Miller, Diane M. (CDC/NIOSH/EID)

From: hondobear@aol.com
Sent: Wednesday, February 09, 2011 3:34 PM
To: NIOSH Docket Office (CDC)
Subject: Comments for Docket NIOSH-189
Attachments: FEMA NIOSH Comments 2911.pdf

Dear Sir/Ms.:
Attached are the comments of the Flavor and Extract Manufacturers Association of the United States (FEMA) on NIOSH's request for information on flavoring substances that may be used as substitutes for diacetyl (76 *Fed. Reg.* 1434; 10 January 2011).
Sincerely,
John Hallagan
FEMA

FLAVOR AND EXTRACT MANUFACTURERS
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9 February 2011

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

RE: Request for Information on
2,3-Pentanedione and Other
Alpha-Diketones Used as
Diacetyl Substitutes.
Docket Number NIOSH-189
76 *Fed. Reg.* 1434. 10 January 2011

Dear Sir/Ms.:

The Flavor and Extract Manufacturers Association of the United States (FEMA) is pleased to respond to the request for information on flavoring substances, including 2,3-pentanedione, that the National Institute for Occupational Safety and Health (NIOSH) suggests may be used as "substitutes" for the flavoring substance, diacetyl. 76 *Fed. Reg.* 1434 (10 January 2011).

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 1996 (FEMA, 2004). Since 1996, FEMA has sponsored four extensive workshops (1997, 2002, 2004, and 2007) which have included training sessions for flavor and food manufacturers. In addition to the workshops, since 2001 FEMA has held numerous information sessions for its members and others. This extensive sharing of information and the resulting awareness has led flavor manufacturers to adopt

appropriate respiratory health and safety measures to protect their flavor manufacturing workers.

Also 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. 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 late 2010 in the implementation of the first workplace safety regulation related specifically to flavor manufacturing.

Flavoring Substances and Their Regulation in the United States

The inclusion of flavoring substances in food is a critical part of food processing and manufacturing in the U.S. How flavors are "compounded" and used in food manufacturing was described by Hallagan and Hall (2009). 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 (Hallagan and Hall, 1995; 2009). Flavoring substances permitted for use in the U.S. may have regulatory status (i.e. "premarket approval") either as substances determined to be approved food additives or substances determined to be "generally recognized as safe" (GRAS) by the FDA, or as flavoring substances determined to be GRAS by FEMA as provided for in FFDCA Section 201(s).

Many flavoring substances have both FDA and FEMA GRAS regulatory status. FDA regulatory status for the vast majority of flavoring substances, including the substances of interest here, means that they may be added to food generally 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 important to note that GRAS evaluations, by FDA or by FEMA, do not require an assessment of potential inhalation toxicity because the "regulated" route of exposure for GRAS substances is ingestion as constituents of food (Hallagan and Hall, 2009). Hence, there generally have been few inhalation toxicity studies conducted on GRAS substances, including flavoring substances.

Information Requested by NIOSH

NIOSH has requested information on 2,3-pentanedione and "other alpha-diketones used as diacetyl substitutes" which may include "those used in food manufacturing such as 2,3-hexanedione and 2,3-heptanedione." 76 *Fed. Reg.* 1434, 1435. We are providing information on four alpha-diketone flavoring substances: 2,3-pentanedione, 2,3-hexanedione, 3,4-hexanedione, and 2,3-heptanedione. In addition, we are providing information on two other flavoring substances and while they are not appropriately classified as alpha-diketone substances they are

structurally-related and therefore of interest as "substitutes" for diacetyl - acetoin (an alpha-hydroxy ketone substance) and diacetyl trimer (a recently developed diacetyl polymer).

In addition to U.S. regulatory status, all of these substances were determined to be safe for ingestion as constituents of food by the Joint FAO/WHO Expert Committee on Food Additives who published reviews of the relevant data upon which their decisions were based (JECFA, 1999; JECFA, 2010). The JECFA reviews contain a thorough description of the relevant oral exposure data for these substances and we do not discuss these data here focusing instead on dermal and inhalation exposure that are more relevant to potential workplace exposures.

2,3-Pentanedione

2,3-Pentanedione (acetyl propionyl; CAS 600-14-6; FEMA 2841; FDA 21 CFR 172.515) is described as having a "creamy, penetrating, cheesy, oily, sweet, buttery, almond-like . . ." organoleptic profile (Zviely, 2009) 2,3-Pentanedione occurs naturally in butter, bread, milk, yogurt, chicken and alcoholic beverages (Zviely, 2009). 2,3-Pentanedione has a low calculated vapor pressure (6.8 mm Hg at 20 ºC) and a boiling point of 108 ºC. Thus, it is considered less volatile than diacetyl. 2,3-Pentanedione had a modest estimated annual poundage of 4,590 lbs. based on data gathered for calendar year 2005 (Gavin et al., 2008). It is possible that the poundage survey currently underway for flavoring substances used during calendar year 2010 may show an increase due to increased use as a substitute for diacetyl.

In addition to the studies cited in the *Federal Register* notice (76 Fed. Reg. 1434, 1435) we have identified some additional studies. Moreno (1977) published an acute oral LD50 of 3000 mg/kg in rats and an acute dermal LD50 of >2500 mg/kg in rabbits. Neat 2,3-pentanedione applied to rabbit skin for 24 hours was moderately irritating (Moreno, 1977), but no irritation was observed in humans exposed to 4% 2,3-pentanedione (in petrolatum) in a 48-hour closed patch test (Epstein, 1976). Furthermore, no sensitization was observed with repeated application of 4% 2,3-pentanedione in a Kligman maximization test performed on human volunteers (Epstein 1976).

Flake et al. (2010) administered 2,3-pentanedione (140 mg/kg) to male Sprague-Dawley rats as a single intratracheal instillation and compared the effects to diacetyl and acetoin. Rats exposed to 2,3-pentanedione demonstrated similar patterns of bronchial/bronchiolar epithelial injury, inflammation, and repair as those exposed to diacetyl or acetoin. Intratracheal instillation is a non-physiologic route that the authors state may not be relevant to human exposure.

2,3-Hexanedione

2,3-Hexanedione (acetyl butyryl; CAS 4437-51-8; FEMA 2558; FDA 21 CFR 172.515) is described as having a "creamy, caramelic, fruity, toasted brown" organoleptic profile (Zviely, 2009). 2,3-Hexanedione is naturally occurring in clams, beer, and coffee (VCF, 2010). 2,3-Hexanedione has a low calculated vapor pressure

(0.3 mm Hg at 20 ºC) and a boiling point of 128 ºC. Thus, it is substantially less volatile than diacetyl. 2,3-Hexanedione had a low estimated annual poundage of 400 lbs. based on data gathered for calendar year 2005 (Gavin et al., 2008). It is possible that the poundage survey currently underway for flavoring substances used during calendar year 2010 may show an increase due to increased use as a substitute for diacetyl.

Acute oral and dermal LD50s in rats exceeded 5000 mg/kg in rats and rabbits, respectively (Moreno, 1977). Dermal application of neat 2,3-hexanedione to rabbit skin for 24 hours induced redness and edema (Moreno, 1977). No irritation was observed when 4% 2,3-hexanedione (in petrolatum) was applied to human skin in a 48-hour closed-patch test. No sensitization occurred with repeated application in a Kligman maximization test performed at the same concentration (Epstein, 1977). We are not aware that inhalation studies have been performed on this substance.

3,4-Hexanedione

3,4-Hexandione (dipropionyl; CAS 4437-51-8; FEMA 3168; FDA 21 CFR 172.515) is described as having an aromatic, toasty, burnt, buttery, nutty, caramel-eggy, pungent odor." (Burdock, 2005). 3,4-Hexanedione is naturally occurring in coffee and honey (VCF, 2010). 3,4-Hexanedione has a low calculated vapor pressure (1.0 mm Hg 20 ºC) and is substantially less volatile than diacetyl.

3,4-Hexanedione had an extremely low estimated annual poundage of 13 lbs. based on data gathered for calendar year 2005 (Gavin et al., 2008). It is possible that the poundage survey currently underway for flavoring substances used during calendar year 2010 may show an increase due to increased use as a substitute for diacetyl. There does not appear to be relevant toxicology data available on this flavoring substance which appears to have been rarely used to formulate flavors based on the extremely low poundage from the most recent survey (Gavin et al., 2008).

2,3-Heptanedione

2,3-Heptanedione (acetyl valeryl; CAS 977043-66-5; FEMA 2543; FDA 21 CFR 172.515) is described as having a "buttery, cheesy, oily" organoleptic profile (Zviely, 2009). 2,3-Heptanedione is naturally occurring in mushrooms, fermented soy, and tomato (VCF, 2010). 2,3-Heptanedione boils at low temperature (62°C at 20 mm Hg).

2,3-Heptanedione had an extremely low estimated annual poundage of 78 lbs. based on data gathered for calendar year 2005 (Gavin et al., 2008). It is possible that the poundage survey currently underway for flavoring substances used during calendar year 2010 may show an increase due to increased use as a substitute for diacetyl.

There are few data available on 2,3-heptanedione, a rarely used flavoring substance. No irritation occurred with 5% 2,3-heptanedione (in petrolatum) in a 48-hour closed patch test on human volunteers (Kligman, 1978). Sensitivity reactions were observed in 2 of 25 volunteers repeatedly exposed to 5% 2,3-heptanedione in a Kligman maximization test (Kligman 1978).

Acetoin

Acetoin (acetyl methyl carbinol; CAS 513-86-0; FEMA 2008; FDA 21 CFR 182.60) is described as having a "sweet, buttery, creamy, sour, fatty, vanilla" organoleptic profile (Zviely, 2009). Acetoin is naturally occurring in a number of foods including asparagus, milk and milk products, cheddar cheese, sherry, tea, coffee, wine, and vinegar (VCF, 2010). Acetoin has a low calculated vapor pressure (6.2 mm Hg at 20 ºC) and high boiling point (148 ºC) and is considered less volatile than diacetyl. Acetoin had a moderate estimated annual poundage of approximately 130,000 lbs. based on data gathered for calendar year 2005 (Gavin et al., 2008). It is possible that the poundage survey currently underway for flavoring substances used during calendar year 2010 may show an increase due to increased use as a substitute for diacetyl.

The acute dermal LD50 for acetoin was >5000 mg/kg in rabbits (Moreno 1977). Neat acetoin produced moderate irritation when applied to the abraded skin of rabbits for 24 hours (Moreno, 1977). A concentration of 10% in petrolatum produced no irritation in a 48-hour closed-patch test and no sensitization with repeated application in a Kligman maximization test performed on human volunteers (Epstein 1976).

Flake et al. (2010) administered acetoin (125 mg/kg) to male rats as a single intratracheal instillation and compared the effects to those of acetyl propionyl (2,3-pentanedione) and diacetyl. The authors concluded that rats exposed to acetoin demonstrated similar patterns of bronchial/bronchiolar epithelial injury, inflammation, and repair as those exposed to diacetyl or acetyl propionyl.

Diacetyl Trimer

Diacetyl trimer (2,5-diacetyl-3a,5,6,6a-tetrahydro-6a-hydroxy-2,3a,5-trimethylfuro[2,3-d]-1,3-dioxole in the form of one of its stereoisomers or in the form of mixture consisting of or containing 2 or more of the stereoisomers; CAS 18114-49-3; FEMA 4303) has been proposed as a substitute for diacetyl. Diacetyl trimer imparts a soft, buttery flavor and lacks the unpleasantly sharp odor of diacetyl. Diacetyl trimer is considered less volatile than diacetyl, and does not substantially decompose when heated to 60-100 ºC. However, it is important to note that under certain manufacturing and food preparation conditions (i.e., in the presence of heat and water) diacetyl trimer will "liberate" diacetyl.

Diacety trimer only recently was granted GRAS status (in 2007) and therefore permitted for use in food. Consequently, there are not yet annual estimated poundage data available. Little toxicology information is available for this

substance. However, when the diacetyl trimer is subjected to processing conditions that include heating in the presence of water, diacetyl will be liberated and therefore the relevant toxicology data on diacetyl should be applied to the trimer.

We would be pleased to provide copies of the references listed below upon request. We would also 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.

Sincerely,

John B. Hallagan

References

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