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

From: Hank Schilling <hank@egilman.com>
Sent: Wednesday, November 16, 2011 10:59 AM
To: NIOSH Docket Office (CDC)
Subject: 245 - Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-pentanedione
Attachments: Egilman_2011_Proposal for safe exposure level for diacetyl.pdf; NIOSH Meeting Egilman Schilling Presentation.pdf

The authors of this email (David Egilman MD, MPH and Hank Schilling) gave comments at the diacetyl public meeting and are writing now to follow-up, reiterate some of those comments and submit some of the oral comments in writing.

1. 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.

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, 5 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-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 TDI and NDI). These comparable, negative LUMO energy values suggest similar biological reactivity and toxicity. The American Conference of Governmental Industrial Hygienists (ACGIH) sets the TDI 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/tlv/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.

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).

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 Illovo Sugar Limited 2009 MSDS, and 2.8 to 5.6 ppb based on Blank et al. 1992 (see attached powerpoint). 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 Diaz et al 2004, or 1.4 ppm based on Lawless et al. 1993.

Statement of interest: David Egilman has served as an expert in diacetyl/flavorings litigation at the request of injured workers and consumers. Hank Schilling is a researcher at David Egilman's consulting company.

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A Proposal for a Safe Exposure Level for Diacetyl

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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

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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.

NIOSH Diacetyl REL Hearing slides

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Dr. Egilman has served as a consultant at the request of workers exposed to diacetyl who were seeking compensation for injuries in worker compensation and tort lawsuits. He was not compensated for work or expenses related to this presentation

Surveillance System

Let's not repeat this mistake again

Establish registries with standard occupational and environment questionnaires with:

1. Lung transplant units
2. Liver transplant units

For these workers:

- Set up a registry for cases
- Work with NIH to set up treatment protocols

REL based on highest exposure

- REL is based on Company G analyses (pg 138). Excess risk of 1/1000 at:

  3-5 ppb (all workers)

  5 ppb (smokers)

  0.9 ppb (non-smokers)

- Company K/L (pooled) 1/1000 at **0.4-0.5 ppb** (all workers) (pg. 138)

Multiple RELs?

- "Excess risk of 1/1000 corresponds to approximately 0.003–0.005 ppm diacetyl (10.5-17.5 µg/m3) in the general population and **0.0009 ppm (3.15 µg/m38) for non-smokers**." (page 138:7-8)
- Exposure level should be based on protecting most sensitive group (non-smokers)
- Standard should be set at **< 1 ppb ALARA**

UNPRECIDENTED and WRONG DOUBLE STANDARD

- NIOSH has never set different standards for smokers and non-smokers
- In this case NIOSH chooses to ONLY protect smokers

THE TLV SHOULD PROTECT ALL WORKERS NOT JUST SMOKERS

QSAR analysis

- Qualitative structure-activity relationship performed by ToxDx for ConAgra
- Compares LUMO (lowest unoccupied molecular orbital) values between diacetyl, 2,3-pentanedione and other known lung toxins
- Negative LUMO values indicate high biological reactivity and toxicity potential
- Similar LUMO values indicate similar toxicity

QSAR analysis

- "Of particular note is that only two of the butter flavor chemical constituents exhibit negative LUMO energy values, indicative of chemicals with greater reactivity and greater potential of causing chronic irritation. Both are di-ketones, diacetyl and 2,3-pentanedione."
- "Three isocyanates were also included in the data set because of their well-established reputation for inducing allergenic bronchiolar asthma. Of note is that the calculated LUMO energy values ate similar to those calculated for diacetyl and 2,3-pentanedione."

ToxDx Report. Consumer Safety Estimate for Inhalation of Synthetic Butter Flavoring Components of Microwave-Ready Popcorn. Submitted April 21, 2005 by Kendall Wallace, Ph.D., DABT

QSAR analysis

- Toluene-2,4,-diisocyanate (TDI), diacetyl and 2,3-pentanedione have comparable LUMO values and therefore comparable reactivity and toxicity.
- ACGIH states that it intends to reduce TLV for TDI from 5 ppb to **1 ppb**[1]

[1] *ACGIH.* Toluene-2,4- or 2,6-Diisocyanate: TLV® Chemical Substances Draft *Documentation*, Notice of Intended Change. Publication #7NIC-140

Other chemicals

- "Although a causative relationship between diacetyl and respiratory disease has been observed, diacetyl may not be the only flavoring ingredient related to health impairment. Other flavoring ingredients such as acetaldehyde, butyric acid, and acetoin, have been associated with adverse health effects [Lockey et al. 1998; van Rooy et al. 2007]" (page 12:11-12:14)

Other chemicals

- Acetaldehyde, butyric acid, and acetoin are not associated with BO
- Key issue is whether these chemicals impact effective dose, i.e. toxicity of diacetyl to induce BO

Butyric acid

- "For example, butyric acid, one of the vapors present in butter flavoring vapors, is a known inhibitor of an enzyme that metabolizes diacetyl. **Currently it is not known if an inhibition of this enzyme would diminish or enhance the effects of diacetyl.**"
  – Dr. Morris expert report, Newkirk vs. ConAgra

Butyric acid

- Morris & Hubbs (2008) results suggest butyric acid enhances diacetyl penetration to lower airways (in rats)
  - Site of injury to humans
- Butyric acid may also enhance diacetyl toxicity by inhibiting detoxification enzyme

NIOSH denies consumer risk

"The CDC's National Institute for Occupational Safety and Health (NIOSH), Environmental Protection Agency, and the Food and Drug Administrations **say there is no reason for consumers to worry.**

'We don't see any evidence for consumer risk,' NIOSH spokesman Fred Blosser tells Web MD."

http://webmd.com/news/20040312/microwave-popcorn-no-consumer-risk-known

Posted 3/12/2004

NIOSH denies consumer risk

"Workers often have different exposure characteristics, including level of exposure, to flavorings than typical consumers. Unlike workers, so far there have not been peer reviewed scientific studies showing that consumers using products such as microwave popcorn that contains butter flavoring chemicals are at increased risk of lung disease. Nor is there any evidence that cooking with butter is associated with increased risk for lung disease...

Currently, even though there is little to suggest significant risk to normal consumers..."

http://www.cdc.gov/niosh/blog/nsb111008_diacetyl.html
Posted 12/4/2008

FDA denies consumer risk

"The FDA classifies diacetyl as being "generally recognized as safe." Last September, the FDA received a citizens' petition to revisit diacetyl's safety status. An FDA spokesperson says the FDA isn't aware of any evidence that consuming diacetyl is unsafe."

http://www.webmd.com/lung/news/20080313/kernel-of-truth-about-butter-flavoring

Posted 3/13/2008

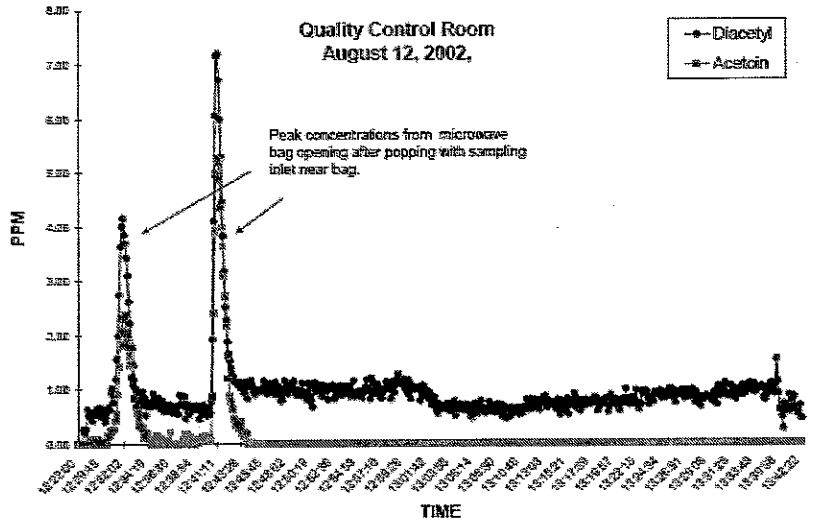
Consumer exposures **exceed** NIOSH recommended exposure

- Jasper GML plant: QC worker's breathing zone exposure as bag of popcorn is opened reached peak of

  4, 7, and 13 ppm

  (FTIR method)

Figure 4. Diacetyl and acetoin air concentrations in the quality control room.



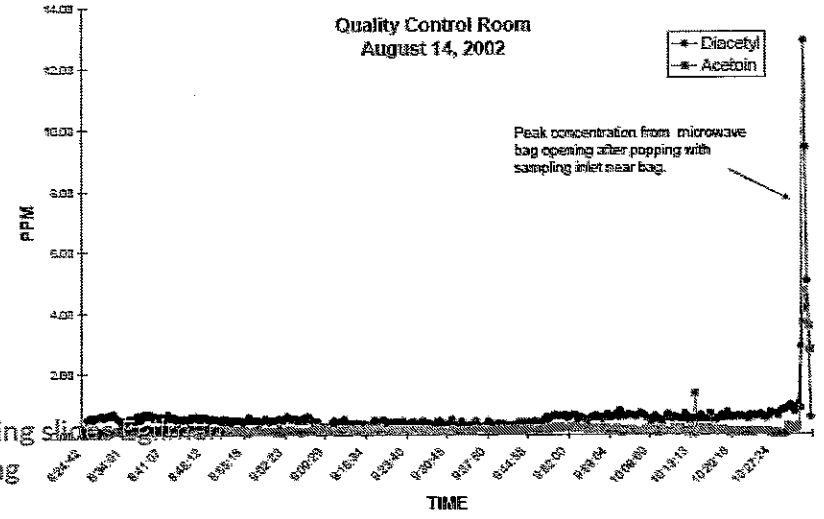
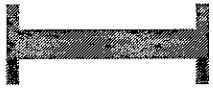


Figure 4, page 28 NIOSH GML HHE

- Diacetyl levels from opening one popcorn bag remain above background levels for **over two minutes**



2:17 minutes

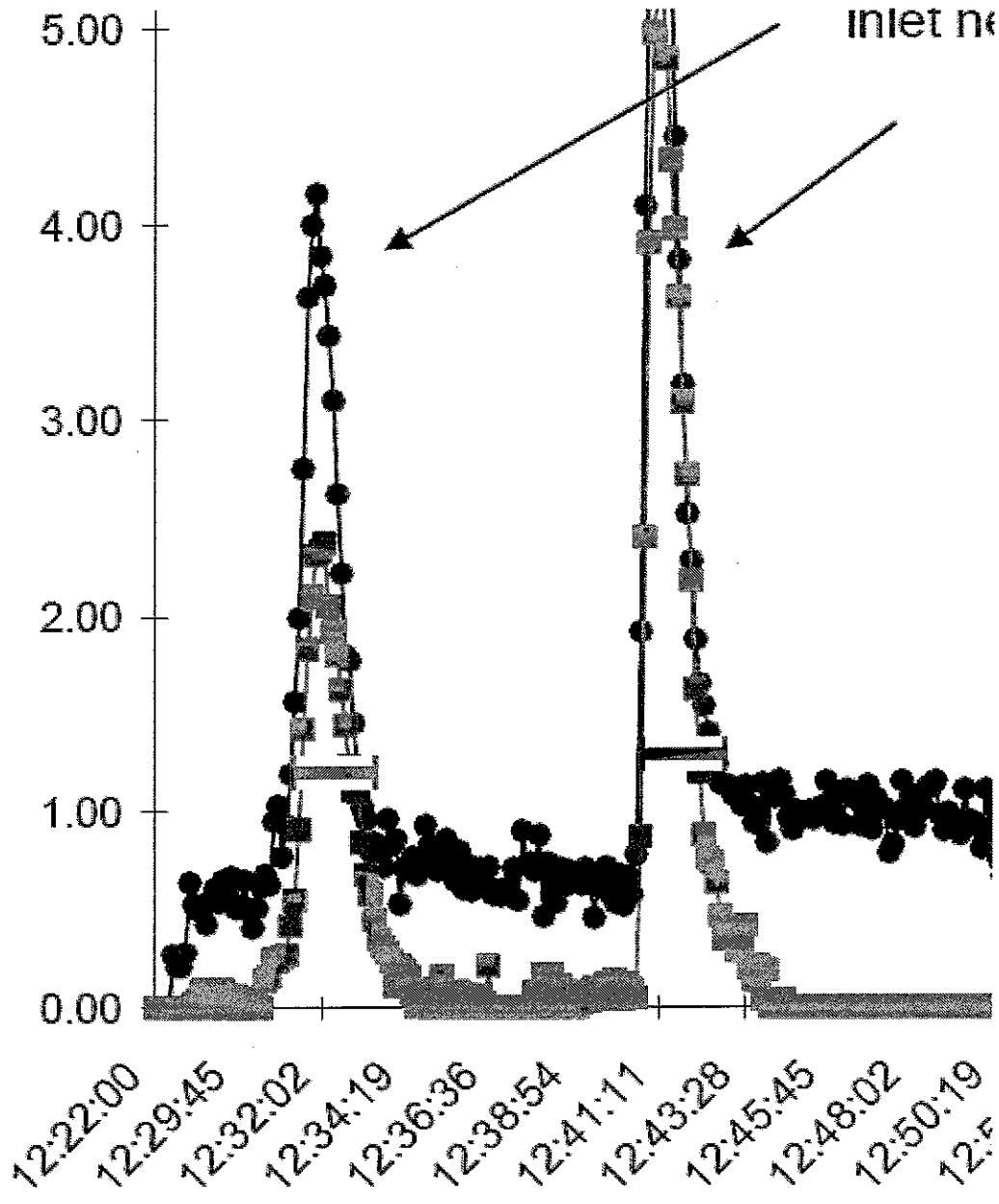


Figure 4, Page 28 NIOSH GML HHE

- 15 sec exposure at peak level for each bag is conservative estimate
- Actual exposure could be determined by taking area under peak curve

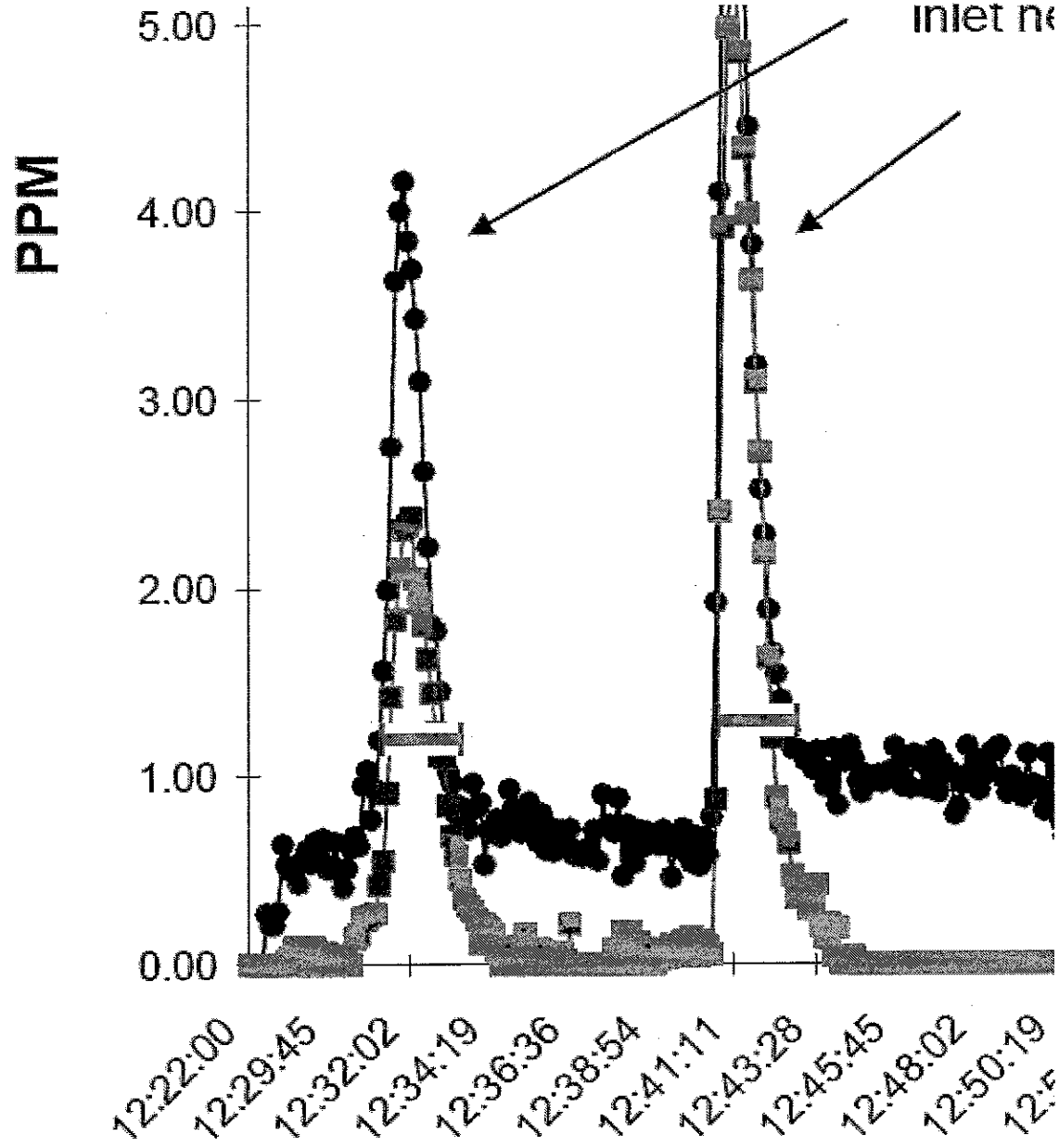


Figure 4, Page 28 NIOSH GML HHE

Consumer exposures **exceed** NIOSH recommended STEL per bag

- NIOSH STEL: **25 ppb** over 15 min
- Assuming peak exposure for 15 sec/bag:

  4 ppm over 15 sec = **67 ppb** over 15 min

  7 ppm over 15 sec = **117 ppb** over 15 min

  13 ppm over 15 sec = **217 ppb** over 15 min

Consumer exposures can exceed NIOSH REL

- NIOSH REL: **5 ppb** for 8-hour day
- Assuming peak exposure for 15 sec/bag:

  4 ppm: **3 bags/day = 6.2 ppb** 8-hour TWA

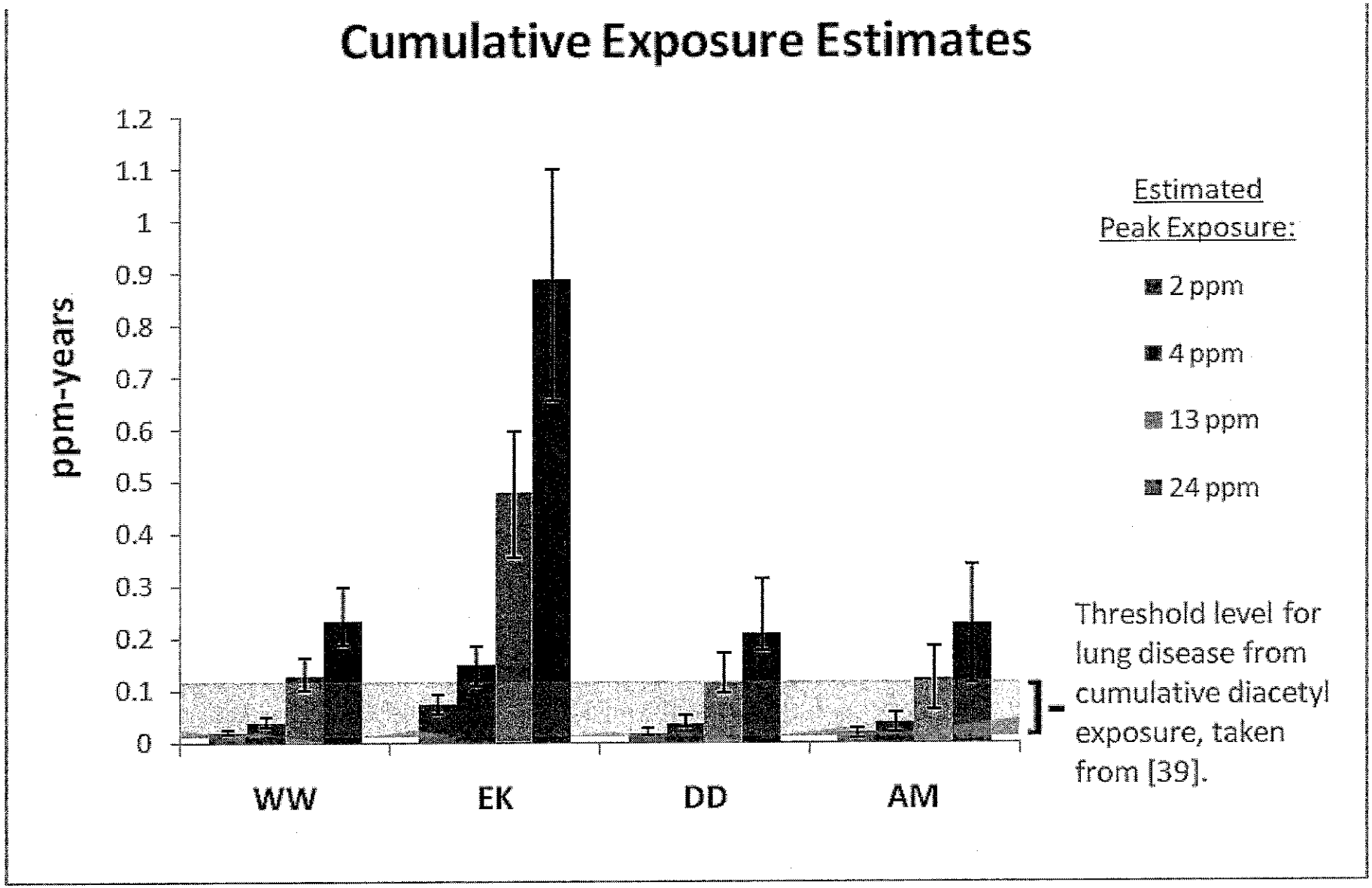
  7 ppm: **2 bags/day = 7.3 ppb** 8-hour TWA

  13 ppm: **1 bag/day = 6.8 ppb** 8-hour TWA

Known consumer cases of BO

Case	Biopsy confirmed BO?	Smoking History	Consumption level
WW	Yes	None	1-3 bags/day, 8 years
EK	Yes	None	3-5 bags/day, 8 years (home) + 30 bags/weekend, 4 years (work-related)
DD	Yes	None	2-3 bags/weekday, 7 years
AM	Yes	None	2-3 bags/day, 7 years

- Differential diagnosis found no other cause of BO in any case



Error bars represent range of consumption estimates.

24 ppm (purple bar) comes from Aspen study: peak of 372 ppm (Orville Redenbacher Butter), converted to 46 L breathing zone.

Lockey et al. (2009) PAPR mixers

- Mixers using PAPRs at 5.7-fold increased risk for obstruction
- Maximum 3 years exposure
- Lockey estimated average exposure level of 0.015-0.044 ppm

  Measured levels / 25

  ("conservative resp. protection factor")
- Cumulative exposure: 0.045 – 0.132 ppm
- → 8-hour TWA: **1 to 2.9 ppb (unsafe)**

Wrong Odor Threshold in Air

- Table 1.1, page 16
- Diacetyl (Illovo Sugar Limited 2009):
  - NIOSH draft: Table 1.1 says **0.09 ppb**
  - In fact, it is 0.09 mg/m^3 = **25 ppb**
- Diacetyl and 2,3-pentanedione (Blank et al. 1992):
  - Table 1.1 says **0.01-0.02 ppb**
  - In fact, it is 10 to 20 ng/L = **2.8 to 5.6 ppb**

Odor Threshold in Water

- Table 1.1, page 15
- Diacetyl (Diaz et al. 2004): 0.05 ug/L = **14 ppb**
- Lawless et al. (1993): 0.005 ug/mL = **1.4 ppm**
  - "Individual thresholds varied over a factor of 256"

$$\frac{ug}{L} = \frac{ppmV\ (12.187)(MW)}{T}$$

Equivalent units:

ug/L = ng/cc = mg/m^3

Odor Threshold

- NIOSH Table 1.1 states odor threshold in air is far below recommended exposure level
- In fact, odor threshold in air and water is above dangerous level
- Thus, diacetyl does not have an odor warning property