MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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February 7, 2017

TO: File for 2,4-Pentanedione (CAS No. 123-54-6)

FROM: Michael Depa, Air Quality Division, Toxics Unit

SUBJECT: Initial Threshold Screening Level Derivation

The Initial Threshold Screening Level (ITSL) for 2,4-pentanedione is 25 µg/m^3 with annual averaging time.

Previously the ITSL for 2,4-pentanedione was 25 µg/m^3 with a 24-hr averaging time. The averaging time is being changed to annual because the derivation method of the ITSL (see attached memo dated 20 September 1999) specifically extrapolates the subchronic exposure of 14-weeks to a chronic (lifetime) exposure. The ITSL was based on a Reference Concentration pursuant to Rule 232(1)(a). According to Rule 232(2)(b), the averaging time is annual. An updated literature review was not done at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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September 20, 1999

TO: File for 2,4-Pentanedione (CAS# 123-54-6)

FROM: Michael Depa, Toxics Unit

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for 2,4-pentanedione (also called acetyl acetone) is 25 µg/m³ based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: EPA's Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, Internationals Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967 – April 10, 1999), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The molecular weight for 2,4-pentanedione is 100.13 g.

In an inhalation pharmacokinetic study, groups of 50 male F344 rats were nose-only exposed to 400 ppm 2,4-pentanedione for up to 6 hours (Bushy Run, 1995). Groups of 3 were removed from the chamber at the blood sampling intervals during the absorption phase. An additional group of 4 animals were kept after the inhalation exposure to collect blood samples for the elimination kinetics phase. The results of the inhalation experiment were compared to dose groups of male rats that were exposed to 2,4-pentanedione via intravenous injection. During the absorption phase, plasma concentrations of 2,4-pentanedione-derived radioactivity increased quickly over the first 3 hours then began to slowly plateau as the plasma approached equilibrium toward the end of the 6-hr inhalation exposure. These concentrations did not appear to reach steady-state, as evidenced by the continued increase in plasma C14 levels, particularly the first 0.5 hr interval sample after termination of the inhalation exposure. The authors stated that the overall clearance of 2,4-pentanedione was slower after inhalation than was observed for the comparable dose when given as a bolus injection IV. The majority of the dose was excreted in the urine within the first 12-24 hr after the exposure, and chromatographic analysis of the urine demonstrated that the 2,4-pentanedione was readily metabolized to several, more polar molecules prior to being voided in the urine.

In a developmental toxicity study, groups of 25 timed-pregnant F344 rats were exposed to 0, 53, 202 or 398 ppm 2,4-pentanedione vapor (0, 217, 826 or 1628 mg/m³) on gestational day 6 through 15 (Tyl et al., 1990). There was no maternal mortality. Body

weight was reduced at 1628 mg/m³ but not at the low and mid dose levels. Histological examination of maternal brains from the 1628 mg/m³ groups showed no abnormalities. No treatment-related effects were seen on number of corpora lutea; total, nonviable or viable implants per litter; pre or post implantation losses, or fetal sex ratio. Reduced fetal body weight per litter was seen at 1628 mg/m³ (males and females and all fetuses) and 826 mg/m³ (males and all fetuses). There was no concentration-related, or statistically significant increase in the incidence of individual malformations, malformations by category (external, visceral or skeletal), or total malformations. Partial fetal atelectasis was increased at 1628 mg/m³, and increased incidence of 17 skeletal variants (out of 79 observed) indicated a consistent pattern of fetal-toxicity at 1628 mg/m³. A maternal and developmental no-observed-adverse-effect-level (NOAEL) of 217 mg/m³ (53 ppm) was identified.

In a dominant lethal study, groups of 20 male Fischer 344 rats were exposed to 0, 99, 412 or 694 ppm 2,4-pentanedione for 6 hours per day for 5 days (Tyl et al, 1989). The day following the final exposure they were bred to unexposed female Fischer 344 rats, 2 per week for 8 consecutive weeks. Weight loss occurred with males during 2,4-pentanedione exposure for the 412 and 694 ppm group, for the first two weeks postexposure. No histopathological change was seen in brain, testes or thymus in the 694 ppm males sacrificed after eight weeks of mating. Relative brain weight was increased ($p<0.05$) in the 694 ppm dose group. Minor transient reproductive and gestational effects were present at 412 and 694 ppm. At week 2 there was a reduction, not statistically significant, in the number of corpora lutea and total and viable implants per dam at 694 ppm, and a slight increase in preimplantation loss. At week 3 the number of pregnant females was slightly reduced at 412 and 694 ppm ($p<0.05$), causing a lowered female fertility index. At week 4 there was a slight reduction in the number of total and viable implants per litter and a significant preimplantation loss at 694 ppm. The NOAEL for dominant lethal effects was 99 ppm (405 mg/m³).

In a 9-day inhalation study, groups of 10 male and female Fischer 344 rats were exposed to 0, 197, 418 or 805 ppm (0, 806, 1710 or 3292 mg/m³) 2,4-pentanedione for 6 hours per day for 5 days, then there was a two day rest, then another 4 days of exposure (Dodd et al., 1986). No animals died. Signs were sensory irritancy presented as partial eyelid closure with periocular and perioral wetness in three females of the 805 ppm group. No signs of sensory irritancy were seen in female rats of the intermediate and low concentration groups or in males of any group. A decrease in body weight was observed during the exposure period for male and female rats of the 805 ppm group. Male rats of the 418 ppm group had statistically significant decreased body weight gains throughout the study. The hematology results indicated a mild (approximately 20% above control value) leukocytosis for rats of the 805 ppm group, which was mainly the result of an increase in lymphocytes. The only other statistically significant alterations in hematologic indices were slight increase in mean corpuscular hemoglobin concentration (male rats only). The authors stated that these alterations in MCH were not toxicologically significant because there was no effect in red blood cell count or in hemoglobin concentration. No hematological changes were found in the animals of the 197 or 418 ppm groups. Relative organ weights were increased in most organs from the 805 ppm group. A noteworthy exception to this trend was the relative thymus gland weights of the 805 ppm male and female rats, where a 25 to 43% decrease from respective mean control values was observed. In addition, the absolute weight of the thymus of the 418 ppm male rats was reduced in comparison with the controls. No

treatment related differences in organ weights were noted at 197 ppm (806 mg/m³). An exposure-related inflammation of the nasal mucosa, seen as multifocal areas of congestion, epithelial vacuolization, and lymphocyte and neutrophil infiltration of the submucosa, was present in all 2,4-pentanedione exposed animals. Necrosis of the nasal mucosa was observed frequently in the 805 ppm rats and occasionally in the 418 ppm animals, but was not observed in the 197 ppm group. The low dose of 806 mg/m³ was determined to be a LOAEL based on nasal irritation.

In a 14-week inhalation study, groups of 20 male and female Fischer 344 rats were exposed to 0, 101, 307 or 650 ppm (0, 413, 1256 or 2658 mg/m³) 2,4-pentanedione for 6 hours per day, 5 days per week (Dodd et al, 1986). Death occurred in all female rats exposed to 650 ppm (2658 mg/m³) and 10 of 30 males. Death occurred between the 2nd and 6th week of exposure. Body weights of the 650 ppm males were significantly reduced throughout the 14 week exposure period and during the 4 week recovery period. Also, females of the 307 ppm dose group had slight, but statistically significant decreased body weight gains for study days 45 through 121.

Table 1 shows the biological parameters that were found to be significantly different from control rats ($p<0.05$). Mean corpuscular volume (MCV) was statistically increased in all dosed groups. Decreased creatinine ($p<0.05$) was observed in the low and high dosed males but not in the mid-dose; therefore, it was not considered biologically significant. There were no other effects besides increased MCV observed at the low dose level. Because the MCV was increased in all dosed groups it was concluded that the lowest dose group tested (i.e., 101 ppm or 413 mg/m³) was the lowest-observed-adverse-effect-level (LOAEL).

Table 1. Biological Effects[2] from Exposure to 2,4-Pentanedione (Dodd et al, 1986)

	101 ppm (413 mg/m³)	307 ppm (1256 mg/m³)	650 ppm (2658 mg/m³)
Male Rats			
mortality			↑
body weight			↓
white blood cell			↑
red blood cell			↓
hematocrit			↓
mean corpuscular hemoglobin			↑
mean corpuscular volume	↑	↑	↑
creatinine	↓		↓
calcium		↓	↓
lung weight			↑
squamous metaplasia in nose			↑
thymic atrophy			↑
testes weight			↑
Female Rats			
mortality			↑
body weight		↓	↓
white blood cell			↑
Continued on next page…			

	101 ppm (413 mg/m³)	307 ppm (1256 mg/m³)	650 ppm (2658 mg/m³)
Female Rats (Table 1. continued)			
red blood cell			↓
hematocrit			↓
mean corpuscular hemoglobin			↑
mean corpuscular volume	↑	↑	↑
calcium		↓	
lung weight		↑	
thymic atrophy			↑

[1] Significantly different compared to controls ($p<0.05$)
[2] If a toxicological effect is not listed then there were either no significant difference between control and dosed animals or the parameter was not analyzed.

The same rats used in the Dodd et al. (1986) study were also examined for neurological effects in a study published by Garman et al. (1986). Again, rats were exposed for 14-weeks to 0, 101, 305 or 650 ppm (0, 413, 1256 or 2658 mg/m³) 2,4-pentanedione for 6 hours per day, 5 days per week. A neurobehavioral Irwin screen was performed prior to the first exposure and monthly thereafter. The brains were divided into five coronal slices and examined by microscope. The five slices included:

cerebral cortex and main body of the caudate nucleus-putamen;
cerebral cortex with thalamus and hypothalamus;
cerebral cortex with midbrain;
cerebellum and pons; and
medulla oblongata.

The actual doses (as in the previous study by Dodd et al. 1986) were 101, 307 or 650 ppm. No clinical signs of neurotoxicity were seen in the 101 or 307 ppm animals. General signs seen in the 650 ppm 2,4-pentanedione exposed rats included hypothermia, excess lacrimation, and encrustation in the perioral, perinasal and periocular areas. Neurological signs in the 650 ppm group included hypoactivity, incoordination ataxia, paresis, and slowed righting reflexes. Neurological signs developed an average of 21 days after the first exposure day for males and 17 days for females. Signs persisted until the time of death. Deaths occurred only at 650 ppm, with all females and 10 of the 30 males dying by the sixth week. Absolute brain weight was reduced ($p<0.05$) in the male rat 650 ppm dose group; however, the relative brain weight was increased compared to control rats in the same rats (caused by a decreased body weight). Every 2,4-pentanedione exposed animal that exhibited an abnormality in the Irwin screen had neuropathological changes in the brain. However, two of the seven surviving rats that had brain lesions did not demonstrate abnormalities in the Irwin screen. Twenty-five of the 30 animals that died, and seven of the 15 males that survived, had light microscopical evidence of degenerative lesions, principally within the caudate/putamen nuclei, nuclei of the cerebellar medulla, and vestibular nuclei. Less frequently involved, in animals that died, were various regions of the cerebral cortex. The early histopathological lesions seen from the 16th study day (12 exposures) to the 38th study day (28 exposures) were characterized by malacia. When present, lesions in male rats surviving the 14-weeks of 650 ppm exposure were characterized by malacia and gliosis. No peripheral nerve lesions were seen by light or transmission electron microscopy. The authors stated that neither mortality nor neuropathology were seen in

rats subchronically exposed to 101 or 307 ppm 2,4-pentanedione; therefore, the high dose group of 650 ppm was determined to be a neurological LOAEL, and the 307 ppm dose group was determined to be a NOAEL.

Derivation of Screening Level

An RfC can be derived from the subchronic inhalation study by Dodd et al. (1986). Since the MCV was statistically increased in all the dosed groups, the lowest dose level of 100 ppm (or 413 mg/m³) was determined to be a LOAEL. However, since the magnitude of the difference in MCV from control was less than 10% it was determined to a "mild" effect. Accordingly, an uncertainty factor of 3 was used to extrapolate from a LOAEL to NOAEL. The duration adjusted exposure concentration was calculated as follows:

$LOAEL_{ADJ}$ = LOAEL x 6 hours/day x 5 days/week

$LOAEL_{ADJ}$ = 413 mg/m³ x 6/24 x 5/7

$LOAEL_{ADJ}$ = 73.75 mg/m³

The human equivalent concentration (HEC) was calculated from the adjusted LOAEL. According to EPA RfC methodology (EPA, 1994) 2,4-pentanedione fits the definition of a category 2 gas. And since the blood/gas partition coefficient is unknown, the $LOAEL_{HEC}$ = $LOAEL_{ADJ}$. The RfC can be derived from the $LOAEL_{HEC}$ as follows:

$RfC = LOAEL_{HEC} \div (UF_1 \times UF_2 \times UF_3 \times UF_4)$

Where,

UF_1 is 10 to account for the uncertainty in extrapolating from animals to humans
UF_2 is 10 to account for the uncertainty in extrapolating from human to sensitive humans
UF_3 is 10 to account for the uncertainty in extrapolating from subchronic to chronic
UF_4 is 3 to account for the uncertainty in extrapolating from LOAEL to NOAEL.

The RfC then becomes:

RfC = 73.75 mg/m³ ÷ (10 x 10 x 10 x 3)

RfC = 0.02458 mg/m³

RfC = 25 µg/m³ (based on a 24-hour averaging time)

According to Rule 232(1)(a) the ITSL shall be equal to the RfC; therefore, the ITSL for 2,4-pentanedione is 25 µg/m³ (based on a 24-hour averaging time). The ITSL of 25 µg/m³ was determined to be protective of the developmental and reproductive effects, especially since neither the developmental or dominant lethal studies by Tyl et al. (1990) showed any adverse effects.

REFERENCES:

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