MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Propylene carbonate [CAS# 108-32-7]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: September 18, 2017

SUBJECT: Propylene carbonate [CAS# 108-32-7] ITSL change in the averaging time from 24 hours to annual

The current initial threshold screening level (ITSL) for propylene carbonate is 700 µg/m^3 based on an annual averaging time. The ITSL of 714 µg/m^3 established on 4/1/1998 is based on a Burleigh-Flayer et al. (1991) 90-day rat inhalation study, which showed periocular swelling in male rats as the critical effect. The ITSL should have been rounded to two decimal places to account for the use of uncertainty involved in generating the screening level, which would have given an ITSL of 700 µg/m^3. When the screening level was derived in 1998 the averaging time was set at 24 hours. As the basis for the screening level used a 90-day inhalation study, the averaging time may appropriately be set at annual. Therefore, the averaging time is being changed from 24 hours to annual.

References:

APCR. 2016. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994. Act 451, as amended (NREPA).

Burleigh-Flayer HD, Kintegh WJ. 1991. Propylene carbonate: nine-day aerosol inhalation study on rats. Project Report 51-633. Bushy Run Research Center R.D. 4, Mellon Road, Export, Pennsylvania 15632. Sponsored by Texaco, Inc., POB 509, Beacon, NY (Ray Papciak)

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 1, 1998

TO: File for Propylene Carbonate (CAS No. 108-32-7)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for propylene carbonate (also called propylene glycol cyclic carbonate) is 714 $\mu g/m^3$ based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967 - November 4, 1997), National Library of Medicine Toxline, 1997 Health Effects Assessment Summary Tables, and NTP Status Report. Review of these sources found that EPA has not established an RfD or RfC for propylene carbonate. The ACGIH and NIOSH have not established occupational exposure limits (OELs). The molecular weight of propylene carbonate is 102.1 g. The vapor pressure of propylene carbonate is 0.03 mmHg (20°C).

ANIMAL STUDIES

The LD50 was reported to be 29,100 mg/kg (23,800 - 35,500 95% C.L.); where groups of 5 Carworth-Wistar rats (90 - 120 g in body weight) were given a single oral dose (by gavage) then observed for 14 days (Smyth et al., 1954).

The following toxicity studies were obtained from the Huntsman Corporation (3040 Post Oak Boulevard, Houston, Texas 77056) after personal communication with Ray Papciak (713 - 235-6406).

In a developmental toxicity study, groups of 27 Sprague Dawley rat dams were exposed by gavage to 1000, 3000, or 5000 mg/kg/day of propylene carbonate on days 6 through 15 of gestation (Pharmakon Research, 1988). A negative control group was dosed with deionized water. The study concluded on day 20 of gestation, with a gross necropsy and cesarean section on each dam. The incidences of the following parameters were recorded in the dosed and control groups: corpora lutea, viable and non-viable fetuses, early and late resorptions, and total implants. All fetuses were externally examined, sexed, and weighted. Approximately one-half of the fetuses were stained and examined for skeletal abnormalities, and the remaining fetuses were stained and examined for "soft" tissue" (neural and visceral) abnormalities.

RESULTS: Maternal toxicity was observed in the high dose group as evidenced by statistically significant changes (decreases) in body weight, rate of weight gain, and food consumption parameters. Food consumption was also decreased for the mid dose group. Seven dams died during the course of this study, two from the mid dose groups and five from the high dose group. No significant differences were observed for any recorded fertility parameters including pre- or post-implantation losses, viable and non-viable fetuses, fetal sex distribution or fetal body weight. No fetal deaths were observed at cesarean section. The authors stated that when observed for gross effects, as well as skeletal and visceral abnormalities, no fetal malformations were observed. The authors also stated that the majority of fetal variations observed involved incomplete or delayed ossification of the sternebrae, skull, and hyoid arch. The authors concluded that propylene carbonate at concentrations of up to 5000 mg/kg/day do not induce developmental toxicity ($NOAEL_{DEV}$ = 5000 mg/kg/day).

Groups of 30 Sprague Dawley rats (15 per sex) were dosed by gavage with 0, 1000, 3000, or 5000 mg/kg/day of propylene carbonate for 90 days (Pharmakon Research, 1989). A recovery groups (high dose) with corresponding control was also included to determine the persistence/ reversibility of any observed toxic effects. The 30 day recovery period began on day 90, after the last dosing of the study animals. An interim sacrifice/necropsy on study day 30 was performed using 10 of the 30 rats per group (except recovery group). The remaining 20 rats per group continued on study until day 90. At all scheduled sacrifices (day 30, 90, and 118) blood samples were collected for clinical chemistry and hematology determinations; opthalmological observation were performed; the animals were necropsied and grossly examined; and a full screen of potential target systems were fixed and retained for histopathology examination. RESULTS: Significant differences were observed between the high dose recovery group males and the recovery control group males with regard to group mean body weight reductions, and decreases in daily food consumption. These differences were noted periodically over the dosing interval. Neither the high dose recovery females, nor the non-recovery high dose (both sexes) had similar weight reductions. When the control male non-recovery and control male recovery group weights were pooled, the difference between the high dose male body weight and the pooled recovery and non-recovery males disappeared. Five animals died during the course of the study; all occurred in the high dose recovery groups (three males and 2 females). The deaths occurred during the dosing portion of the study. An examination of the rats dying during the study revealed findings supporting upper respiratory infections as the cause of death in three of the five rats. The tissues from the remaining two rats suffered from varying degrees of autolysis, and could not provide a clear indication of the cause of death. At terminal necropsy (day 118), the high dose absolute kidney weights were significantly reduced in the male rats. At terminal necropsy, the high dose male relative testes weights were significantly increased. The high dose male recent kidneys to brain weight were significantly decreased at the day 30 interim necropsy. No additional significant relative organ to brain weight changes were noted at necropsy. Several clinical chemistry and hematology parameters were noted to be significantly different when compared to controls. At day 30 interim necropsy, significant increases were observed in the high dose male albumin, creatinine and chloride values. Total bilirubin was significantly increased in the male low dose group. High dose female albumin and calcium were significantly increased, whereas, the phosphorous values were significantly decreased. Significant increases were observed in the mid and high dose male phosphorous values and high dose male chloride

levels at the day 90 sacrifice. Significant increases in females at the day 90 sacrifice included (low dose) total bilirubin, phosphorous and (high dose) sodium levels. Significant decreases were observed in the low and high dose glucose levels. At the terminal necropsy, significant decreases were observed in the high dose male and female total protein and albumin levels. Statistically significant decreases were observed in the high dose male GGPT and globulin values and high dose female calcium levels. Significant increases were observed in the high dose female red blood cell counts, hematocrit and hemoglobin values. Neither the blood chemistry no hematologic changes observed were dose-dependent. The authors stated that histopathological examinations of the control and high dose group (5000 mg/kg) at the 90 day sacrifice did not reveal any lesions considered to be attributable to propylene carbonate. No significant differences were noted in spermatogenesis, ovarian activity, and bone marrow activity, when comparisons were made between high dose groups and controls. The authors concluded that concentrations up to 5000 mg/kg/day propylene carbonate did not induce any significant toxic effects when ingested over a 90 day period.

In a subacute inhalation study, four groups of 5 male and 5 female Fischer 344/CDF rats received whole-body exposures for 6-hours/day, for 9 days over an 11-day period to either filtered air or to aerosol of propylene carbonate at target concentrations of 0, 1000, 2500, and 5000 mg/m^3 (Burleigh-Flayer et al., 1989). Parameters for toxic effects included clinical observations, body and organ weights, and macroscopic and microscopic evaluations. RESULTS: Mean gravimetric concentrations of 996, 2489 and 5092 mg/m^3 were obtained. In the first week of the study there were clinical signs of ataxia and emaciation at the 5092 mg/m^3 dose. These clinical signs were absent by week two. No mortality occurred during the study. No effects on absolute body weight were observed but decreases in body weight gain occurred for both male and female rats at all exposure concentrations. Female animals exposed to 5000 mg/m^3 propylene carbonate had increased absolute and relative (as % of body weight) liver weights along with and increased relative kidney weight. Four of five females at the 5000 mg/m^3 had swollen eyelids and swollen periocular tissue; in the 2500 mg/m^3 female group the incidence was one of five. No significant gross lesions were found in male rats exposed to propylene carbonate. The lesions observed microscopically in the nasal cavities included squamous metaplasia of the maxillary and/or nasal turbinates in two of five female animals and respiratory epithelial necrosis in one of five females of the 5000 mg/m^3 group. Significant histologic changes occurred only in the larynx and eye of one male rat exposed to 5000 mg/m^3.

In a subchronic inhalation study, groups of 30 (15 per sex) Sprague Dawley rats were exposed to aerosol concentrations of 0, 102, 500 or 1010 mg/m^3 propylene carbonate 6 hours per day, 5 days per week for 90 days (Burleigh-Flayer et al., 1991). The mass mean aerodynamic diameters (MMAD) for the 100, 500 and 1000 mg/m^3 concentrations were 5.32, 4.62, and 4.72 μm, respectively, with geometric standard deviations (σ_g) 2.74, 2.52, and 2.32. RESULTS: No animals died during the course of the study. No significant differences were observed between any test article group and the controls with regard to body weights. With the exception of swollen periocular tissues noted in the propylene carbonate exposure groups, no other significant signs of toxicity were noted during the study. No changes in body weight or food consumption were noted during the course of the study. Significant decreases in relative (as a % of body and brain weight) lung weight were observed for male animals of all three propylene carbonate

exposure groups; however, there were no histopathologic changes and were believed to be spurious by the authors. Hematology, clinical chemistry and urinalysis evaluations showed no changes resulting from exposure to propylene carbonate. The incidence of periocular swelling in males rats at was 0/15, 2/15, 3/15 and 5/15 in control, low, medium and high dose, respectively. The incidence of periocular swelling was found to be statistically significant (P=0.021) at 1000 mg/m^3 by Fisher's Exact P. The incidence of periocular swelling in the dosed female rats was not statistically different from control animals (8/15, 4/15, 10/15, and 11/15 in control, low, medium and high dose, respectively). In addition, occasional inflammatory lesions such as rhinitis, tracheitis, or laryngitis, were observed in various exposure groups but not at statistically significant incidences. No significant lesions were detected in the lungs of any treated animals. No systemic toxicity was observed during the course of the study. A neurotoxicity evaluation using a Functional Observational Battery was also performed. The authors reported that no behavioral alterations were observed. A LOAEL of 1000 mg/m^3 was identified based on perioccular swelling. A NOAEL of 500 mg/m^3 was also identified.

The ITSL was developed according to EPA (1994) methodology using the male rat NOAEL of 500 mg/m^3 from the 90-day inhalation study (Burleigh-Flayer et al., 1991). A regional deposited dose ratio (RDDR) of 2.516 for extrarespiratory effects (i.e. perioccular swelling) was calculated from the EPA (1994) RDDR computer program. The study specific data required for this program included: rat, weight of rat (349g), the MMAD of 4.62 μm and σ_g of 2.52 μm (taken from Burleigh-Flayer et al., 1991). The NOAEL of 500 mg/m^3 was time adjusted as follows:

$NOAEL_{adj}$ = NOAEL x hrs/day x days/week

$NOAEL_{adj}$ = 500 mg/m^3 x 6/24 x 5/7

$NOAEL_{adj}$ = 89.29 mg/m^3

$NOAEL_{adj}$ = 89.3 mg/m^3

The $NOAEL_{adj}$ was then converted to the human equivalent concentration (HEC) by multiplying the $NOAEL_{adj}$ by the RDDR of 2.398 as follows:

$NOAEL_{HEC}$ = $NOAEL_{adj}$ x RDDR

$NOAEL_{HEC}$ = 89.3 mg/m^3 x 2.398

$NOAEL_{HEC}$ =214 mg/m^3

Uncertainty factors (UFs) are then applied to account for recognized uncertainties in the extrapolation from the experimental data conditions to an estimate appropriate to the assumed human scenario. The RfC was calculated as follows:

$RfC = NOAEL_{HEC}/(UF_1 \times UF_2 \times UF_3)$

Where UF1 = 10; to account for the uncertainty of sensitive individuals,
UF_2 = 10; to account for the uncertainty of subchronic to chronic extrapolation,
UF_3 = 3; to account for interspecies variability

RfC = 214 mg/m³/(10 x 10 x 3)

RfC = 0.714 mg/m³

RfC = 714 µg/m³ (based on a 24-hour averaging time)

According to Rule 230(1)(a) the ITSL shall equal the RfC; therefore the ITSL for propylene carbonate is 714 µg/m³ based on a 24-hour averaging time.

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Burleigh-Flayer HD, Kintegh WJ. 1989. Propylene carbonate: nine-day aerosol inhalation study on rats. Project Report 51-633. Bushy Run Research Center R.D. 4, Mellon Road, Export, Pennsylvania 15632. Sponsored By Texaco, Inc., POB 509, Beacon, NY (Ray Papciak)

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MD:SLB
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