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

From: David Egilman [degilman@neveragainconsulting.com]
Sent: Sunday, August 28, 2011 9:15 AM
To: David Egilman; NIOSH Docket Office (CDC)
Cc: hank@egilman.com; kxk2@cdc.gov; Degilman@egilman.com; hank@egilman.com
Subject: RE: 245 - Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-pentanedione

The attachments will be sent separately since your email system rejected them.

August 28, 2011

Dear Sir/Ms:

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.

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-Pentanedione 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 114(1), 316. I have attached this poster. This study shows that pentanedione is more toxic than diacetyl.

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.

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.

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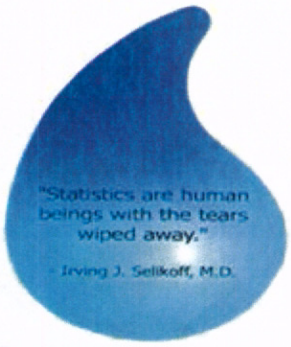
Letters to NEJM are peer reviewed prior to publication by the editors and often by others and reviewed by the authors of the paper to which they refer.

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.

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.



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A Proposal for a Safe Exposure Level for Diacetyl

DAVID S. EGILMAN, JOHN HENRY SCHILLING, LELIA MENENDEZ

Diacetyl is a naturally occurring compound that has been used in concentrated form as a food additive, particularly in butter flavorings. Inhalation of diacetyl and butter flavoring fumes has caused a variety of respiratory diseases in workers and consumers including bronchiolitis obliterans (BO), a relatively rare, severe, and irreversible lung disease. A safe level of exposure to diacetyl has not been established. We review the literature on diacetyl and flavoring toxicity and critique a recent proposal for an occupational exposure limit (OEL) of 0.2 ppm for diacetyl. We present unpublished data and novel analyses in support of our proposal for a safe level of exposure. Our findings indicate that a safe level of exposure exists around or below a time-weighted average of 1 ppb for an eight-hour workday. The levels of exposure we found to be unsafe include ranges that popcorn consumers may potentially be exposed to, indicating a risk of severe lung disease (including BO) for some consumers. *Key words*: diacetyl, butter flavorings, popcorn lung, occupational exposure limit, bronchiolitis obliterans, safe exposure level, occupational disease

INT J OCCUP ENVIRON HEALTH 2011;17:122–134

Diacetyl (IUPAC systematic name: 2,3-butanedione) is a vicinal diketone (two adjacent C=O groups) with the molecular formula $C_4H_6O_2$.[1] Diacetyl occurs naturally in a variety of foods including milk, milk products, and coffee, and is produced during the fermentation of alcoholic beverages.[2] It is used as a food additive because of the buttery flavor it imparts.[2] Prior to the advent of microwave popcorn, diacetyl levels in finished products were relatively low.[3] Generally, exposure levels from these products were below the measurable threshold although often above the odor threshold of 1.5 ppb.[3,4] The need to produce highly concentrated flavorings for microwave popcorn resulted in much higher diacetyl exposure levels in worker and consumer breathing zones, often in the range of 4–13 ppm.[5]

Inhalation of diacetyl and butter flavoring fumes has caused lung disease in workers, including bronchiolitis obliterans (BO), a relatively rare, severe, and irreversible lung disease.[2] As a result, hundreds of workers and some popcorn consumers have sued diacetyl, flavoring, and microwave popcorn manufacturers for compensation, resulting in hundreds of millions of dollars in verdicts.[6]

In response to this recent litigation, companies that use diacetyl in food manufacturing hired Toxicology Excellence for Risk Assessment (TERA) to develop a proposal for a "safe level" of diacetyl for use in defending lawsuits.

> The current regulatory framework being proposed by California and Federal OSHA will likely be limited to establishing performance based exposure standards without establishing either an exposure limit or a threshold for safety for diacetyl. This will leave employees in the food processing industries confused regarding the safety of diacetyl as well as *continue to expose companies who handle diacetyl to potential implied legal liability.* [Emphasis added][7]

TERA'S OCCUPATIONAL EXPOSURE LIMIT IS DERIVED FROM SELECT LIMITED DATA

The TERA researchers proposed an occupational exposure limit (OEL) of 0.2 ppm for a permissible exposure to diacetyl over the course of an eight-hour workday.[8] TERA's proposed OEL is based on a single animal experiment involving a total of 30 exposed mice and 10 controls, only 15 of which were exposed for up to 30 hours per week for 12 weeks.[9] As a sponsor company, ConAgra was "asked to review the material and provide technical comment" (pg. 295). ConAgra did not provide TERA with confidential data they possess relating to diacetyl's toxicity (Melissa Kohrman-Vincent, personal communication, 7/23/2010). This confidential data, which has been released pursuant to legal discovery includes the underlying data from an epidemiological study suggesting a health risk to popcorn consumers, and a quantitative structure activity relationship (QSAR) analysis, which found that diacetyl's toxicity was comparable to isocyanates.[10–12] Isocyanates have a TLV of 1 ppb, 200 times lower than TERA's proposed OEL for diacetyl.[13]

TERA Fails to Include Epidemiological Studies in their OEL Determination

As previously noted, TERA bases their OEL solely on the analysis of one mouse experiment from a single paper.[9] The use of quality epidemiology studies in determining human exposure guidelines is well established. For example, a review of the use of animal studies to determine human risks states that "Threshold

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Disclosures: David Egilman has served as a consultant at the request of plaintiffs in diacetyl/flavorings litigation. John Henry Schilling and Lelia Menendez have served as research assistant consultants to plaintiffs in diacetyl/flavorings litigation.

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Emissions from Cooking Microwave Popcorn

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This study characterized chemicals released into a chamber in the process of cooking microwave popcorn. Seventeen types of microwave popcorn from eight different brands were studied. The work proceeded in two phases: phase one investigated chemicals emitted during popping and opening, phase two investigated chemicals emitted at discrete intervals from 0–40 minutes post-pop opening. The research was performed using a microwave oven enclosed in a chamber with ports for air sampling of particulate matter (PM) and volatile organic compounds (VOCs). VOCs in the air samples were identified and quantified using gas chromatography/mass spectrometry (GC/MS). PM was characterized using both an aerodynamic particle sizer (APS) and a scanning mobility particle sizer (SMPS) to cover a full range of emitted sizes. The compounds measured during popping and opening included butter flavoring components such as diacetyl, butyric acid, acetoin, propylene glycol, 2-nonanone, and triacetin and bag components such as p-xylene and perfluorinated alcohol 8:2 telomer. The greatest chemical quantity is emitted when the bag is opened post-popping; more than 80% of the total chemical emissions occur at this time.

Keywords air sampling, diacetyl, perfluorinated compounds, volatiles

INTRODUCTION

This study identified and quantified chemical emissions released in the process of popping and opening a bag of microwave popcorn. Microwave popcorn, a product that is used extensively worldwide and in a large number of households and businesses in America, is thought to have a detrimental effect on lung health in the manufacturing industry (Kreiss et al., 2002; Kullman et al., 2005). This research was initiated in response to an occupational incident in 2000 in which eight workers at a microwave popcorn production plant in Missouri were diagnosed with the severe lung disease, bronchiolitis obliterans (Kreiss et al., 2002; Kullman et al., 2005). These plant workers were exposed to not only the raw corn and salt used in microwave popcorn production, but the oil, flavorings, and the microwaveable packagings (Kreiss et al., 2002; Kullman et al., 2005). The National Institute for Occupational Safety and Health (NIOSH) identified more than 100 volatile organic compounds inside of the Missouri plant (Kullman et al., 2005). Quality control (QC) personnel, who pop corn and open bags, had a high incidence of respiratory and dermal symptoms (Kanwal et al., 2006; Kreiss et al., 2002). NIOSH scientists confirm that workers in the QC areas have shown an increased risk of lung disease (Kanwal et al., 2006). This prompted EPA's interest in what is released into the immediate environment when microwaving popcorn, and its potential to impact indoor air quality.

Seventeen types of microwave popcorn from eight different brands were studied. Data on volatile chemicals produced from microwave popcorn packaging during cooking were documented previously in 1993 (McNeal and Hollifield, 1993; Risch, 1993), but some manufacturers have changed their bag formulations. Limited data were available on the indoor concentrations of particulate matter less than 10 microns in diameter (PM_{10}) and particulate matter less than 2.5 microns in diameter ($PM_{2.5}$) released during the popping of a single type of microwave popcorn (Fortmann et al., 2001). No data on particulate matter (PM), characterization, flavoring, or corn emissions during the cooking of microwave popcorn, was found in the literature. Thus, this is the first study to take a comprehensive look at chemicals released while microwaving an entire conventional microwave popcorn product.

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Lung Function and Pathogenesis of Bronchiolitis Obliterans in Rats Exposed to 2,3-Pentanedione

Morgan, DL[1], Price, HC[2], Johnson, CL[3], Jokinen, MP[3], Gwinn, WM, and Flake, GP[1]

[1]National Institute of Environmental Health Sciences, DHHS, NIH, RTP, NC, USA; [2]Alion Science and Technology, RTP, NC, USA; [3]Charles River Laboratories, RTP, NC, USA

Abstract

2,3-Pentanedione (PD) is a vicinal diketone used as a replacement for diacetyl in artificial butter flavorings. PD was recently shown to cause bronchiolitis obliterans (BO) in rats after 12 exposures to 200 ppm. The objectives of this study were to characterize airway lesions at early time points, to determine if early lesions progress to fibrosis after exposure is terminated, to determine if fibrosis progresses after termination of exposure, and to determine if lung function is impaired. Male, Wistar-Han rats were exposed to air or 200 ppm PD 6hr/day, 5 days/wk for 1, 3, or 7 exposures. On the morning following each time point the lungs were harvested from control rats (4) and half the exposed rats (6) for histopathology. The remaining exposed rats (6/timepoint) were held without additional exposure and lungs harvested on day 17. Additional rats received 12 exposures to air or 200 ppm PD. After the last exposure lung function was evaluated in half the rats and then the lungs were harvested (day 17). The remaining rats were held an additional 2 wks without exposure before evaluating lung function and harvesting lungs (day 30). With the exception of minimal bronchial necrosis in 1 rat, neither bronchial epithelial necrosis, nor fibrosis of bronchi, bronchioles, or alveolar walls occurred after 1 or 3 exposures, even when animals were held for 2 wks prior to sacrifice. Bronchial intraluminal and intramural fibrosis were observed immediately after 7 exposures, and when held for an additional wk after exposure. When rats were subjected to 12 exposures and then held an additional 2 wks, fibrosis was also observed in the alveolar walls. Airway resistance was 8-fold greater on day 30 compared to day 17 after 12 exposures to PD. Furthermore, dynamic and static lung compliance were decreased by 76% and 46%, respectively, suggesting that lung function progressively worsens after terminating exposure. This study provides important information needed to understand the pathogenesis of BO and to identify potential treatment strategies.

Introduction

2,3-Pentanedione (PD, acetyl propionyl) is a commonly used constituent of synthetic flavorings used to impart a butter, strawberry, caramel, fruit, rum, or cheese flavor in beverages, ice cream, candy, baked goods, gelatins and puddings. PD also occurs naturally as a fermentation product in beer, wine, and yogurt, and is released during roasting of coffee beans. The US Food and Drug Administration (FDA) granted PD "generally recognized as safe" status as a food additive, and consumption of the low levels of PD present in food products has not been reported to cause adverse health effects.

PD is structurally similar to diacetyl (2,3-butanedione), a component of artificial butter flavoring that has been implicated as a cause of bronchiolitis obliterans (BO) in microwave popcorn packaging and flavoring industry workers. BO is a potentially fatal lung disease characterized by bronchial wall thickening and constrictive bronchiolitis. Because of growing concerns about the toxicity of inhaled diacetyl, it is being replaced by PD in some artificial flavorings.

Recently we reported that inhalation exposure to 200 ppm PD for 2-weeks caused BO in rats; however, the pathogenesis of these lesions has not been investigated. The objectives of this study were to characterize airway lesions at early time points during the 2-week exposure, to determine if early lesions progress to fibrosis after exposure is terminated, to determine if airway fibrosis progresses after termination of exposure, and to determine if lung function is impaired.

Materials and Methods

Animals

Male, 6 -7 wk old Wistar-Han rats (CR - Raleigh, NC) were individually housed for 7 days after arrival, and were acclimated to the inhalation exposure chambers for 3 days just prior to exposure. Food was removed during the exposures and water was always available.

Vapor Generation and Monitoring

2,3-Pentanedione (≥ 99.0% pure) was purchased as a single lot from Acros Organics, Morris Plains NJ. The vapor generation system consisted of a metering pump (Fluid Metering, Inc., Syosset, NY) and a heated vaporization flask. Chemical was metered into a flat bottomed flask mounted on top of a stirring hot plate maintained at 65°C. Using compressed breathing air the vapor was swept from the flask and into the process air stream where it was further diluted before entering the exposure chamber. Chamber concentration was monitored using an FTIR spectrophotometer (Hamilton Sunstrand, Pomona, CA).

Inhalation Exposures

Rats were exposed to 0 (air) or 200 ppm PD in Hazleton 1000 exposure chambers, 6 hr/d, 5 d/wk for 1, 3, or 7 exposures. On the morning following each time point the lungs were harvested from control rats (4) and half the exposed rats (6). The remaining exposed rats (6/timepoint) were held without additional exposure and lungs harvested on day 17. Additional rats received 12 exposures to air or 200 ppm PD. After the last exposure lung function was evaluated in half the rats and then the lungs were harvested (day 17). The remaining rats were held an additional 2 wks without exposure before evaluating lung function and harvesting lungs (day 30).

Pulmonary Function Assessment

Pulmonary function was measured using the FlexiVent mechanical ventilator and data acquisition system (SCIREQ, Montreal, PQ, Canada) on the morning after 12 exposures (day 17), and 2-weeks after 12 exposures (day 30) to PD (n = 8) or air (n = 4). Values for total resistance (R), dynamic compliance (C) and static compliance (Cst) obtained after each cycle were averaged for each animal and these values were then averaged within each experimental group.

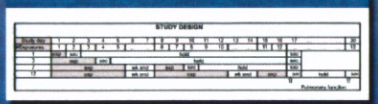
Histopathology

Animals were euthanized (Nembutal/thoracotomy) and the lungs + ½ trachea, were collected and fixed in 10% formalin, then processed, embedded in paraffin, sectioned and mounted on slides. Slides were stained with H&E and evaluated by light microscopy. Lesions were diagnosed and their severity graded on a 4 point scale of 1=minimum, 2=mild, 3=moderate, and 4=marked. The severities of bronchial intraluminal and intramural fibrosis were graded according to the number of lesions present. The total number of lesions of each type was determined and the severity was graded based upon the total number of individual fibrotic lesions present as follows: 1-5 lesions= +1, 6-10 lesions = +2, 11-15 lesions = +3, and >15 lesions = +4. In addition the total number of combined intraluminal and intramural fibrotic lesions in each lung was determined and a Fibrosis Score, representing the total amount of bronchial and bronchiolar fibrosis in the lung, was assigned to the lung using the same grading criteria presented previously.

Statistical Analysis

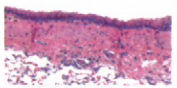
Statistically significant ($p<0.05$) treatment-related changes in pulmonary function were determined by 1-way ANOVA and Tukey's multiple comparison test.

Timeline



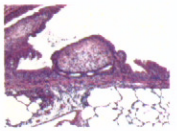
Results

Bronchus: Normal Mucosal Epithelium



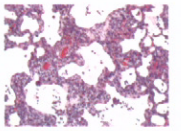
Control rat sacrificed on Day 8. The normal mucosal epithelium of the bronchus consists of uniform, well differentiated, columnar ciliated cells.

Bronchus: Intraluminal Fibrosis



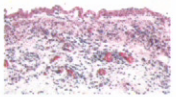
12 Exposures, sacrifice on Day 13. Polypoid fibrous excrescences project into the bronchial lumen.

Alveolar Wall (Interstitial) Fibrosis



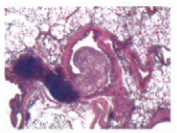
12 Exposures, sacrifice on Day 30. The alveolar walls are markedly thickened by fibrosis and chronic inflammation.

Bronchus: Epithelial Necrosis



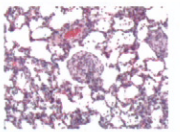
5 Exposures, early death on Day 7. The mucosal epithelium has been replaced by a thin layer of fibrin and cell debris. Inflammatory infiltrate is present in the underlying tissue.

Bronchus: Intraluminal Fibrosis



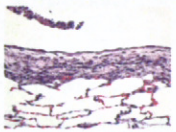
12 Exposures, sacrifice on Day 13. This intraluminal fibrous polyp largely occludes the lumen of the bronchus. The adjacent bronchial-associated lymphoid tissue is prominent.

Intraalveolar Fibrotic Polyp



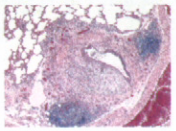
12 Exposures, sacrifice on Day 30. Fibrotic polyps, similar to those noted in the bronchi, project into alveolar spaces.

Bronchus: Epithelial Regeneration



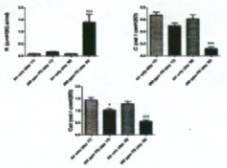
12 Exposures, sacrifice on Day 13. The normal columnar epithelium has been eroded and replaced by a single layer of flattened and elongated regenerating epithelial cells which are attempting to cover the denuded surface.

Bronchus: Intramural Fibrosis

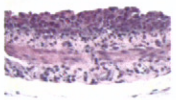


12 Exposures, sacrifice on Day 30. The bronchial lumen is largely occluded by circumferential, constrictive fibrous proliferation within the wall of the bronchus.

Delayed Impairment of Pulmonary Function in PD-exposed Rats

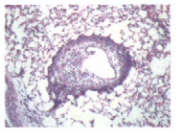


Bronchus: Regenerative Epithelial Hyperplasia with Mild Atypia



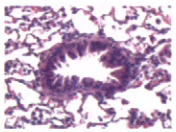
7 Exposures, sacrifice on Day 8. Mucosal epithelial regeneration in this area is excessive and characterized by multiple layers of disorganized cells with enlarged, hyperchromatic nuclei.

Bronchiole: Intramural Fibrosis



12 Exposures, sacrifice on Day 13. The bronchiolar lumen is compromised by intramural fibroblastic proliferation.

Bronchiole: Epithelial Hyperplasia



7 Exposures, sacrifice on Day 17. The bronchiolar epithelium is thickened, and composed of hypertrophic cells with enlarged nuclei that sometimes appear to be stratified.

Table 1.

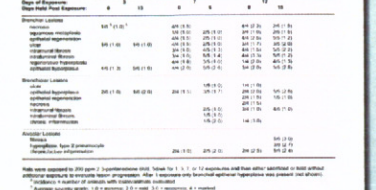
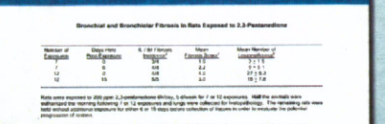


Table 2.



Summary

Exposure to the artificial flavoring ingredient, PD (200 ppm) caused bronchiolitis obliterans in rats. The incidence and severity of airway lesions increased with increasing number of exposures and time to sacrifice. Exposure of rats for 1 or 3 days caused hyperplasia of the bronchial epithelium in some animals. Two weeks after terminating the exposure, the incidence and severity of epithelial hyperplasia had increased but did not progress to fibrosis.

Intraluminal and intramural bronchial fibrosis were observed in rats immediately after 7 exposures to PD. Bronchial epithelial lesions were more prevalent and severe than after 3 exposures and included necrosis, ulceration and regenerative hyperplasia with mild atypia. When the animals were held for 1 week without additional exposure, the incidence and severity of bronchial fibrosis increased, and intraluminal and intramural fibrosis developed in the more distal bronchioles.

The incidence and severity of bronchial and bronchiolar fibrosis were further increased in animals receiving 12 exposures to PD, and resulted in mild decrements in lung function. Bronchial and bronchiolar fibrosis were still present 2 weeks after the exposures. In addition, alveolar epithelial hyperplasia and alveolar fibrosis developed during the 2 weeks following termination of the exposure and resulted in significant reductions in pulmonary function.

This study provides important information needed to help understand the pathogenesis of PD-induced bronchiolitis obliterans. These results will be used to help identify potential intervention and treatment strategies.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIEHS
National Institute of Environmental Health Sciences

Safety data sheet
according to Regulation (EC) No 453/2010

Diacetyl

ILLOVO SUGAR (SOUTH AFRICA) LIMITED

1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1 Product identifier

Chemical name	2,3-Butanedione		
Synonyms	Butanedione, Butane-2,3-dione, 2,3-Butadione, Biacetyl, Dimethyl diketone, 2,3-Dimethyl glyoxal.		
Formula	$C_4H_6O_2$		
Molecular mass	86,09	**FL-No.**	07.052
CAS-No.	431-03-8	**FEMA-No.**	2370
EC-No.	207-069-8	**Annex VI No.**	–
Registration number			

1.2 Relevant identified uses of the substance and uses advised against

Flavouring agent.

1.3 Details of the supplier of the safety data sheet

Manufacturer	Illovo Sugar (South Africa) Limited
Address	Gleneagles Park no. 3C Mount Edgecombe 4300 South Africa
Telephone number	+27 31 508 43 00
Telefax number	+27 31 508 43 10
E-mail address	treed@illovo.co.za
Only representative	Otentic Customs BV
Address	Rederijweg 25, 4906 CX Oosterhout, The Netherlands
Telephone number	+31 162 48 80 65

1.4 Emergency telephone numbers

– **Local South Africa**	0800 17 27 43	
– **International**	+27 11 815 60 15	+27 82 775 33 05

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance

EU-GHS / CLP

Hazard Class(es) / Hazard Class- and Category Code(s)

Flammable liquid	Flam. Liq. 2
Acute toxicity	Acute Tox. 4 (oral, inhalation)
Serious eye irritation	Eye Irrit. 2
Skin irritation	Skin Irrit. 2
Specific target organ toxicity – repeated exposure	STOT RE 2

EU-DSD / DPD

Indication(s) of danger and risk phrase(s)

Highly flammable	R11
Harmful	R20/22-48/20
Irritant	R36/37/38

2.2 Label elements

EU-GHS / CLP

Hazard pictogram(s)

Signal word	Danger
Hazard statement(s)	
H225	Highly flammable liquid and vapour
H373	May cause damage to organs (lung) through prolonged or repeated exposure.
H302	Harmful if swallowed.
H332	Harmful if inhaled.
H315	Causes skin irritation.
H319	Causes serious eye irritation.

H335	May cause respiratory irritation.
Precautionary statements	
P210	Keep away from heat / sparks / open flames / hot surfaces – No smoking.
P233	Keep container tightly closed.
P241	Use explosion-proof electrical lighting and equipment.
P242	Use only non-sparking tools.
P243	Take precautionary measures against static discharge.
P260	Do not breathe vapours.
P264	Wash hands thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P271	Use only outdoors or in a well-ventilated area.
P280	Wear protective gloves / protective clothing / eye protection protection.
P301 + P312	IF SWALLOWED: Call a POISON CENTER or doctor / physician if you feel unwell.
P302 + P352	IF ON SKIN: Wash with plenty of soap and water.
P304 + P340	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.
P305 + P351 + P 338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P312	Call a POISON CENTER or doctor / physician if you feel unwell.
P330	Rinse mouth.
P332 + P313	If skin irritation occurs: Get medical advice / attention.
P337 + P313	If eye irritation persists: Get medical advice / attention.
P370+P378	In case of fire: Use powder, alcohol-resistant foam, water spray, carbon dioxide for extinction.
P403 + P233	Store in a well-ventilated place. Keep container tightly closed.
P501	Disposal: Dispose of contents / container to a specialised waste disposal plant in accordance with local / regional regulations.

2.3 Other hazards Not applicable.

3. COMPOSITION / INFORMATION ON INGREDIENTS

Main constituent	Identity		Percentage
2,3-Butanedione	CAS-No.	431-03-8	>98 %
	EC-No.	207-069-8	

4. FIRST AID MEASURES

4.1 Description of first aid measures

Inhalation Fresh air, rest. Get medical advice / attention if you feel unwell.

Skin contact Remove contaminated clothes, rinse skin with water or shower. If skin irritation occurs: Get medical advice / attention.

Eye contact First rinse with plenty of water (remove lenses if possible). If eye irritation persists: Get medical advice.

Ingestion Rinse mouth. Get medical advice / attention if you feel unwell.

4.2 Most important symptoms and effects, both acute and delayed

Acute symptoms and effects

May cause damage to lung by brief exposure to high concentrations.
Serious eye irritation.
Skin and respiratory irritation.

Delayed symptoms and effects

May cause damage to lung through prolonged or repeated exposure.

4.3 Indication of any immediate medical attention and special treatment needed

Not applicable.

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Alcohol-resistant foam, carbon dioxide, powder, water spray.

Safety data sheet
according to Regulation (EC) No 453/2010

Diacetyl

ILLOVO SUGAR (SOUTH AFRICA) LIMITED

1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1 Product identifier

Chemical name	2,3-Butanedione		
Synonyms	Butanedione, Butane-2,3-dione, 2,3-Butadione, Biacetyl, Dimethyl diketone, 2,3-Dimethyl glyoxal.		
Formula	$C_4H_6O_2$		
Molecular mass	86,09	**FL-No.**	07.052
CAS-No.	431-03-8	**FEMA-No.**	2370
EC-No.	207-069-8	**Annex VI No.**	–
Registration number			

1.2 Relevant identified uses of the substance and uses advised against

Flavouring agent.

1.3 Details of the supplier of the safety data sheet

Manufacturer	Illovo Sugar (South Africa) Limited
Address	Gleneagles Park no. 3C Mount Edgecombe 4300 South Africa
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Specific target organ toxicity – repeated exposure	STOT RE 2

EU-DSD / DPD

Indication(s) of danger and risk phrase(s)

Highly flammable	R11
Harmful	R20/22-48/20
Irritant	R36/37/38

2.2 Label elements

EU-GHS / CLP

Hazard pictogram(s)

Signal word Danger

Hazard statement(s)

H225	Highly flammable liquid and vapour
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H315	Causes skin irritation.
H319	Causes serious eye irritation.

H335	May cause respiratory irritation.
Precautionary statements	
P210	Keep away from heat / sparks / open flames / hot surfaces – No smoking.
P233	Keep container tightly closed.
P241	Use explosion-proof electrical lighting and equipment.
P242	Use only non-sparking tools.
P243	Take precautionary measures against static discharge.
P260	Do not breathe vapours.
P264	Wash hands thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P271	Use only outdoors or in a well-ventilated area.
P280	Wear protective gloves / protective clothing / eye protection protection.
P301 + P312	IF SWALLOWED: Call a POISON CENTER or doctor / physician if you feel unwell.
P302 + P352	IF ON SKIN: Wash with plenty of soap and water.
P304 + P340	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.
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P403 + P233	Store in a well-ventilated place. Keep container tightly closed.
P501	Disposal: Dispose of contents / container to a specialised waste disposal plant in accordance with local / regional regulations.

2.3 Other hazards Not applicable.

3. COMPOSITION / INFORMATION ON INGREDIENTS

Main constituent	Identity		Percentage
2,3-Butanedione	CAS-No.	431-03-8	>98 %
	EC-No.	207-069-8	

4. FIRST AID MEASURES

4.1 Description of first aid measures

Inhalation Fresh air, rest. Get medical advice / attention if you feel unwell.

Skin contact Remove contaminated clothes, rinse skin with water or shower. If skin irritation occurs: Get medical advice / attention.

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Ingestion Rinse mouth. Get medical advice / attention if you feel unwell.

4.2 Most important symptoms and effects, both acute and delayed

Acute symptoms and effects

May cause damage to lung by brief exposure to high concentrations.
Serious eye irritation.
Skin and respiratory irritation.

Delayed symptoms and effects

May cause damage to lung through prolonged or repeated exposure.

4.3 Indication of any immediate medical attention and special treatment needed

Not applicable.

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Alcohol-resistant foam, carbon dioxide, powder, water spray.

5.2 Special hazards arising from the substance

Brief exposure through inhalation to high concentrations may cause lung disease.
Highly flammable liquid and vapour.
In case of fire toxic gases are formed (carbon monoxide and/or carbon dioxide).

5.3 Advice for firefighters

Self-contained breathing apparatus.
In case of fire: keep tanks / drums cool by spraying with water.

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures

Additional ventilation.
Gloves, boots.
Self-contained breathing apparatus.

6.2 Environmental precautions

Do not discharge into sewer, surface water or soil.

6.3 Methods and material for containment and cleaning up

Eliminate all sources of ignition or open fire that may come into contact with the spill.
Take up small amounts spilled substance with an inert absorbent. Dispose of as hazardous waste.
Dam in large amounts spilled substance and carefully remove with explosion protected vacuum cleaner; recycle if possible. Take remainder up with an inert absorbent.
Dispose of as hazardous waste.

6.4 Reference to other sections

See also the sections 8 and 13.

7. HANDLING AND STORAGE

7.1 Precautions for safe handling

Use only in well-ventilated areas.
Use protective breathing masks until ventilation and other controls are determined to be effective.
Wear suitable protective clothing and gloves.
Keep equipment entirely closed, open equipment only for inspection.
Use explosion protected electrical equipment and lighting.
Take precautionary measures against static discharges.
Keep away from sources of ignition – No smoking.

7.2 Conditions for safe storage, including any incompatibilities

Keep container in a well-ventilated place.
Keep container tightly closed.
Fireproof, separated from oxidants, reducing agents, strong bases and acids.
The substance affects many synthetic materials; store only in original packing.

7.3 Specific end use(s)

If used in food: comply with food safety regulation (HACCP).

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

8.1 Control parameters

Limit values				
8 hours (TWA)		Short term (15 min.)		Notation
mg/m³	ppm	mg/m³	ppm	
n.d.		n.d.		

n.d. not determined
The exposure limits may be exceeded before the odour is perceived.

8.2 Exposure controls

8.2.1 Appropriate engineering controls

Closed equipment.
Ventilation and local exhaust.
Reduction of the operating temperature.

Caution to assure that polluted air of the general and local exhaust ventilation does not spread contaminants to other areas in the plant.

8.2.2 Individual protection measures, such as personal protective

a) Eye/face protection

Safety goggles.

b) Skin protection

Hand protection	Gloves butyl rubber 0,7 mm	Breakthrough time > 8 hours
	Gloves neoprene 0,75 mm	Breakthrough time > 4 hours
	Gloves viton 0,7 mm	Breakthrough time > 8 hours
Other	Protective clothing.	

c) Respiratory protection

In case of insufficient local exhaust and/or handling with open equipment: breathing protection with a filter for organic vapours (filter type A -EN141 or NIOSH-approved).

d) Thermal hazards

Not applicable.

8.2.3 Environmental exposure controls

Direct polluted air of the local exhaust ventilation out of the plant in a manner in accordance with environmental regulations.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

Appearance	Yellowish-green liquid
Odour	Buttery
Odour threshold (mg/m3)	0,09
pH (30% solution)	3,2
Melting point / freezing point (°C)	–2,4
Boiling point (°C) at 1013 hPa	89 - 90
Flash point (°C)	7 (tag closed cup)
Evaporation rate (ether=1)	Not available
Flammability (solid, gas)	Not applicable
Upper/lower explosive limits (vol%)	2,4 – 13,0
Vapour pressure at 20 °C (hPa)	52
Vapour density (air=1)	2,97
Relative density (water=1)	0,99
Solubility(ies)	
– **Water solubility at 20 °C (g/l)**	200
– **Fat solubility**	Good
Partition coefficient (log K octanol/water)	–1,34
Auto-ignition temperature (°C)	365
Decomposition temperature	Not available
Viscosity at 20 °C (mPa.s)	Not available
Explosive properties	None
Oxidising properties	None

9.2 Other information

Miscibility with	Ethanol, ether, propylene glycol.
Conductivity (pS/m)	Not available
Heat of combustion (kJ/kg)	Not available

10. STABILITY AND REACTIVITY

10.1 Reactivity

Not reactive.

10.2 Chemical stability

Stable. In case of contact with sunlight decomposition.

10.3 Possibility of hazardous reactions

In case of strong heat polymerization.

10.4 Conditions to avoid

Avoid contact with open flames, warm surfaces. Protect against direct sunlight.

10.5 Incompatible materials

Avoid contact with oxidants, reducing agents, strong bases and acids.

10.6 Hazardous decomposition products

Upon decomposition emits carbon monoxide, carbon dioxide and/or low molecular weight hydrocarbons.

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute toxicity

LD50 (oral, rat) (mg/kg)	1580
LD50 (dermal, rabbit) (mg/kg)	> 5000
LC50 (inhalation, rat, 4 hours) (mg/l)	2,25 – 5,2

Likely routes of exposure

The substance may be absorbed into the body by inhalation of vapour or spray and after ingestion.

Effects from short-term exposure

Harmful by inhalation and if swallowed.
Intermittent and subchronic exposures to occupationally-relevant butanedione concentrations caused lymphocytic bronchitis and bronchiolitis in mice. Lymphocytic bronchitis may be a precursor lesion to obliterative bronchiolitis (OB). (Morgan, 2008)
Even brief exposure through inhalation to high concentrations may cause OB. The loss of pulmonary function associated with this illness is permanent.
Irritating to eyes, skin and respiratory system.

- **Inhalation** Sore throat, coughing, dullness, tiredness, unconsciousness.
- **Skin** Redness.
- **Eyes** Redness, pain.
- **Ingestion** Sore throat, abdominal pain.

Effects from long-term exposure

Prolonged exposure to high concentrations may cause lung disease (bronchiolitis obliterans).
May cause sensitization by skin contact. Repeated eye contact may cause conjunctivitis.

12 ECOLOGICAL INFORMATION

12.1 Toxicity

LC50 (fish, 96 hours) (mg/l)	46 - 100
EC50 (Daphnia, 48 hours) (mg/l)	Not available
IC50 (algae, 96 hours) (mg/l)	Not available

12.2 Persistence and degradability

Biodegradability	Readily biodegradable. Decomposes to acetic acid and next to carbon dioxide.
Oxygen demand	
– **biological (5 days) in gO2/g (BOD_5)**	Not available
– **biological (20 days) in gO2/g (BOD_{20})**	Not available
– **chemical in gO2/g (COD)**	Not available

12.3 Bioaccumulative potential

BCF (Bioconcentration factor)	1,0
(conc in organisms / conc. in water)	Risk of bio accumulation is low (BCF < 500 and log Kow < 4).

12.4 Mobility in soil

Adsorption coefficient (Koc) solid phase / liquid phase	1 Highly mobile

12.5 Results of PBT and vPvB assessment

Not available

12.6 Other adverse effects

Ozone depletion potential (ODP) (CCl_3F = 1)	Not applicable
Photochemical ozone creation potential (C_2H_4 = 1)	Not available
Global warming potential (GWP) (CO_2 = 1)	Not applicable
Water hazard class (WGK Germany)	2 (hazardous to water)

13 DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Recycling by distillation.
Removal to an authorized waste incinerator for solvents or as chemical waste in accordance with local regulations. Do not discharge wastewater into sewer.

European waste list (EURAL) 07 01 04

14 TRANSPORT INFORMATION

14.1	**UN No.**	2346
14.2	**UN proper shipping name**	BUTANEDIONE
14.3	**Transport hazard class(es)**	3
14.4	**Packinggroup**	II
14.5	**Environmenal hazards**	
	Marine pollutant	No
14.6	**Specials precautions for user**	
	Risk label(s)	3
	Tunnel category	(D/E)
	Hazard Identification Number (Kemler code)	33
	ERICard	3-09
	Emergency Schedules (EmS)	
	– **Fire schedule**	Alfa (F-E)
	– **Spillage schedule**	Alfa (S-D)

14.7 Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

Ship type required	Not available
Pollution category	Not available

15 REGULATORY INFORMATION

15.1 Safety, health and environmental regulations/legislation specific for the substance

Not available.

15.2 Chemical safety assessment

A Chemical Safety Assessment has not been carried out for butanedione.

16 OTHER INFORMATION

Changes to the previous version.

Classification and labelling according to Regulation (EC) No 453/2010.

Abbreviations and acronyms

DNEL	Derived No Effect Level
DMEL	Derived Minimal Effect Level
DSD / DPD	Dangerous Substances Directive / Dangerous Preparations Directive
EC50	Effect Concentration, 50 percent
ERIC	Emergency Response Intervention Card
GHS / CLP	Globally Harmonised System / Classification, Labelling and Packaging
IC50	Inhibitory Concentration, 50 percent
LC50	Lethal Concentration, 50 percent
LD50	Lethal Dose, 50 percent
PBT	Persistent, Bioaccumulative and Toxic
PNEC	Predicted No Effect Concentration
TOD	Total Oxygen Demand
TWA	Time Weighted Average
vPvB	very Persistent and very Bioaccumulative

Literature references and sources for data

Joint FAO/WHO Expert Committee on Food Additives;
W. Auttachoat e.a., Diacetyl induces contact sensitization in mice, Abstract No. 1153, NC: Society of Toxicologie;
Chemical Information Review Document for Artificial Butter Flavoring (support to the National Toxicology Program), Integrated Laboratory Systems, Inc., January 2007.
R. Kanwal, e.a., J. Occupational Environmental Medicine, 48(2), 149-157, 2006.
D. Morgan, e.a., Toxicological Sciences, Respiratory Toxicity of Diacetyl in C56B1/6 Mice, January 27, 2008.

Full text of indication(s) of danger, R phrases and safety advise which are not written out in full under Sections 2 to 15

R11	Highly flammable.
R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation (lung disease).
R20/22	Harmful by inhalation and if swallowed.
R36/37/38	Irritating to eyes, respiratory system and skin.

2,3-BUTANEDIONE

ICSC: 1168

Date of Peer Review: April 2009

Diacetyl
Dimethylglyoxal
Dimethyl diketone
2,3-Diketobutane
Butanedione

CAS #	**431-03-8**	**$CH_3COCOCH_3$ / $C_4H_6O_2$**
RTECS #	**EK2625000**	**Molecular mass: 86.1**
UN #	**2346**	
EC/EINECS #	**207-069-8**	

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Highly flammable.	NO open flames, NO sparks, and NO smoking.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Vapour/air mixtures are explosive.	Closed system, ventilation, explosion-proof electrical equipment and lighting.	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE		**PREVENT GENERATION OF MISTS!**	
Inhalation	Cough. Drowsiness. Nausea. Headache. Sore throat.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain. Burns	Safety goggles or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Sore throat.	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Seek medical attention if you feel unwell

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Remove all ignition sources. Personal protection: filter respirator for organic gases and vapours adapted to the airborne concentration of the substance. Do NOT let this	

chemical enter the environment. Collect leaking liquid in covered containers. Absorb remaining liquid in sand or inert absorbent and remove to safe place.	
EMERGENCY RESPONSE	**STORAGE**
NFPA Code: H2; F3; R0	Fireproof. Store in an area without drain or sewer access. Separated from : See Chemical Dangers.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities © IPCS, CEC 2005

SEE IMPORTANT INFORMATION ON BACK

2,3-BUTANEDIONE

ICSC: 1168

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE:
GREEN TO YELLOW LIQUID

PHYSICAL DANGERS:
The vapour is heavier than air and may travel along the ground; distant ignition possible.

CHEMICAL DANGERS:
Heating may cause violent combustion or explosion. Reacts violently with strong acids strong bases and oxidants

OCCUPATIONAL EXPOSURE LIMITS:
TLV not established. MAK not established.

ROUTES OF EXPOSURE:
The substance can be absorbed into the body by inhalation and by ingestion.

INHALATION RISK:
No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE:
The substance is severely irritating to the eyes. The substance is irritating to the skin and the respiratory tract. The substance may cause effects on the central nervous system lungs and respiratory tract. Exposure at high levels could cause lowering of consciousness.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:
Lungs may be affected by repeated or prolonged exposure to the vapour, resulting in impaired functions. SEE NOTES

PHYSICAL PROPERTIES

Boiling point: 88°C
Melting point: -2.4°C
Relative density (water = 1): 1.1
Solubility in water: at 25 °C 20 g/100 ml
Vapour pressure, kPa at 25°C: 7.6
Relative vapour density (air = 1): 3

Relative density of the vapour/air-mixture at 20°C (air = 1): 0.99
Flashpoint: 6°C c.c.
Auto-ignition temperature: 365°C
Explosive limits, vol% in air: 2.4-13 vol%
Octanol/water partition coefficient as log Pow: -1.34

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

Irreversible obstructive lung disease has been documented among workers exposed in a variety of settings. These include 2,3-butanedione (diacetyl) production in the chemical industry, production of 2,3-butanedione (diacetyl)-containing flavorings, and production of diacetyl-containing, butter-flavored food products such as microwave popcorn. Many cases have been confirmed to have severe clinical bronchiolitis obliterans. Environmental effects from the substance have not been investigated adequately. Do NOT take working clothes home.

ADDITIONAL INFORMATION

See Also:
Toxicological Abbreviations

Report – Study on the acute inhalation toxicity LC_{50} of diacetyl FCC as a vapor in rats 4-hour exposure

DEEMED CONFIDENTIAL

Exposure Simulation to Diacetyl from Popcorn by

Dr. Su-Jung (Candace) Tsai and Dr. Michael Ellenbecker –

DEEMED CONFIDENTIAL

Consumer safety estimate for inhalation of synthetic butter flavoring component of microwave-ready popcorn –

DEEMED CONFIDENTIAL