MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Diacetyl (CAS No. 431-03-8)

FROM: Michael Depa, Toxicologist, Air Quality Division

SUBJECT: Screening Level for Derivation of Diacetyl

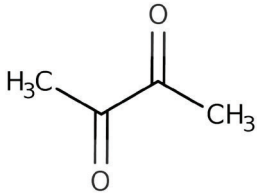
DATE: September 20, 2023

The Initial Threshold Screening Level (ITSL) for diacetyl (also known as butane-2,3-dione) is 0.2 micrograms per cubic meter (µg/m³) with an 8-hour averaging time.

A literature review was conducted to determine an ITSL for diacetyl. The following references and databases were searched to derive the screening level: United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2022 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Chemical Abstract Service (CAS) SciFinder, PubMed, USEPA Computational Toxicology (CompTox) Database, National Technical Information Service (NTIS), and California Office of Environmental Health Hazard Assessment (OEHHA).

Diacetyl has a molecular formula of C4-H6-O2, and a molecular weight of 86.09 g/mol. NIOSH derived a Reference Exposure Level of 5 parts per billion (ppb) for diacetyl (NIOSH, 2016). ACGIH derived a time weighted average (TWA) TLV for diacetyl of 10 ppb (ACGIH, 2012). USEPA, Agency for Toxic Substances Disease Registry (ATSDR), OEHHA, and OSHA have not derived health benchmarks for diacetyl.

Figure 1. Molecular Structure of Diacetyl



Diacetyl is a yellow liquid with an intensely buttery flavor and is added as a flavoring to some foods to impart its buttery flavor; it occurs naturally in alcoholic beverages (Wikipedia, 2023). As a food ingredient diacetyl is designated by the U.S. Food and Drug Administration as “Generally Recognized as Safe” (FDA, 1983).

Physical Values (NIOSH, 2016)

Vapor pressure: 52.2 mmHg (20°C)
Henry's Law: 2.95×10^{-5} atm-m^3/mol
Odor detection threshold: 0.27 – 1.2 ppb (0.95 – 4.2 µg/m³)

Diacetyl in Food[1]

Diacetyl and 2,3-pentanedione have a long history as components of food, suggesting that exposures can occur in diverse workplaces. They occur as natural products in many foods (Jiang et al., 2013; Majcher and Jelen, 2005; Majcher et al., 2013; Rincon-Delgadillo et al., 2012; Santos et al., 2013). Diacetyl imparts the flavor and aroma of butter to many common foods and drinks including butter, cheese, yogurt, beer, and wine (Jang et al. 2013; Rincon-Delgadillo et al., 2012). Roasted coffee also contains appreciable amounts of diacetyl (CDC, 2013; Daglia et al., 2007a; Daglia et al., 2007b). Because diacetyl is not a component of green coffee beans, it appears to be a product of the roasting process (Daglia et al., 2007a). Bacteria and yeast produce diacetyl during fermentation (Chuang and Collins, 1968).

Respiratory Dosimetry

The respiratory tract was modeled as a series of airways: nose, trachea, main bronchi, large bronchi, small bronchi, bronchioles, and alveoli with tissue dimensions obtained from the literature (Gloede et al., 2011). Airborne vapor was allowed to absorb (or desorb) from tissues based on mass transfer coefficients. Transfer of vapor within tissues was based on molecular diffusivity with direct reaction with tissue substrates and/or metabolism being allowed in each tissue compartment. In vitro studies were performed to provide measures of diacetyl metabolism kinetics and direct reaction rates allowing for the development of a model with no unassigned variables. Respiratory tract uptake of halothane, acetone, ethanol and diacetyl was measured in male F344 rats to obtain data for model validation. The human model was validated against published values for inspired vapor uptake. For both the human and rat models, a close concordance of model estimates with experimental measurements was observed, validating the model. The model estimates that limited amounts of inspired diacetyl penetrate to the bronchioles of the rat (<2%), whereas in the lightly exercising human, 24% penetration to the bronchioles is estimated. Bronchiolar tissue concentrations of diacetyl in the human are estimated to exceed those in the rat by 40-fold. These inhalation dosimetric differences may contribute to the human-rat differences in diacetyl-induced airway injury.

Animal Toxicology

Groups of 50 male and female rats (Wistar Han) and mice (B6C3F1/N) were exposed via inhalation 6 hours per day, 5 days per week to 0, 12.5, 25, or 50 ppm diacetyl (2,3-butanedione) for 105 weeks (NTP, 2018). Under the conditions of these 2-year inhalation studies, there was some evidence of carcinogenic activity of 2,3-butanedione in male rats based on the combined incidences of squamous cell papilloma and squamous cell carcinoma of the nose. There was some evidence of carcinogenic activity of 2,3-butanedione in female rats based on the incidences of squamous cell carcinoma of the nose. There was no evidence of carcinogenic activity of 2,3-butanedione in male mice exposed to 12.5, 25, or 50 ppm. There was equivocal evidence of carcinogenic activity of 2,3-butanedione in female mice based on the occurrences of adenocarcinoma of the nose. Exposure to 2,3-butanedione resulted in

[1] Excerpts from NIOSH, 2016.

increased incidences of nonneoplastic lesions of the nose, larynx, trachea, lung, and eye in male and female rats and mice. Note that increased squamous cell carcinomas of the nose in female rats were only seen at the highest dose. There were no trends for increases of squamous cell carcinomas at the lower doses; therefore, linear low dose extrapolation methods like USEPA's Benchmark Dose Software cannot be used. Diacetyl was shown to be mutagenic in Salmonella typhimurium base-substitution strains TA100, TA102, and TA104, with and without rat liver S9 activation (NTP, 2018). Based on the respiratory dosimetry differences in rats and humans suggested by Gloede et al. (2011), the rat inhalation study by NTP (2018) may not be appropriate for quantitative human risk assessment purposes without the development of a physiologically based pharmacokinetic model, which is beyond the scope of this risk assessment.

Human Toxicology

Diacetyl is associated with bronchiolitis obliterans, a severe respiratory illness producing fibrosis and obstruction of the small airways (Harber et al., 2006). In addition to bronchiolitis obliterans, spirometry abnormalities (fixed airflow obstruction) and respiratory symptoms have been associated with exposure (Harber et al., 2006). A direct effect on the respiratory epithelium with the disorganized fibrotic repair appears most likely as the underlying mechanism (Harber et al., 2006).

Using cross-sectional pulmonary function data from diacetyl-exposed employees, NIOSH (2016) conducted assessments to determine the exposure-response relationship and to identify risk of pulmonary function decrease at various levels of diacetyl exposure. NIOSH (2016) evaluated duration of diacetyl exposure and average diacetyl exposure concentration to calculate cumulative exposures. Peak exposures were not available from full-shift (8-hour) TWA concentrations.

The quantitative risk assessment used to derive the NIOSH REL was based solely on human (employee) data, but the results were informed and supported by animal risk assessments. NIOSH performed several Health Hazard Evaluations and found a statistically significant exposure-associated reduction in the Forced Expiratory Volume in one second (FEV1) per Forced Vital Capacity ratio, percent predicted FEV1, and an exposure-associated incidence of obstructive lung disease. NIOSH (2016) quantified these exposure-response relationships and determined the exposure levels that correspond to a variety of risks (NIOSH, 2016: Chapter 5, Table 5-35). Excess lifetime risks in the range of 1:1,000 corresponded to a working lifetime diacetyl exposure of approximately 5 ppb.

ACGIH (2012) derived a TWA-TLV for diacetyl of 10 ppb.

> A TLV-TWA of 0.01 ppm (0.04 mg/m^3) is recommended for occupational exposure to diacetyl. Several cases of bronchiolitis obliterans-like illness were reported among microwave popcorn workers exposed to diacetyl used as a flavoring agent in 2002. The continued investigation of this issue identified what the authors considered to be a case of bronchiolitis obliterans-like illness in a mixer employee at a popcorn manufacturing plant that had a mean exposure for mixer employees estimated by area sampling, as 0.2 ppm, and by personal sampling as 0.02 ppm. Exposures in the mixing rooms of popcorn manufacturing plants were likely heterogeneous, and the worker may have had short-term peak exposures much higher than

this, possibly greater than 80 ppm. Lockey et al. reported employment as a mixer employee before the introduction of powered air purifying respirators (PAPR) as well as an estimated cumulative exposure level of 0.8 ppm-years or greater to be associated with a greater risk of decreased FEV1 on lung function testing. The same study reported that workers outside the mixing rooms of popcorn manufacturing plants had no identifiable reduction in mean FEV1 at mean levels of exposure of 0.01 to 0.07 ppm. However, other studies have described bronchiolitis obliterans-like illness occurring in workers outside the mixing room type environment.

Derivation of the Screening Level

Pursuant to Rule 232(1)(c), the ITSL for diacetyl is derived as follows:

ITSL= OEL/100

Where OEL is the occupational exposure limit; and the OEL is either the ACGIH TLV or NIOSH REL.

The NIOSH REL of 5 ppb is more appropriate to use for the derivation of the ITSL. While both ACGIH (2012) and NIOSH (2016) provided rationale for their respective OELs, NIOSH provided detailed descriptions of exposure assessments at four facilities (including exposure and job category). NIOSH also controlled for race, ethnicity, gender, and smoking. NIOSH stated that in identifying cases, a date of onset for a condition resulting in impairment and possibly representing early obliterative bronchiolitis was estimated as the average of the dates on which the employee reported the start of one or more continuing symptoms (cough, wheezing, shortness of breath, tightness of chest or phlegm, based on questionnaire items), provided those symptom dates were after their date of first exposure to diacetyl. NIOSH's statistical modeling of exposure-response provided a robust chemical risk assessment generally not available for derivation of a screening level.

The REL units of ppb were converted to $\mu g/m^3$ using the molar volume of air (24.45 liters/mol) and molecular weight (MW) of diacetyl (86.09 g/mol) as follows:

$\mu g/m^3 = (ppb \times MW)/(24.45)$
$\mu g/m^3 = (5 \times 86.09)/24.45$
$\mu g/m^3 = 17.6$

The ITSL was then calculated as:

$ITSL = (17.6\ \mu g/m^3)/100$
$ITSL = 0.176\ \mu g/m^3$

Rounding to 1 significant figure, yields an ITSL of 0.2 $\mu g/m^3$. Pursuant to Rule 232(2)(a) the averaging time is 8 hours.

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