative toxicity of diacetyl

			inhaled as a powder compared to the same quantity of diacetyl inhaled as a vapor?
Tox-5	Deborah Gold, MPH, CIH on behalf of Cal/OSHA and Barbara Materna, Ph.D, CIH, California Department of Public Health	2. What is the relative toxicity of diacetyl inhaled as a powder as compared to the same quantity of diacetyl inhaled as a vapor?	See response to Tox-4.
Tox-6	Dana M. Hollins, MPH, ChemRisk, LLC	**The animal toxicology data indicate that the effects of diacetyl are limited to the upper respiratory tract and there is no evidence to indicate that diacetyl is a cause of bronchiolitis obliterans.** *Diacelyl vs. BO inducers: comparison of physico-chemical parameters and other metrics* There are several well-established chemical risk factors for BO in humans. These chemicals are highly reactive (or are converted to highly reactive compounds in the body) and exert clearly demonstrable destructive effects on the small, lower airways and alveoli of animals at relatively low concentrations. For example, nitrogen dioxide (N02), which is one of the most common chemical agents associated with BO in humans, is often present in silo gases and every year there are numerous case reports of farm workers developing BO as a result of silo gas exposures. Nitrogen dioxide is highly toxic because it is hydrolyzed to a reactive and biologically destructive acid (nitric acid) throughout the respiratory tract, including the alveoli. In studies involving rats and other animal species, 4-hours of exposure to N02 concentrations as low as 0.25-2 .0 ppm will cause	To respond to the Hollins comments and to improve the criteria document, we have added a new first paragraph, edited the current first paragraph as a revised second paragraph, and added an additional final paragraph to section 4.2.6 to clarify the literature on target cells for bronchiolitis obliterans, organic agents that cause bronchiolitis obliterans in man but predominantly damage the nasal epithelium of rats, and data on diacetyl-induced damage to the respiratory epithelium. We added the following new first paragraph to section 4.2.6: “Four converging lines of evidence support the relevance of diacetyl inhalation studies in rats and mice to humans. First, diacetyl inhalation causes damage to respiratory epithelium in rats and mice. This is an important finding because injury to the respiratory epithelium of the deep lung is the accepted cause for bronchiolitis obliterans.

		significant protein leakage into alveoli and injury to Type I alveolar lining cells (IPCS, 1977). Other inducers of BO include: mustard gas, sulfur dioxide, methyl isocayanate, ammonia, hydrogen fluoride, and hydrogen chloride. These compounds are all severe respiratory irritants and/or they are converted to biologically destructive compounds in the respiratory tract. In each case, the mechanism of toxic action is well understood. Diacetyl clearly does not fit this profile. It is an organic compound, not an inorganic compound. It is not an acid. It is neither biologically reactive nor caustic at low concentrations nor is it metabolized to any compounds that are known to be reactive or caustic. In fact, diacetyl has been "generally recognized as safe" (GRAS) by the FDA since 1983. Furthermore, unlike the known BO inducers, diacetyl is present naturally in many foods, naturally occurs in the body (as a biochemical intermediate), and is a common food additive. If diacetyl exposure was analogous to exposure to mustard gas, it is reasonable to expect that adverse effects on workers handling even small volumes would have been easily recognizable. Even if one were to believe that diacetyl is an "atypical" inducer of BO, any reasonable scientist would expect that a "mechanism of action" would be suggested or established to explain how diacetyl causes destruction of the deep lung in humans. As noted above, known inducers of BO have clearly understood mechanisms of toxic action. Yet no such theories have been put forth that satisfactorily explains bow a relatively benign compound such as diacetyl should be considered an inducer of BO that ranks with the likes of chlorine and mustard gas.	Second, dosimetry calculations indicate that diacetyl concentration in respiratory epithelium of the human deep lung under working conditions may be much higher than diacetyl concentrations in laboratory animals. Third, another organic compound, sulfur mustard, implicated in causing bronchiolitis obliterans in man has recently shown a similar pattern of predominantly nasal injury in rats exposed by nose-only inhalation. Fourth, repeated inhalation exposure to either diacetyl or 2,3-pentanedione causes fibrosis of intrapulmonary airways [Morgan et al. 2012]. Each of these findings supports the conclusion that with appropriate dosimetry studies, damage to the respiratory epithelium of the upper airways of rodents should be considered when evaluating risk for man." We removed the last two sentences of the first paragraph, "As detailed below, computational fluid dynamic-physiologically based pharmacokinetic models indicate that these differences in site of injury reflect interspecies differences in diacetyl dosimetry within the respiratory tract [Gloede et al. 2011; Morris and Hubbs 2009]. Nevertheless, the toxicological effects observed in rodents are consistent with the epithelium as the initial cell target in the airways [Hubbs et al. 2008; Morgan et al. 2008]." The revised second paragraph is "Animal exposure studies have revealed that the upper airways of rodents are sensitive to flavoring-induced toxicity, whereas the lower airways of humans are most affected by these agents. Importantly, diacetyl exposures

			in rodents caused extensive damage to the respiratory epithelium lining the nose and the trachea [Hubbs et al. 2008; Morgan et al. 2008]. The cell types that are injured in the nose and trachea are very similar to the respiratory epithelium lining the airways of the deep lung of man that are the accepted target for bronchiolitis obliterans [Borthwick et al. 2009; King 1989]. In addition, the bronchi were damaged at high concentrations in acute exposures and at lower concentrations in subchronic exposures in mice. Thus, inhalation toxicology studies showed that diacetyl could damage respiratory epithelium, providing biological plausibility for its etiologic role in bronchiolitis obliterans. Indeed, at the time of the first inhalation toxicology studies of diacetyl, no accepted cause of bronchiolitis obliterans in man had been demonstrated to cause bronchiolitis obliterans in rodents. Recently, repeated inhalation exposures to diacetyl or 2,3-pentanedione have been shown to cause fibrosis of intrapulmonary airways in rats, demonstrating a pathologic change in the rodent model which is very similar to bronchiolitis obliterans in man [Morgan et al. 2012]. Interpretation of the species difference in the anatomic location of diacetyl-induced damage to respiratory epithelium may be explained by species differences in respiratory tract anatomy, breathing patterns and diacetyl dosimetry.” The new final paragraph to section 4.2.6 is “Damage to the nose of rodents has recently been described for another agent implicated

			in causing bronchiolitis obliterans in man, sulfur mustard [Bis(2-chloroethyl)sulfide] , a chemical warfare agent. Bronchiolitis obliterans is considered a major cause of progressive respiratory disease in survivors of sulfur mustard exposure [Ghanei et al. 2004a; Ghanei et al. 2004b; Ghanei et al. 2008; Rowell et al. 2009]. Nose-only inhalation exposures of F344 rats to sulfur mustard caused severe mucosal damage in the rat nose but the changes in the lung were absent or minimal [Weber et al. 2010]. When the nose was bypassed using intubation with tubing lined by Teflon, sulfur mustard did indeed cause necrosis of the epithelium lining the proximal airways [Weber et al. 2010]. This suggests comparable sensitive of the respiratory epithelium at different levels of the respiratory tract to an accepted cause of bronchiolitis obliterans, sulfur mustard. Thus, predominantly nasal injury has been seen in rodent inhalation studies with both organic agents implicated in causing bronchiolitis obliterans.”

Tox-7	Dana M. Hollins, MPH, ChemRisk, LLC	*Animal inhalation studies with diacetyl indicate that only the upper respiratory tract is affected* As noted above, the physico-chemical properties of diacetyl are highly inconsistent with those of known risk factors for BO and in fact they suggest diacetyl is not particularly reactive. Animal exposures involving diacetyl-containing artificial butter flavoring (ABF) and pure diacetyl show that inhalation of diacetyl vapor causes effect on the upper respiratory tract but does not cause alveolar or any other deep lung effects, even at concentrations that are: I) far beyond those measured in the workplace, and 2) high enough to cause severe necrosis of the upper respiratory tract and even death. In 2002, the National Institute for Occupational Safety and Health (NIOSH) published a study in which male Sprague-Dawley rats were exposed to heated ABF vapors for six hours at diacetyl concentrations of 20 3 , 285 , and 352 ppm (Hubbs et al, 200 2). The total VOC levels were: 298, 446, and 578 ppm, respectively. Other animal groups were exposed to intermittent "pulses" of ABF vapor with diacetyl concentrations ranging up to 9 40 ppm. The pulsed exposures were intended to represent intermittent workplace exposures to high ABF concentrations. The investigators described the pathology of different segments of the nasal epithelium (the beginning of the respiratory tract), the large upper airways, and the alveoli. The most consistent morphologic change was necrosis of the nasal epithelium, which was observed in all animals in all exposed groups. Severe necrosis of the of the upper pulmonary airways was observed in all animals in the 285 ppm and 352 ppm-diacetyl groups, and in one rat in the 203 ppm-diacetyl group. Two rats died (post-exposure) in the 285 ppm and 352-ppm diacetyl groups. The authors indicated that the alveoli "were unaffected" in all groups. The authors then repeated the above	Chapter 6 has been rewritten.

		study, this time with pure diacetyl (Hubbs et aI., 2004 and 2008). Consistent with the findings of the ABF study, they reported that continuous 6-hour exposure to heated vapors of pure diacetyl (at 99 ,198 , and 295 ppm) resulted in necrosis of the nasal epithelium in all animals at 198 and 295 ppm, but that such effects were not observed at 99 ppm. Effects on the upper respiratory epithelium were observed in 2/6 animals in the 295 ppm group; no such effects were noted in the 99 and 198 ppm group. Furthermore, as the authors note, the findings at 2 95 ppm "only bordered on statistical significance" using the exact p value of 0 .0 5 4 . In other words, even at the highest pure diacetyl concentration of 295 ppm the authors failed to note a clear biologically significant response in the upper airway epithelium. Also, *none of the diacetyl exposures were reported to cause any effects on the alveoli or deep lung tissue*. This is true even for rats that were exposed to numerous 15 minute "pulses" of *1,800 ppm diacetyl*. In another inhalation study of diacetyl, Morgan et al. (2008) exposed mice to 200 and 400 ppm diacetyl for 6 hours/day for 5 days. These exposures were longer than those used in the Hubbs studies (single 6 hour exposure), and many of the mice either died or were euthanized before the end of the exposure period. Not surprisingly, there was extensive necrosis of the upper airways; and yet, as indicated by the authors "No lesions of the bronchioles [lower airways] were noted". Similarly, no deep lung effects were observed in rats exposed to multiple 15 minute pulses of 1200 ppm diacetyl.	

Tox-8	Dana M. Hollins, MPH, ChemRisk, LLC	*Comparison of animal diacetyl exposures to workplace conditions* It is critical to note that the exposure concentrations employed in the Hubbs and Morgan studies are far higher than those that could be considered representative of workplace diacetyl exposures. The diacetyl concentrations used by Hubbs et al and Morgan et al. (99 -400 ppm constant exposures; multiple pulsed exposures of up to 1 8 00 ppm) were in fact much higher than the levels measured in the A B F mixing rooms, where the highest airborne diacetyl concentrations have been found. Specifically, I have examined all of the mixing room data from the numerous microwave popcorn facilities examined by NIOSH (Kanwal et aI., 2006; Kullman et aI., 2 005 ; NIOSH, 2003 a, 2004), and I find that few time-weighted-average (TWA) samples of 60 min or longer exceed 3 ppm and in fact most TWA samples are less than 1 ppm.	See response to Tox-6.
Tox-9	Dana M. Hollins, MPH, ChemRisk, LLC	*Comparison of diacetyl no-effect levels to adverse effect levels for known B0 inducers* As noted earlier, 4 -hours of exposure to N02 concentrations as low as 2 .0 ppm will cause significant protein leakage into alveoli and injury to Type I alveolar lining cells in rodents (IPCS, 1977). These findings indicate that N02 has an "effect level" on the alveoli that is at least as low as 8 ppm-hours, and may in fact be much lower. Similarly, 30 minutes of exposure to 65 ppm (32 .5 ppm-hours) of hydrogen fluoride or 5 minutes of exposure to 75 ppm (about 4 ppm-hours) sulfur dioxide will cause alveolar necrosis in mice (IPCS, 2002 and ATSDR, 1998). In short, known BO inducers wdestroy the alveoli of rodents at doses less than 50 ppm-hours. In contrast, Morgan et al. (2008) exposed mice to 400 ppm diacetyl for 6 hours/day for 5 days and did not observe even minimal alveolar effects. Hence, diacetyl has a "no effect level" at least as high as 10,200 ppm-hours, and in fact the no-effect level is likely to be much higher.	See response to Tox-6.

Tox-10	Dana M. Hollins, MPH, ChemRisk, LLC	None of the inhalation studies conducted to date have reported any effects, even minimal effects, on the deep lung (terminal bronchioles or alveoli) in animals exposed to very high diacetyl concentrations, including concentrations that are both well beyond workplace levels and are high enough to kill the animals. Conversely, damage to the deep lung in animals has been observed with every single known inducer of 80, even at low exposures. While it is unclear whether direct affects on the alveoli or deep lung are a pre-requisite for induction of BO, certainly it cannot be concluded that a chemical (such as diacetyl) that only causes irritation of the upper respiratory tract, even at very high concentrations, "fits the profile" of a 80 risk factor. If one is to maintain that diacetyl is a risk factor for BO, then one must argue that diacetyl is a unique compound with toxic properties never before observed with any other chemical. There is no reason to believe diacetyl possesses such novel characteristics.	See response to Tox-6.
Tox-12	Gary K. Whitmyre, M.A, D.A.B.T, toXcel, LLC	**Comment 9: Available animal data provide a more understandable dose-response curve.** Based on available inhalation studies in animals, the lowest observed adverse effect concentration (LOAEC) In rats for bronchial damage from a single 6-hour inhalation exposure to either diacetyl appears to be approximately 300 ppm, with a no-observed-adverse-effect concentration (NOAEC) near 200 ppm (Morgan et al. 2008; Hubbs et al. 2010; Hubbs et al. 2008). The NOAEC for subchronic inhalation studies In mice administered diacetyl for 6 hours/day, 5 days/week for 6 or 12 weeks was 50 ppm (Morgan et aJ. 2008). NIOSH stated that it believes the bronchiolar region for humans is 10-fold more sensitive to damage from diacetyl than in rats or mice (NIOSH 2011a). This is supported by a study by Gloede et al. (2011) in which estimated airway concentrations in humans exposed to 1 ppm diacetyl	The Whitmyre comment that the animal data provide a more understandable dose-response curve is a true statement. However, if human data is available and suggests greater susceptibility of humans than rodents, protecting human health needs to consider the human data.

		were 3 to 7 fold higher than those in rats exposed to the same level of diacetyl. If, for example, this 10-fold adjustment was applied to the subchronic NOAEC, this would produce a "point of departure" of (50 ppm)/(10) = 5 ppm, or 5,000 ppb for development of an allowable TWA.	
Tox-13	James P. McCarthy on behalf of Sensient Flavors and Fragrances, LLC	Page v: "While the focus of this document is on diacetyl and 2, 3-Pentanedione, NIOSH has concern about other flavoring substitutes with structural similarities to diacetyl or moieties that are biologically active and capable of producing similar toxic effects as diacetyl. Therefore, NIOSH recommends that such exposures also be considered and controlled to as low as reasonably achievable." This statement is not supported by any facts. If there is evidence of harmful effects, then the exact compounds should be identified. If not, this statement should be removed. Terms such as "similar toxic effects" and "as low as reasonably achievable" are inappropriately vague and imply hazards without any factual basis. Sensient Flavors has similar concerns with Section 1.1 Purpose, where it states that "the intended outcome of the [criteria] document is to ... prevent flavorings-related lung diseases."	While the focus of this document is on diacetyl and 2,3-pentanedione, NIOSH has concern about other flavorings capable of producing similar toxic effects. Volatile and reactive flavorings are of concern. Therefore, NIOSH recommends that such exposures also be considered and controlled in consultation with workplace safety professionals.
Tox-14	Kendall B.Wallace, Ph.D, StrataTox, LLC	As authors of the evidence in question, we would like to correct a significant error in Dr. David Egilman's comments to NIOSH regarding the use of ELUMO calculations to support the proposed REL for diacetyl of 5ppb. These comments begin on page 215 of the document and our rebuttal addresses specifically the errors made on pages 218-219 where Dr. Egilman made the following statement: *"I am just going to talk about some other data that supports the TL V as it exists. ConAgra hired an ex-EPA person to do a structure activity analysis. By the way, all of the data that I am*	LUMO, which indicates comparable "potential" reactivity and toxicity, is both relevant and interesting for diacetyl. The burden would be to demonstrate that in the case of diacetyl, the potential reactivity is not in fact occurring in the biological systems of concern. Because diacetyl does not share the same reaction mechanisms as toluene diisocyanate, acrolein, and acrylates and does not in any way imply absent reactivity of toxicological importance for diacetyl.

		talking about is in a peer review paper by myself and Hank Schilling, which I will drop off here. It is titled A Proposal for Safe Exposure Levels of Diacetyl. /I is peer reviewed, and it came out about four months ago, but it is not mentioned in the document. And it is not a personal thing but I have data in there that is relevant to the discussion, the data that I have been referring to over and over again. This data, for example, only appears in that published paper. And what they have found was that structure activity relationship of this material was similar to TOI, which is not the most toxic of the isocyanates; HOI probably is. And that based on that analogy, the TL V would be about one part per billion because that is what the TL V is for isocyanates. So that is another piece of independent analysis performed at the funding of ConAgra that comes out with a 1.0 ppb number. " In his statement to NIOSH, Dr. Egilman is referring to sophisticated and theoretical quantum chemical calculations performed by ToxDx, LLC to first distinguish reactive from non-reactive chemicals identified in complex mixtures such as flavors and fragrances and then to rank-order chemicals within a group sharing a common reaction mechanism, such as Michael addition, nuclear substitution, SN2, etc. The ultimate objective was to identify those compounds in the mixture that might present the greatest concern for potential adverse human health effects. As the authors of this approach, it is our opinion that Dr. Egilman misinterpreted the scientific meaning and application of the results; he then published his misinterpretation in a journal devoted to occupational and environmental health. At the NIOSH public meeting, Dr. Egilman referred to his publication as being reviewed and authenticated by peers. Unfortunately, this erroneous interpretation of our results was not recognized during the review of his article prior to publication. In the	

		following paragraphs we hope to shed light on the theory and proper interpretation of these calculations. Chemicals that share similar structural and physical chemical properties tend to have similar behaviors when administered or exposed to humans. Application of these principles of quantitative structure-activity relationships (QSAR) has enormous potential for informing regulatory decisions, especially for the thousands of chemical identities for which little if any toxicity data is available; diacetyl and 2,3-pentadione are good examples. When untested chemicals are grouped and compared with well-studied chemicals that share similar structural and physical chemical properties, initial estimates of chemical hazard and safety can be formed. Although strictly theoretical and not sufficient for final rule-making, such projections, when properly applied, offer important insight into identifying those chemicals within a complex mixture that warrant the greatest concern for further toxicity testing. One such measure of chemical similarity is the ability of chemicals to "react" with biological molecules to form a stable (covalent) bond. Such chemicals are referred to as "reactive" because they have the potential to form stable bonds with possible critical biologic target molecules (protein, DNA, etc.); this distinguishes them from "nonreactive" chemicals that cannot form stable bonds with molecular targets. Grouping chemicals based on chemical reactivity can be accomplished by calculating parameters that describe what might happen when a chemical comes in contact with body tissues. For chemicals to be reactive, a stable bond is formed by an exchange of electrons between biological molecules and the chemical. Chemicals have greater tendencies to accept those electrons (become reactive) when the energy of certain empty molecular orbitals of the chemical is lower than the energy of the electrons of the donor molecule	

		(biological target), and a chemical bond may form spontaneously. A calculated parameter called LUMO (defined as the energy of the lowest unoccupied molecular orbital) is used to identify chemicals that could react with biological molecules and distinguish them from chemicals that are not reactive. There are many quantum chemical computer programs publically available that can be used to calculate these LUMO energies, as well as many other important theoretical parameters of chemicals. However, while LUMO may be a useful parameter to identify reactive chemicals among complex mixtures of hundreds of chemicals, LUMO only describes the potential of a chemical to react; It is a measure of chemical reactivity. LUMO does not predict how rapidly the chemical will react nor do LUMO values predict which specific sites in membranes, proteins, or DNA will be the likely targets of the chemical. Since the toxicological effects of reactive chemicals depend on both the reaction rate and the reaction site (physical chemical properties of the molecular target) not to mention exposure and dosimetry, LUMO is a necessary first step in grouping chemicals based on potential to react but it does not indicate that two reactive chemicals that differ significantly in other important chemical structure or physical properties will have similar biological targets or potential adverse effects. Based on his understanding, Dr. Egilman asserted in his comments to NIOSH and in his published manuscript, that chemicals with similar LUMO values should have the same toxicological effects, and that one can rank-order the degree of risk based only on LUMO values. Dr. Egilman advocates that since diacetyl and the isocynates have comparable LUMO values, they should have similar safety levels (exposure limits). Unfortunately, this fails to recognize the limitations of LUMO. Although LUMO can be used to distinguish between reactive and nonreactive	

		chemicals across broad chemical groups, its use in rank ordering of individual chemicals is valid only when applied within a group of chemicals that share the same chemical reaction mechanism, which is not the case for α,β-substituted diketones such as diacetyl and isocyanates. Chemicals like diacetyl and 2,3-pentanedione can be detected by olfaction at low levels because they belong to a special class of reactive chemicals with a highly specialized reactivity mechanism. In this case, LUMO might suggest that diacetyl is reactive, but it cannot be used to predict how selective it is for certain binding sites in the airway. The acrylates used in the coatings industry are also reactive, but they bind with sulfur atoms in cysteine residues whereas diacetyl will not react with sulfur moieties. Consequently, diacetyl and acrolein may have similar LUMO values and share some short-term effects such as irritation of the nasal-pharyngeal surfaces, but the long-term effects are completely different due to the different binding capabilities. In the case of the isocynates, the differences are even greater. Isocynates are highly reactive with a wide variety of biological tissues and react by a mechanism completely distinct from diacetyl. Diacetyl reacts with guanidine moieties whereas isocynates react with a wide variety of biological molecules and are classified as carcinogens (1). Thus, TDI (toluene diisocyanate) poses a significant long-term risk of cancer, which is not the case for diacetyl or 2, 3-pentanedione. To suggest that LUMO values can be applied in read across approaches to set safety limits of dramatically dissimilar chemicals like diacetyl and TOI is inappropriate on the basis of fundamental scientific principle. In conclusion, based on a sound scientific understanding of LUMO, we assert that Dr. Egilman's testimony that the calculated LUMO	

		for diacetyl and 2,3-pentanedione support the proposed REL for diacetyl of 5ppm is scientifically flawed.	

Follow-up review of new content (revised Chapter 6 and new section of Chapter 8), December 2013

Tracking Number	Commenter	Full comment (copied verbatim)	Response
GC-501	John B. Halligan, Flavor and Extract Manufacturers Association of the United States (FEMA)	Dear Sir/Ms.: The Flavor and Extract Manufacturers Association of the United States (FEMA) is responding to the request for comments on the draft revised Chapters 6 and 8 of the document "Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione" ("Criteria Document"). 78 Fed. Reg. 78363. 26 December 2013. The Criteria Document was initially made available for review and comment in 2011 by the National Institute of Occupational Safety and Health (NIOSH). 76 Fed. Reg. 44338. 25 July 2011; 76 Fed. Reg. 64353. 18 October 2011. FEMA presents these comments in the spirit of its longstanding policy of collaboration and cooperation with NIOSH on this critically important matter.	No response required
GC-502	John B. Halligan , FEMA	**The Flavor and Extract Manufacturers Association of the United States** FEMA, founded in 1909, is the Washington, D.C.-based national association of the U.S. flavor industry. FEMA's members include flavor manufacturers, flavor users, flavor ingredient suppliers, and others with an interest in the U.S. flavor industry. FEMA's flavor manufacturing members include all of the twenty-five largest flavor manufacturers in the U.S., and FEMA's flavor manufacturing members produce >95% of all flavors consumed in the U.S. FEMA and its members are committed to assisting flavor manufacturers in having the safest workplaces possible.	No response required

GC-503	John B. Halligan , FEMA	**FEMA's Program on Respiratory Health and Safety in Flavor Manufacturing** FEMA has been very active in assisting flavor manufacturers on respiratory health and safety matters since the initiation of FEMA's efforts in 1997 (FEMA, 2012). Since 1997, FEMA has sponsored workshops including extensive training sessions for flavor and food manufacturers on the safe handling of flavors, proper medical surveillance of workers, and hazard communication. In addition to the workshops, FEMA has held numerous information sessions for its members and others in an effort to share relevant information in a timely manner. Since 2001, FEMA has had numerous meetings and discussions with NIOSH, the Occupational Safety and Health Administration (OSHA), and the California Department of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA) on these matters and has shared extensive information with these agencies in cooperative and collaborative relationships. Representatives of NIOSH, OSHA, and Cal/OSHA have attended FEMA meetings and workshops, and have also made presentations at a number of these sessions. FEMA supported the regulatory efforts of Cal/OSHA which resulted in 2010 with the implementation of the first workplace safety regulation related specifically to flavor manufacturing. FEMA has provided extensive information to NIOSH on the manufacture, use, and regulation of flavors. A brief summary of this information is in Appendix 1.	No response required
GC-504	John B. Halligan , FEMA	**FEMA Supports the Completion of the Criteria Document** FEMA supports the completion of the Criteria Document. The document will be a very important and useful document for the flavor manufacturing industry and its food manufacturing customers. Much of the advice and many of the recommendations contained in the draft Criteria Document are consistent with the advice and recommendations that FEMA has provided to flavor and food manufacturers for many years through reports (e.g. FEMA, 2012) and workshops.	No response required

GC-505	John B. Halligan , FEMA	**Revising the Draft Criteria Document Chapter by Chapter Is Not An Appropriate and Effective Way to Revise the Document** We are surprised that NIOSH released two revised chapters for the draft Criteria Document rather than a complete and intact revised document. Releasing revised chapters without integrating them into the document creates several obvious and significant issues. For example, if the chapter on risk assessment based on animal data (Chapter 6) is to be revised then so should the chapter in which NIOSH discusses and analyzes the available animal data - Chapter 4 on toxicology. Several new references included in revised Chapter 6 must be included and discussed in Chapter 4. There are numerous other examples of parts of the draft Criteria Document that must be revised to account for the revised Chapters 6 and 8. Furthermore, as will be addressed later in these comments, there is additional new information that must be included and discussed in both Chapters 4 and 6, among others.	NIOSH revised Chapter 6 of the criteria document based on animal data that became available after the 2011 draft criteria document was published. In addition, NIOSH drafted a new subsection in Chapter 8 which proposed GHS classifications for diacetyl and 2,3-pentanedione. NIOSH submitted the revised Chapter 6 and new subsection of Chapter 8 for peer review and public comment because this analysis was thought to be significantly different than what was provided in the draft document originally released in August 2011. Since this revised content still supports the conclusions in the draft criteria document, it could be reviewed independently of the entire document. The other chapters in the original draft document were revised based on the comments received as part of the peer review and public comment process in 2011. NIOSH will post files containing all of the comments received during the peer review and public comment period as well as responses to those comments when the final criteria document is released.

GC-506	John B. Halligan , FEMA	**The Credibility of the Criteria Document - What is NIOSH's Process for Revising the Draft Criteria Document?** The credibility of the final Criteria Document is critical to its acceptance and application by the flavor and food industries. The document must be objective and unbiased and reflect the most up to date information. The credibility of the document will rely in large part on the process through which it was developed. NIOSH has provided little if any information on its process for revising the draft Criteria Document. There is no mention of a process in the original Federal Register notices soliciting comments on the draft Criteria Document (76 Fed. Reg. 44338. 25 July 2011; 76 Fed. Reg. 64353. 18 October 2011) nor in the Federal Register notice announcing the availability of revised Chapters 6 and 8 (78 Fed. Reg. 78363. 26 December 2013). There also is no description of a process available on the NIOSH docket (http://www.cdc.gov/niosh/docket/archive/docket245.html). In November 2011, FEMA submitted extensive comments on the draft Criteria Document. FEMA has not received a response from NIOSH to these comments nor any indication whether issues addressed in the comments were considered by NIOSH. The docket for the Criteria Document can be accessed at http://www.cdc.gov/niosh/docket/archive/docket245.html and shows that twenty sets of comments were submitted by interested parties. FEMA and others provided NIOSH with specific comments on the original Chapters 6 and 8 in the draft Criteria Document. Were these comments considered by NIOSH and were revisions made to the revised Chapters 6 and 8 based on these comments?	See GC-505.
GC-507	John B. Halligan , FEMA	**FEMA Requests a Description of NIOSH's Process for Completing the Criteria Document and An Opportunity to Review and Comment on the Completed Draft Final Document** FEMA requests that NIOSH describe the process that it intends to follow in producing a final draft version of the Criteria Document. FEMA requests that NIOSH's description of its process contain an explanation of how it intends to respond to the comments it has received and address the requests for revisions to the document contained in those comments. A description of the process should also include a timeline for next steps and the completion of the document. FEMA has two specific requests: 1. FEMA requests that a description of NIOSH's process for completing the Criteria Document be provided at least 180 days before the final version of the draft document is	The development of this document has fulfilled all of the requirements for a significant guidance document as outlined by the Office of Management and Budget Good Guidance Practices Bulletin and for a highly influential scientific assessment as outlined by the Office of Management and Budget Peer Review Bulletin. The peer review plan for this document included selecting external peer reviewers with expertise and without conflict of interest, publishing a Federal Register Notice announcing the availability of the draft criteria document for

		released to the public for review and comment so that FEMA and others may comment on the NIOSH process. 2. FEMA requests the opportunity to review and comment on a final draft Criteria Document that accounts for comments received by NIOSH and that integrates all proposed changes to the draft document.	public comment, conducting a public meeting to convey the agency's policies, responding to requests for clarification, and addressing questions. Information about the public meeting, charge to reviewers, and peer, stakeholder, and public comments received are available on the NIOSH diacetyl criteria document docket page: http://www.cdc.gov/niosh/docket/archive/docket245.html. After the first peer review and public comment process was initiated, the National Toxicology Program released a new dataset on diacetyl and 2,3-pentanedione. Chapter 6, titled Quantitative Risk Assessment Based on Animal Data, was updated to accommodate this new dataset. Additionally, the Occupational Safety and Health Administration promulgated a revised Hazard Communication Standard aligned with the Globally Harmonized System of Classification and Labeling of Chemicals. A new section of Chapter 8 including classifications of these chemicals based on the OSHA GHS criteria was developed. These two chapters went through an additional round of external review of peer reviews and public comment. Information about the charge to reviewers, and peer, stakeholder, and public comments received are available on the NIOSH diacetyl criteria document docket page at http://www.cdc.gov/niosh/docket/archive/docket245A.html and at https://www.regulations.gov/document?D=CDC-2013-0021-0001.

			The peer reviewer comments focused on exposure assessment, risk assessment, epidemiology, toxicology, medical issues, and engineering control information in the criteria document. Twenty stakeholder and public comment submissions were received with 265 comments in 10 scientific areas. The peer review period extended from August 2011 until May 2012 so that peer reviewers had the opportunity to review and respond to the public comments as well as the additional charge questions posed by OSHA. The peer reviewers provided 160 diverse, thought-provoking comments in 111 pages of comments. The NIOSH response to these topics and issues is detailed in the attached "NIOSH Response to Public and Stakeholder Comments and the NIOSH Response to Peer Review Comments." Although we appreciate FEMA's request, the document development process for this document has provided two opportunities for peer, stakeholder, and public input. It has fulfilled all of the requirements for a significant guidance document as outlined by the Office of Management and Budget Good Guidance Practices Bulletin and for a highly influential scientific assessment as outlined by the OMB Peer Review Bulletin. The document and the NIOSH responses to the reviewer comments have been finalized at this time, consistent with the NIOSH process for policy documents.

RA-501	John B. Halligan , FEMA	**Comments on Revised Chapter 6: Quantitative Risk Assessment Based on Animal Data** NIOSH has included in revised Chapter 6 only some of the new information that has become available in the years since the publication of the draft Criteria Document in 2011 (e.g references cited as "NTP, 2011," "Morgan et al. 2012a" and "Morgan et al. 2012b"). FEMA requests that NIOSH also review and include in its analysis the following reports that may have an effect on the conclusions in this chapter: Anderson et al., 2013; Dworak et al., 2013; Hubbs et al., 2013; More et al., 2012b; Morgan et al., 2013; Singal et al., 2012; and Zaccone et al., 2013.	The Anderson et al. [2013], More et al. [2012b], and Zaccone et al. [2013] papers cited by FEMA are reviewed in Chapter 4 of the criteria document. Studies currently available only in abstract form, such as Hubbs et al. [2013], Morgan et al. [2013], and Singal et al. [2012] are not included in the criteria document. The Dworak et al. [2013] study cited by FEMA was examined but was not considered useful for quantitative risk assessment as it does not include quantitative dose-response information.
RA-502	John B. Halligan , FEMA	Several of the reports not included by NIOSH in revised Chapter 6 are important because they have implications for understanding the possible mechanism of action of diacetyl and 2,3pentanedione in animals (e.g. Anderson et al., 2013; Hubbs et al., 2013; More et al., 2012b).	The mechanism of action of diacetyl and 2,3-pentanedione is discussed in Chapter 4 of the document.
HC-501	John B. Halligan , FEMA	**Comments on Revised Chapter 8: Hazard Prevention and Control of Exposure to Diacetyl and 2,3-Pentanedione** The draft Criteria Document did not include information on hazard communication and this was a significant deficiency in the document as noted in FEMA's previously submitted comments. The proposed revisions to Chapter 8 rectify this significant deficiency. Table 8-2 (Page 2) cites "Anderson et al., 2011" relative to the GHS endpoint of skin sensitization. We note that the citation provided is to an abstract while the full report is published (Anderson et al., 2013). We also note that an additional report should be reviewed and addressed by NIOSH on the subject of the sensitization potential of diacetyl (Dworak et al., 2013).	The Anderson et al. [2011] abstract was removed from the GHS subsection of Chapter 8 and replaced by the Anderson et al. [2013] and Roberts et al. [1999] studies as the basis for the rationale for skin sensitization GHS classification. Dworak et al. [2013] provides a secondary citation, Roberts et al. [1999], of an EC3 value for diacetyl of 11%. The EC3 values reported by Anderson et al. [2013] (15.4%) and Roberts et al. [1999] (11%) are similar and result in the same GHS classification. Both of these studies were cited as the rationale for the NIOSH GHS classification for skin sensitization.
HC-502	John B. Halligan , FEMA	Pages 5 and 6 of the revised Chapter 8 note that FEMA has provided guidance on hazard communication for diacetyl, 2,3-pentanedione and mixtures containing these substances. The text of the revised chapter (Page 6) correctly notes that the language provided by FEMA is inconsistent with the newly standardized GHS terminology. FEMA is in the process of updating its report (FEMA, 2012) and this inconsistency will be corrected.	No response required

GC-508	John B. Halligan , FEMA	**Additional Comments on the Draft Criteria Document** A number of new reports have become available since NIOSH published the draft Criteria Document in 2011. We request that NIOSH incorporate information from the newly available reports in the appropriate chapters of the Criteria Document.	See GC-509.
GC-509	John B. Halligan , FEMA	**Chapter 2: Assessing Occupational Exposure in Workers** Please review and incorporate information from the following references: Huff et al., 2013; Kreiss, 2012; Kreiss et al., 2011; Lee, 2012; Roberts et al., 2012; Ronk et al., 2013a; Ronk et al., 2013b.	Chapter 1 provides a description of what time period, databases, and data sources were evaluated for inclusion in the criteria document. Peer reviewed literature identified since the draft criteria document was published in 2011 was also evaluated for inclusion in the final version of the criteria document as described in Chapter 1.
GC-510	John B. Halligan , FEMA	**Chapter 3: Effects of Exposure in Workers** Please review and incorporate information from the following references: Anderson et al., 2013; Dworak et al., 2013; Finley et al., 2012; Huff et al., 2013; Kreiss, 2012; Kreiss et al., 2011; Lee, 2012; Pierce et al., 2013; Roberts et al., 2012; Ronk et al., 2013a; Ronk et al., 2013b.	See GC-509.
GC-511	John B. Halligan , FEMA	C**hapter 4: Toxicology of Diacetyl and 2,3-Pentanedione** Please review and incorporate information from the following references: Anderson et al., 2013; Dworak et al., 2013; EFSA, 2013; Hubbs et al., 2013; More et al., 2012a; More et al., 2012b; Morgan et al., 2013; Singal et al., 2012; Zaccone et al., 2013.	See GC-509.
GC-512	John B. Halligan , FEMA	**Chapter 5: Quantitative Risk Assessment Based on Worker Data** Please review and incorporate information from the following references: Finley et al., 2012; Pierce et al., 2013; Roberts et al., 2012; Ronk et al., 2013a; Ronk et al., 2013b.	See GC-509.
GC-513	John B. Halligan , FEMA	**Chapter 7: Basis of Recommended Standards for Diacetyl and 2,3-Pentanedione** This chapter should integrate all new and relevant information noted above for Chapters 2, 3, 4, and 5.	See GC-509.

GC-514	John B. Halligan , FEMA	**Appendix 1** **Flavoring Substances and Their Regulation and Use** The inclusion of flavoring substances in food is an important part of food processing and manufacturing in the U.S. Many individual flavoring substances, such as diacetyl, are commonly present in food as natural constituents. For example, diacetyl is commonly found in butter, dairy products, and in many other foods often as a product of fermentation. Diacetyl is endogenous in humans and is the single substance most responsible for the human perception of the taste of butter. The "compounding" of flavors and how they are used in food manufacturing was described by Hallagan and Hall (2009). Compounded flavors typically contain individual flavoring substances at levels well below 1.0% of the compounded flavor. Compounded flavors are in turn most often added to foods also at levels below 1.0%. So, the concentration of individual flavoring substances in food is most often in low ppm concentrations (i.e. 10-200 ppm). Before they may be marketed and added to food, flavoring substances must comply with the requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA) through the premarket approval requirements instituted by the Food and Drug Administration mandating that these substances be safe for ingestion. In most instances, flavoring substances permitted for use in the U.S. have regulatory status as substances determined by FDA to be approved food additives or substances determined to be "generally recognized as safe" (GRAS), or as flavoring substances determined to be GRAS by FEMA (Hallagan and Hall, 1995; 2009). About 600 flavoring substances, including diacetyl and 2,3-pentanedione, have both explicit FDA regulatory status and FEMA GRAS status. Both diacetyl and 2,3-pentanedione are permitted for use in food by FDA (21 CFR 184.1278 as a GRAS substance and 21 CFR 172.515 as an approved food additive, respectively). Like the vast majority of flavoring substances, this regulatory status means that they may be added to food consistent with good manufacturing practices (GMP). The use of flavoring substances and other food ingredients consistent with GMP means that the substances should be used in the minimum amount to achieve their desired technical effect in food.	No response required

GC-515	Anders Abelmann, Cardno-ChemRisk	**Comments on Chapter 6, Quantitative Risk Assessment Based On Animal Data, of the NIOSH Draft Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-pentanedione** I, Anders Abelmann, am submitting comments as a response to the NIOSH notice of request for comments regarding Chapter 6 of the NIOSH draft criteria document, addressing proposed occupational exposure limits for diacetyl and 2,3-pentanedione, dated December 26, 2013. Cardno-ChemRisk is a scientific consulting firm focused on occupational and environmental health issues, particularly as they pertain to human health risk. As such, we believe we have a professional responsibility to share information with government bodies as they explore matters germane to our expertise. We have carefully studied diacetyl and other flavorings compounds, performing original research, as well as detailed reviews and commentaries over the last decade, and have developed a substantial body of knowledge with respect to flavorings compounds and human health risk assessment. Thank you for your time and consideration of these comments.	No response required

RA-503	Anders Abelmann, Cardno-ChemRisk	**General Comments on Chapter 6** In order to provide additional transparency, we request that NIOSH provide an appendix discussing the details of the benchmark dose models that were developed for each health endpoint according to sex. The past draft document included such an appendix (NIOSH 2011) and it was a critical supplement that aided in evaluating the methodology of the analysis performed. The lack of these details provided in the current draft of the benchmark dose analysis raises questions regarding the basis for the BMCs and BMCLs presented in Table 6.6. Our questions include: • How well did the model fit the data according to sex and health endpoint? • What is the variability associated with the slopes for the various severity levels that were modeled? • How much separation was found between the curves for each severity level? • Are there consistent differences in response between males and females at each studied health endpoint? With the limited amount of detail provided in the current draft chapter, one can not address these important questions.	Additional information on model fit and parameter values is available upon request.
RA-504	Anders Abelmann, Cardno-ChemRisk	Next, the endpoints evaluated in the BMC analysis presented in Chapter 6 include minimal to mild lesions in the upper respiratory tract (URT), primarily the nasal region. The endpoints representing the deepest region of the lung appeared to have designated as minimal to mild inflammation and bronchial regeneration. One would assume that any threshold based on fixed pulmonary obstruction or bronchiolitis obliterans would likely be substantially higher. We are unaware of any other instance where NIOSH has selected the most sensitive possible response as a benchmark for their evaluation. Furthermore, several of the endpoints evaluated were observed in control animals, a concerning finding that has not been addressed or commented upon, and provides cause for concern regarding the wisdom of the approach selected. We request that NIOSH provide responses to our comments and questions above, so that other independent scientists can conduct a careful review of the results being reported.	Although the toxicity of inhaled diacetyl in the rodent is more severe in the upper respiratory tract than in the lower respiratory tract, the observation of bronchial epithelial regeneration in mice exposed to diacetyl indicates that the toxicity is sufficient to induce hyperplastic alterations. Chronic bronchial inflammation is commonly associated with the regenerative response in animals exposed to respiratory toxicants. NIOSH notes that the Gloede et al. [2011] PBPK model for diacetyl indicates that inhaled diacetyl penetrates to the lower respiratory tract in humans to a much greater extent than in rodents, so that the development of bronchial inflammation in subchronically exposed mice is suggestive of more severe

			toxicity in humans exposed to diacetyl. NIOSH further notes that chronic bioassay data for diacetyl are not yet available, and that the inflammatory response seen in the subchronic study may well progress in chronic exposures. Therefore, NIOSH considers the development of an inflammatory response in the bronchi of diacetyl-exposed mice in a subchronic study to be suggestive of the development of more severe toxicity from chronic exposures, and relevant to the development of human bronchial disease.
RA-505	Anders Abelmann, Cardno-ChemRisk	**Section-Specific Comments** <u>6.2.2.1 Benchmark concentration analysis for rats exposed to diacetyl</u> In this section, NIOSH discusses the use of a cumulative logistic model to estimate the benchmark concentrations (BMCs) and their related 95% lower confidence limits (BMCLs) for diacetyl based on the rat data from the unpublished NTP data. However, this method is not a customary approach for estimating BMCs from animal toxicity data. While this method is appropriate for evaluating studies with response data in terms of level of severity, and while it has been used previously to develop BMCs (Guth et al. 1997), it is still sufficiently novel that we would request NIOSH provide detail, including appropriate citations to the peer-reviewed literature, for why this technique is an appropriate approach for diacetyl.	The benchmark dose and benchmark concentration approach has become much more developed since its introduction [Crump 1984] and currently is an established approach for risk assessment including assessments based on animal toxicity data. Although the comment suggests that our having combined it with ordinal regression is novel, it is actually straightforward. Our revised version of Chapter 6 includes additional support and citations with the McCullagh [1980] citation being especially germane.
RA-506	Anders Abelmann, Cardno-ChemRisk	Additionally, the manner in which a significant dose-response was determined for each endpoint we feel was not adequately described. It was indicated that a likelihood ratio test for a (non-null) dose-response was performed; however, this is not a typical method for establishing dose-response relationships, and other more widely used methods, such as trend testing, are readily available. We would also request an explanation for why this was selected, ideally with references where this approach was used successfully in similar environments. In addition, it would be helpful to present the resulting p-values from performing this test either in Tables 6.6 to 6.9 or in an appendix.	Although a trend test is readily available for quantal data we didn't attempt to extend it to ordinal data because the null hypothesis is equivalent for each type of test with each having the same asymptotic Type I error rate. However, because the ordinal data have more information our test has superior power to the quantal trend test over a wide range of dose-response alternatives.

RA-507	Anders Abelmann, Cardno-ChemRisk	6.2.2.2 Benchmark concentration analysis for mice exposed to diacetyl The comments made for section 6.2.2.1 are relevant for this section as well. First, it is unclear whether NIOSH's use of a quadratic term in the mouse models represented a valid approximation, since the data were not shown and quantitative information from modeling results was also not provided. NIOSH should provide a table in an appendix with a summary of the residual errors for each dose group (for both the rat and mice data) so that the reader might be able to evaluate the magnitude of the over-prediction for the high dose groups compared to the residual errors for the low dose groups (across all models).	It is unnecessarily burdensome to calculate and examine residuals across all models. However, examination of residuals of models that are candidates for making interpretations is prudent. In response to this comment (also made by several others) about the inclusion of a quadratic term in the models of the data on mice we have added Figure 6.1 which illustrates the systematic over-prediction at high doses that results when the quadratic term is omitted. The Pearson residuals of Figure 6.1, in the revised Chapter 6, describe the deviations of the observed responses from their predicted values under the fitted linear-in-concentration model. These residuals have mean equal to zero asymptotically if the model is correct and the plot shows them together with a horizontal reference dotted line at zero. The distributions of the residuals for the data appear to be systematically shifted above zero at 50 ppm and shifted downward at 100 ppm in Figure 6.1 providing evidence against the linear-in-concentration model for these data and providing support for a modification of the dose-response model that allowed for a larger rate of increase with concentration up to approximately 50 ppm and a subsequent reduction in the rate of increase above 50 to 100 ppm. The addition of a quadratic term to the model provides such a modification. Since mice have demonstrated an ability to substantially reduce their rates of ventilation in response to inhalation exposures [Alarie and Stokinger 1973; Larsen et al. 2009] the linear-in-concentration model was modified by adding a quadratic effect parameterized so

			that its coefficient was consistent with a directly proportional reduction of ventilation in units of controls' ventilation per 100 ppm.
RA-508	Anders Abelmann, Cardno-ChemRisk	Second, while the use of minute volumes from rats in Gloede et al. (2011) seems reasonable, given that the PBPK modeling estimates from those rats were extrapolated to mice, we do not believe it is appropriate to use the minute volumes of the mice in Morgan et al. (2008) to extrapolate from rats to mice. The minute volumes of the mice in Morgan et al. (2008) were significantly higher than U.S. EPA (1994) default values, and there is no reason to believe that they would be similar to the mice studied in the NTP 90-day study. Although the minute volumes of the mice in the NTP 90-day study were not reported, an average minute volume can be determined using the default mouse coefficients and equations provided by the U.S. EPA (1994). Since the body weights of the mice in the NTP study were reported and the default values can be adjusted by the body weights of the study animals, use of this approach is more likely to accurately estimate the minute volumes for the mice in the NTP study [as opposed to inserting the minute volumes from Morgan et al. (2008)]. In summary, we request that NIOSH explain the assumptions and methodologies they employed when selecting the quadratic terms within their model. Furthermore, they should also provide their rationale for utilizing the Morgan et al. (2008) data in their calculations. Ideally, we feel that NIOSH should repeat their analysis using the U.S. EPA (1994) default minutes volumes. These additional details would serve to not only provide a more appropriate range of possible results, but also to elucidate the methodology and to provide for a more comprehensive peer review.	NIOSH believes it is more appropriate to use empirical data than defaults when empirical data are available. Clarification of the quadratic term of the model has been added to Chapter 6.

RA-509	Anders Abelmann, Cardno-ChemRisk	Section 6.2.2.3 Extrapolation of rodent benchmark concentrations to humans, page 8, lines 19 – 22 In order to produce an appropriate average concentration of diacetyl experienced by mucosal surfaces in the mainstem bronchus and the surfaces of smaller bronchi in the rat and human from Gloede et al. (2011), we suggest that NIOSH use a weighted average based on the surface area of the two sets of tissues to account for anatomical differences between the species and its respective tissue. Because of the differences in surface area, the typical average amount of diacetyl may not be representative of the average amount of diacetyl found in both tissue types. Surface area information for the different regions of the upper and lower respiratory tract for humans and rats has been measured, and is available (Mercer et al. 1994a; Mercer et al. 1994b; Yeh et al. 1979).	The NTP 90-day study pathology data do not distinguish between mainstem bronchi and smaller bronchi when summarizing bronchial toxicity; therefore, the average value for mainstem and small bronchi was used.
RA-510	Anders Abelmann, Cardno-ChemRisk	Table 6.4 Factors to rodent-to-human extrapolation of airway tissue concentrations of diacetyl, based on Gloede et al. [2011] The human-to-rat ratio for average bronchi of 28 presented in the fifth column of Table 6.4 does not match the animal-to-human PK factor of 15.7 presented in Table 6.6 for the lung endpoints. The value of 15.7 is used in Table 6.6 to estimate the BMCHEC and BMCLHEC. If the ratio of 28 is used, the BMCLHEC for the two male rat lung endpoints are 1.1 and 0.79 ppm, respectively and the corresponding BMCLREL are 0.046 and 0.033 ppm, respectively. This might be a typographical and calculation error in which case it should be corrected. However, if it is not an error, then we suggest NIOSH provide an explanation for the value used, and how/where it originated.	The rodent-to-human extrapolation factor for rat alveoli is not identical to the factor for the average bronchus. The factor for alveoli was based on the estimated fractional penetration of diacetyl through the bronchioles in the Gloede et al. PBPK model, per personal communication with John Morris. A footnote will be added to Table 6.4 to clarify this.
RA-511	Anders Abelmann, Cardno-ChemRisk	Table 6.5 Calculation of RGDR for mouse-to-rat extrapolation The mouse TB RGDR of 3.6 presented in Table 6.5 is an incorrect value. The correct mouse TB RGDR is 3.2. However, based on the human-to-rat ratios and human-to-mouse ratios in Table 6.4 for the rat and the mouse, it appears that the correct value of 3.2 was used to develop the mouse animal-to-human PK factors. This may just be a typographical error, but should be explained or corrected.	The mouse TB RGDR of 3.6 presented in Table 6.5 was in fact a typographical error, and has been corrected. We thank the commenter for pointing out this error.

RA-512	Anders Abelmann, Cardno-ChemRisk	Section 6.2.2.6 Application of uncertainty factors The application of uncertainty factors to account for uncertainty in animal-to-human extrapolation and inter-individual variability as applied by NIOSH in this section has also been applied by other investigators who have used benchmark concentration modeling of animal data in making OEL recommendations (Maier et al. 2010). However, the application of an uncertainty factor in extrapolating sub-chronic exposures to chronic exposures was specifically excluded from Maier et al. (2010). Although the possibility of progressive decline in pulmonary health outcomes is a concern, according to Maier et al. (2010), human data generated from occupational exposures to diacetyl and pulmonary function outcomes did not demonstrate progression of effects with exposure duration over the course of one year (Lockey et al. 2009). Upon a review of other less robust epidemiological studies, Maier et al. (2010) concluded that the evidence was "not definitive regarding the need to account for additional uncertainty due to the absence of full worker-lifetime studies or chronic rodent data." After considering the above, if NIOSH still wishes to include this uncertainty factor, we feel that a more detailed rationale for its use should be provided.	The current toxicological database for diacetyl does not include a full 2-year bioassay. The current studies are limited to 6, 12, and 13 weeks' duration. NIOSH believes that the possibility that greater toxicity might be observed in animals if a full 2-year bioassay was performed cannot be excluded; therefore, the application of an uncertainty factor for less than lifetime exposure is warranted.
RA-513	Anders Abelmann, Cardno-ChemRisk	Section 6.2.2.7 Joint analysis of the data on mice from the diacetyl and 2,3 pentanedione bioassays In this section, NIOSH discusses the use of complementary cumulative logistic models to determine the relative potency of 2,3-pentanedione compared to diacetyl. Similar to the logistic modeling approach used to develop the rat and mouse BMCs, NIOSH has not provided any discussion for why this approach should be appropriate, and has not provided any examples of where it may have been used in the past for similar types of evaluations. In addition, this approach appears to be overly complicated for the intended purpose and poorly explained by NIOSH. Given that there is only one study we are aware of that has performed an animal study of 2,3-pentanedione (Morgan et al. 2010), this approach may result in an over-analysis of the available data. Similar to the other dose-response modeling sections, we request that NIOSH provide the details of how they employed this analysis in order to provide greater transparency for their results.	Additional background and support of the approach to modeling of the data on rats and mice has been added to Chapter 6. Given the small numbers of rodents in each treatment group it was our goal to fully utilize the information in the ordinal response data. However, we acknowledge that the extension of the model for the analysis of the data on mice required a more thorough description, which has been added to Chapter 6. And, we acknowledge the "overanalysis" concern and developed two lines of evidence on whether the parameters were not identified by these data due to overparameterization. Both lines of evidence support the parameters of the model as having been identified, and this evidence has

			been added to Chapter 6. However, it is clear that the parameters for the female mice are not identifiable with these data unless a strong assumption about exposure duration is made and the resulting estimates are sensitive to it.
RA-514	Anders Abelmann, Cardno-ChemRisk	<u>Section 6.2.2.8 Benchmark concentration analysis using quantal models</u> As noted earlier with respect to sections 6.2.2.1, 6.2.2.2, and 6.2.2.7, NIOSH has not presented details associated with their benchmark analysis, using typical approaches for working with quantal data. An appendix that discusses these details would be helpful and provide greater transparency for their methods and results. An important question that cannot be answered with the information provided is whether or not the three types of models that were averaged together (multistage, Weibull, and log-probit) are equivalent in their ability to provide a fit for the data. An answer to this question would provide clarity as to whether or not it is appropriate to use model averaging to estimate a BMC.	A model fit statistic, the average model *P* value, has been added to Table 6.9 to clarify the issue of the goodness of fit of the averaged model.

RA-515	Anders Abelmann, Cardno-ChemRisk	<u>Section 6.3.2 2,3-Pentanedione</u> NIOSH states that according to their relative potency evaluation, the results of which are presented in Table 6.10, equal or greater toxic potency for 2,3-pentanedione relative to diacetyl cannot be ruled out based on the available data. However, according to their results presented in Table 6.10, it appears that 2,3-pentanedione has a toxic potency that is equal to or less than diacetyl, and there is no evidence to suggest that its relative potency is greater than diacetyl. We request that NIOSH provide an explanation for this apparent discrepancy. In order for an endpoint to have a relative potency that is significantly less than one (i.e., 2,3-pentanedione is more potent than diacetyl), the 95% upper confidence limit of the relative potency should be less than 1. If an endpoint has a relative potency that is significantly greater than one (i.e., 2,3-pentanedione is less potent than diacetyl), the 95% lower confidence limit should be greater than one. None of the endpoints have 95% upper confidence limits less than one, indicating that there is no evidence, based on the evaluation performed, that 2,3-pentanedione is more potent than diacetyl. In contrast, nine of the fourteen endpoints presented in Table 6.10 have lower confidence limits that are greater than one and the other five have confidence intervals that include one. This suggests that 2,3-pentanedione has a toxic potency equal to or less than diacetyl, not equal to or greater than diacetyl.	Twelve of the 14 point estimates of the relative potency of diacetyl and 2,3-pentanedione suggest that 2,3-pentanedione may be less toxic that diacetyl; however, two of the 14 estimates suggest the opposite. Furthermore, all seven estimates of relative potency among females were derived from a smaller amount of data that were devoid of information on the effect of exposure duration. This void was addressed by incorporating an assumption that the effect was identical to that of males. However, an evaluation of the duration parameter based on profiling the likelihood indicated that the seven estimates among females depended sensitively on the duration parameter and jointly so because they changed in unison. However, the seven estimates for males were not nearly as sensitive nor did they change in unison. Hence, a large degree of caution is warranted when interpreting the estimates of relative potency among the females. In addition, the overdispersion-adjusted 95% lower confidence limits for the relative potency suggest that 2,3-pentanedione could be more toxic than diacetyl in five out of the seven comparisons among males. In view of the limited data on the toxicity of 2,3-pentanedione and the uncertainty of the estimated relative toxicity of the two compounds, NIOSH believes that it is prudent to regard 2,3-pentanedione as approximately equal to diacetyl in toxicity.

EPI - 501	Anders Abelmann, Cardno-ChemRisk	**Specific comments regarding NIOSH's assertion that general causation for diacetyl and obstruction or BO has been established** NIOSH believes that there is sufficient evidence to indicate that occupational diacetyl exposure has caused bronchiolitis obliterans (BO) and other serious lung disorders (obstruction). We believe there is an abundance of highly contradictory evidence that does not allow NIOSH to make such a sweeping statement. Therefore, we suggest that NIOSH explain how their position can be consistent with the following: 1) Since most known inducers of BO in humans also cause BO in animals at low exposures, why is that diacetyl does not cause any form of deep lung damage in animals even at levels that cause death due to URT necrosis? It has previously been suggested that these observations could be the result of differences in the scrubbing mechanism between humans and animals. However, most known BO inducers in animals are highly water soluble (just like diacetyl) and would therefore be efficiently "scrubbed" in the URT (i.e., similar to diacetyl). Even if one was to accept the suggested scrubbing hypothesis, according to PBPK modeling studies performed by Morris and Hubbs (Morris and Hubbs 2009) and Gloede et al. (2011), the amount of diacetyl reaching the deep lung for the highest exposure groups in the published (Hubbs et al. 2002; Hubbs et al. 2008; Morgan et al. 2008; Morgan et al. 2012) and unpublished (NTP) animal inhalation studies is still in the ppm range, a finding that is inconsistent with the NIOSH proposition that a 5 ppb OEL is needed to sufficiently decrease the risk for reduced lung function and the development of BO in workers.	NIOSH has addressed the issue of causation, including a thorough discussion of the Hill criteria in Chapter 3 of the criteria document.

EPI - 502	Anders Abelmann, Cardno-ChemRisk	2) Claims of BO, yet only de minimis diacetyl exposures at Yatsko As noted in the NIOSH Health Hazard Evaluation (HHE) for Yatsko (NIOSH 2007), the entire workforce allegedly had BO or "BOS", yet the concentrations of diacetyl based on personal sampling were found to be below the limit of quantification. NIOSH even acknowledged that in the future they would need a more systematic approach to identify the agent that was responsible for the alleged respiratory effects in the facilities, rather than focusing almost exclusively on diacetyl. [Despite this, NIOSH did not heed their own advice and continued to focus heavily on diacetyl even after the Yatsko evaluation had been completed.] If diacetyl was the obvious cause of BO in the workforce, how does NIOSH explain the fact that diacetyl was found to be below the limit of quantification at Yatsko?	The comment that "the entire workforce allegedly had BO or 'BOS'" is incorrect. The NIOSH health hazard evaluation for Yatsko [NIOSH 2007] documents that all three of the workers employed at Yatsko had findings consistent with work-related asthma that developed during employment; one had died of status asthmaticus. Two of the three workers had HRCT scans of the chest with findings of possible bronchiolitis obliterans. With respect to exposure, diacetyl was detectable but below the limit of quantification in all thermal absorption tubes analyzed by gas chromatograph with a mass selective detector and was quantifiable in the headspace of a butter-flavored oil in the plant at 0.14 ppm. As noted in the health hazard evaluation report, the company had previously used other butter-flavored oils with unknown historical exposures. In the report, NIOSH did not attribute the work-related respiratory disease to diacetyl and discussed the multitude of other volatile organic chemicals that may have played a role. The comment has mischaracterized the NIOSH findings and report.

EPI - 503	Anders Abelmann, Cardno-ChemRisk	3) Lack of obstruction in numerous studies of "diacetyl-exposed workers" A majority of the published studies of flavoring and popcorn workers have failed to identify any evidence of an increased incidence of obstruction relative to national background and/or unexposed workers [e.g., the Apkinar-Elci et al. studies of the GML workers (2004; 2006), Kanwal et al. (2006); van Rooy et al. (2009)]. This observation also applies to many of the HHEs. Almost all of the published and unpublished studies have been conducted by NIOSH. Since BO is an obstructive disease, we ask that NIOSH explain how workers with high diacetyl exposures have often not been found to have evidence of an increased incidence of fixed obstructive lung disease.	The comment that the majority of published studies of flavoring and popcorn workers have failed to identify any evidence of an increased incidence of obstruction relative to national background and/or unexposed workers is incorrect. In the cross-sectional studies that are available, no incidence of obstruction is possible; cross-sectional studies give prevalence of obstruction. The Akpinar-Elci paper [2004] is a former worker case series of obliterative bronchiolitis with no comparison to national or unexposed workers. The Akpinar-Elci paper [2006] is a cross-sectional study of current workers in November 2001, divided into a high and a low exposure group to ascertain if exhaled nitric oxide measures might be useful as a sensitive marker. No data on obstructive abnormalities are given in this paper, but the mean percent predicted FEV_1 for each group was 92%–93%, both lower than the 100% predicted that would be expected for a population without lung disease. Many of the workers identified in November 2000 as having obstructive abnormalities had left employment by this time, and some exposure controls had been put in place. The Kanwal [2006] paper aggregates six microwave plant populations for combined analyses. Of these six plants, five had cases of clinical obliterative bronchiolitis, and four of the plants with more than eight workers had excesses of obstructive lung disease in comparison to national population estimates (Gilster-Mary Lee, Agrilink, ConAgra, and American Popcorn). One plant with only five workers who were administered spirometry had three cases of obstructive or borderline

			obstructive abnormalities, each unresponsive to bronchodilator (B.K. Heuerman Popcorn, Inc.). Thus, in contradiction to the commenter's statement that there was no evidence of increased obstruction, the individual health hazard evaluation reports document that there was increased prevalence of obstruction in nearly all microwave popcorn plants. In the Kanwal [2006] paper, comparisons were made between categories of high-exposed and lower-exposed workers based on job title, and for mixers based on tenure. In few plants "unexposed" workers were tested. In the Kanwal 2006 paper, there is ample evidence of indices pertinent to obstruction, such as obstructive abnormality, percent predicted FEV_1, and symptoms; those in higher exposure categories had worse indices pertinent to obstruction. The van Rooy [2009] epidemiologic paper followed the 2007 report of four diacetyl manufacturing workers with obliterative bronchiolitis in a historical cohort. The presence of four severe cases of a rare disease among 102 chemical operators is evidence in itself of an occupational hazard in diacetyl-exposed workers. While it is the case that there was no significant difference in percent predicted lung functions in comparison to the Dutch population, there were exposure-related differences in chest symptoms and doctor diagnoses of respiratory disease (asthma). That asthma may have been a misdiagnosis (as seen in other diacetyl-exposed populations) is consistent with the significantly different prevalences of reports of continuously having trouble with breathing, as occurs in a

			bronchodilator-unresponsive airways condition such as obliterative bronchiolitis. In addition, evidence of a relationship existed between years of exposure and pulmonary function. With respect to other investigators' work on microwave popcorn workers, James Lockey at the University of Cincinnati found excesses of obstruction in workforces of four Conagra plants. The California Department of Public Health found an excess of obstruction in workers in 16 companies and work-related risk factors for obstruction, including annual poundage of diacetyl used in the company, having a coworker with obstruction, production work, and work tenure. In NIOSH investigations of flavoring-exposed workers in industries other than microwave popcorn, we have found significant excesses of obstructive abnormality in a flavoring plant and a coffee manufacturing plant or cases of obliterative bronchiolitis in small flavoring. We have reported no excess of obstruction in only two flavoring manufacturing plants, one of which had a substantial excess of restrictive spirometric abnormalities. In conclusion, it appears that the commenter has selectively picked references and then inaccurately reported on the findings. In addition, we have now published the observations that obliterative bronchiolitis demonstrated pathologically can be accompanied by obstructive, restrictive, and normal spirometry. If we use the criterion of any spirometric abnormality, all microwave popcorn plants and flavoring manufacturing plants have had cases consistent with obliterative bronchiolitis. Respiratory symptom prevalence

			has usually been higher than spirometric abnormality, with the larger studies showing excess symptoms compared to national population prevalences.

EPI - 504	Anders Abelmann, Cardno-ChemRisk	4) van Rooy et al. (2009) van Rooy et al. (2009) is the only study thus far of workers exposed primarily to diacetyl (as opposed to the NIOSH studies, where the workers being studied were exposed to numerous chemicals in the workplace). These workers actually showed an improvement in lung function with increasing diacetyl exposure. We ask that NIOSH explain how this is consistent with their conclusion that a causal relationship exist between exposure to diacetyl and development of BO, and demonstrates a dose/response relationship for exposure and observed disease.	The van Rooy study had only 36 historical area exposure measurements, of which 26 were between 1995 and 2001, and 10 were after 2001 before the plant closed in 2003. The plant had only four task-based samples when workers tapped diacetyl containers. Thus the exposure of individuals was estimated based on production volume, enclosure of processes, conversion of batch processes to continuous processes, automation that decreased exposure hours per day, and tenure in different time periods. Accordingly, the likely miscategorization of exposure may have obscured quantitative exposure-response relations, as discussed by the authors. The paper does report higher risks for obliterative bronchiolitis, respiratory symptoms, and lung function decrements within highly exposed groups of workers. The authors suggest that their finding of higher pulmonary function with increasing exposure proxies may be a reflection of a healthy worker effect bias, which could not be evaluated with the available information. The authors also raise the possibility that peak exposures may be a risk factor to explain process-related risk of indices of respiratory disease. The van Rooy paper remains important because diacetyl was the principal exposure among three other exposures that were low compared to occupational standards (acetaldehyde) or not known to cause obliterative bronchiolitis (acetic acid and acetoin). Thus the four cases and process-related risks are supportive of diacetyl causing obliterative bronchiolitis and indices of occupational respiratory disease. Science usually proceeds in an iterative fashion with

			accumulation of consistent evidence from many studies. Each paper may have limitations and individually may not show a conclusive relationship between diacetyl exposure and health outcome.
EPI-505	Anders Abelmann, Cardno-ChemRisk	5) Diacetyl in cigarette smoke A recent study (in press) has shown that cigarette smoke may contain upwards of 200-300 ppm diacetyl. This means that many smokers have much higher cumulative and peak diacetyl exposures compared to any worker cohort that NIOSH has ever studied. Yet, there have not been any reports of an increased incidence of BO among smokers in the general population. This observation is directly contradictory to NIOSH's assertion that diacetyl causes BO, and we would appreciate comments from NIOSH as to how these recent findings could be compatible with their views. We will be happy to provide a copy of this paper once it is available for dissemination.	NIOSH has described the Pierce et al. paper [2014] and the relevant points in Chapter 4.

EPI - 506	Anders Abelmann, Cardno-ChemRisk	**Specific comments regarding the validity and practicality of the proposed REL of 5 ppb** 1) The use of numerous common consumables would result in an exceedance of the proposed REL of 5 ppb. As noted above, cigarette smoke contains 200-300 ppm diacetyl. Furthermore, concentrations of naturally occurring diacetyl from coffee processing and in the headspace of a glass of wine have been shown to far exceed 5 ppb. There are likely numerous other currently marketed and consumed products worldwide that contain diacetyl (naturally or added as an ingredient) with human airborne exposures to diacetyl that regularly exceed 5 ppb. We request that NIOSH explain how they expect the proposed REL to be practically implemented. Will every coffee shop, designated "smoking area," ice cream parlor, brewpub and winery be required to install engineering controls to protect the workers and consumers from developing fixed obstructive lung disease?	NIOSH has discussed the REL and relevant achievability issues in Chapter 7. NIOSH RELs are applicable to the occupational environment over an 8-hour work shift or 15-minute time period when compared to a STEL.
EPI - 507	Anders Abelmann, Cardno-ChemRisk	2) Off-site exposures to respiratory irritants in the GML cohort The proposed NIOSH REL is based on an evaluation of the GML workers. However, as described by Kreiss et al. (2002a), it is known that a large fraction of the workers had off-site exposures to known respiratory irritants, including chemicals that have been associated with BO. We would like to see what sort of analysis NIOSH has done to exclude these confounding exposures.	As documented in the Kreiss et al. [2002] New England Journal of Medicine article, we demonstrated that our internal comparison group without diacetyl production exposures were significantly more likely to have at least one outside exposure than the microwave popcorn production group. Quartiles of increasing cumulative exposure to diacetyl had significantly decreasing rates of farming exposures. In light of these two observations, we did not pursue additional epidemiologic analyses of outside exposures in relation to health outcomes. From an epidemiologic point of view, there was no reason to think that outside exposures would correlate with diacetyl exposure and hence confound our analyses of diacetyl exposure-response relations. Outside exposures are primarily of interest in the differential diagnosis of conditions in individuals,

			as performed by clinicians rather than epidemiologists.
EPI - 508	Anders Abelmann, Cardno-ChemRisk	3) NIOSH did not evaluate other workplace chemicals at the GML facility Based on the available information, hundreds of volatile organic compounds were present in the mixing room at GML, many of them respiratory irritants. We ask to see the analyses conducted by NIOSH that exclude these compounds as possible causes of any symptoms in the GML workers. In a 2002 letter to the editor of the New England Journal of Medicine, Taubert et al. (2002) indicated that they believed that tannins may have played a causal role in the development of respiratory disorders, including BO, in the GML workers. In response, Kreiss noted that NIOSH did not sample for tannins at GML (2002b). In the absence of a more comprehensive response to this suggestion, it is unclear what analyses did NIOSH conduct to exclude tannins. Similarly, in the NIOSH HHE for GML, respirable dust exposures were highly correlated with respiratory disorders [an observation that was not included in the Kreiss et al. (2002a) publication]. What analysis did NIOSH conduct to eliminate respirable dusts as a possible cause? (We once again note that in van Rooy et al. (2009), where no dusts or tannins were present, lung function improved with increasing diacetyl exposure.)	NIOSH made no attempt to exclude tannins as a causative agent for obliterative bronchiolitis at Gilster-Mary Lee. We made no attempt to exclude respirable dusts as a possible cause. With respect to our presentation of exposure-response relations between increasing quartiles of cumulative respirable dust exposure and spirometric obstruction, abnormal spirometry, and percent predicted FEV_1 (given in the August 22, 2001, interim report to Gilster-Mary Lee), the increase in these spirometric indices was not smooth, as it was for diacetyl quartiles. The highest quartile was the third quartile and not the highest fourth quartile. In contrast, each of the cumulative diacetyl quartiles had worse spirometric indices than the preceding quartile, lowest to highest. The preponderance of evidence favored diacetyl as the cause of occupational respiratory ill health over respirable dust.
EPI - 509	Anders Abelmann, Cardno-ChemRisk	Thank you for the opportunity to comment on this very important issue. The use of proven scientific methodology is critical to enable reproducibility and we believe that the comments and suggestions outlined herein will assist in this process and help move the science forward. We would be more than happy to provide further insight at your request. Please direct any communication to anders.abelmann@cardno.com.	No response required

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