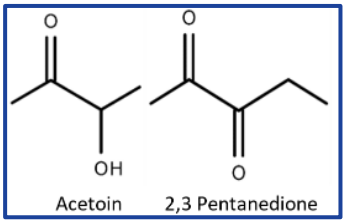
SUMMARY

Background: Acetoin and 2,3-pentanedione are volatile, water-soluble molecules regularly used as flavoring agents and are two major components of artificial butter flavoring (ABF). 2,3-pentanedione has been used as a substitute for 2,3-butanedione (or diacetyl) in some ABF due to concerns about the respiratory toxicity of 2,3-butanedione; however, 2,3-pentanedione is chemically very similar to 2,3-butanedione. The toxicity of inhaled ABF (using 2,3-butanedione) first came under scrutiny in 2000 after an unusually high percentage of young employees at a microwave popcorn plant were diagnosed with obliterative bronchiolitis (OB), an irreversible airway obstruction disease that is often fatal. OB has also been diagnosed in workers in other microwave popcorn manufacturing plants, as well as in the flavoring and baking industries. Humans can be exposed to acetoin and 2,3-pentanedione through ingestion and inhalation. Although acetoin and 2,3-pentanedione in ABF are considered safe to eat by the Food and Drug Administration, it is unknown whether they are safe to inhale. Occupational exposure to acetoin and 2,3-pentanedione is currently not regulated, partly because of a lack of inhalation toxicity data. The effects of 2-week or 3-month whole-body inhalation exposure to acetoin and/or 2,3-pentanedione in male and female rats and mice were studied to identify potential respiratory tract toxicity that could be relevant to humans.



Methods: Exposure concentrations for the 3-month study were selected on the basis of preliminary 2-week studies, wherein groups of five male and five female rats and mice were exposed to acetoin or 2,3-pentanedione vapors for 6 hours per day, 5 days per week. For the 3-month studies, groups of 10 male and 10 female rats and mice were exposed to air acetoin vapors at concentrations of 50, 100, 200, 400, or 800 parts per million (ppm) in air or to 2,3-pentanedione at concentrations of 6.25, 12.5, 25, 50, or 100 ppm for 6 hours per day, 5 days per week. Control animals for all studies were exposed to 0 ppm (no chemical vapor in air). Body weight measurements and clinical observations were reported during the studies. At the end of the studies, tissues from more than 40 sites were examined for signs of disease in all control and high-exposure concentration animals. Affected organs were examined further in all exposure groups.

Results: There were no significant exposure-related adverse effects in rats or mice exposed to acetoin for either 2 weeks or 3 months. All rats and mice exposed to 2,3-pentanedione for 3 months survived to the end of the study. In mice, males and females exposed to 50 or 100 ppm did not gain weight at the same rate as control animals and weighed substantially less at the end of the study. In contrast, all groups of rats gained weight similarly over the course of the study. Clinical observations in rats and mice exposed to 50 or 100 ppm included abnormal breathing, sneezing, and eye abnormality. Noncancerous tissue abnormalities were observed in the organs of the respiratory tract, including the nose, larynx, trachea, and lungs, as well as the eyes. Although inhalation of 2,3-pentanedione for 3 months caused significant adverse airway effects in rats and mice, no bronchial or (distal) bronchiolar fibrosis (similar to OB) was observed at the exposure concentrations tested. The lung weights (relative to body weight) of female rats and male and female mice exposed to 100 ppm were greater than that of control animals. White blood cell counts, lymphocytes, monocytes, and neutrophils were consistently elevated in female rats exposed to 50 and 100 ppm at various points during the 3-month study including the end of the study, indicative of inflammation. In male rats, neutrophil counts were similarly elevated, and lymphocyte counts were reduced by the end of the study. Blood cell counts were not assessed in mice. Tests evaluating the potential for acetoin or 2,3-pentanedione to damage DNA in rats and mice were negative.

Conclusions: *Under the conditions of the 3-month studies, inhalation exposure to 2,3-pentanedione resulted in noncancerous tissue abnormalities in the organs of the respiratory tract of rats and mice, but no OB-like fibrotic lesions were observed. Lower body weights were observed in male and female mice exposed to 50 ppm or more. Abnormal breathing and sneezing were observed in rats and mice, and noncancerous eye abnormalities were observed in rats and female mice. In contrast to 2,3-pentanedione, exposure to acetoin did not cause adverse effects in rats or mice under the conditions of the studies.*