MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

November 9, 2015

To: File for 1-Propoxy-2-Propanol (CAS No. 1569-01-3)

From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

Previously, the averaging time (AT) assigned to 1-Propoxy-2-Propanol was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from The Scientific Advisory Panel dated April 14, 1995). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

RECOMMENDATIONS
OF THE
SCIENTIFIC ADVISORY PANEL

1-PROPOXY-2-PROPANOL

CAS # 1569-01-3

April 14, 1995

Basis for Previous ITSL

A CAS-online literature search conducted for 1-propoxy-2-propanol (1P2P) in July 1992, found only one article by Ballantyne et al, (1988) which reported the results of acute oral, inhalation, and irritation studies. The inhalation study did not provide the minimum data requirements that would allow the setting of an LC50. However, an oral rat LD50 study did provide enough information to calculate an LD50 of 2.83 ml/kg for female rats. This LD50 value was used to calculate an ITSL of 8 $\mu g/m^3$ based on annual averaging time.

Summary of Public Comment:

The only public comment received for this compound was from the American Automobile Manufacturers Association. They stated that subsequent to the 1988 study by Ballantyne, the Union Carbide Company submitted to the Environmental Protection Agency (EPA) three, 1P2P toxicity studies on rats, rabbits, and guinea pigs. The AAMA requested these studies be used by the Scientific Advisory Panel in revising the existing ITSL for 1P2P.

Response to Public Comment:

According to Patty's Industrial Hygiene and Toxicology (4th ed.), propylene glycol-n-monopropyl ether or 1- propoxy-2-propanol is of moderate acute oral toxicity and is slightly toxic by skin absorption. The material is severely irritating to the eyes and can cause mild corneal injury, which may be slow in healing. It is essentially nonirritating to the skin by acute contact; however, prolonged or occluded contact can cause severe irritation. Because of its relatively low vapor pressure, inhalation is not anticipated to present a significant hazard under conditions of ambient temperatures.

In early studies (1950s) conducted at Union Carbide's Bushy Run Research Center (BRRC), the acute oral LD50 in rats for undiluted 1P2P was found to be 3.25 ml/kg (2.9 g/kg). In addition, two separate twenty-four hour occluded percutaneous LD50 rabbit studies listed values of 4.0 ml/kg (3.5 g/kg) and 3.17 ml/kg (2.8 g/kg). Eye irritation, in the form of iritis and lacrimation was observed during one of the percutaneous toxicity tests. Irritation tests on rabbits showed minimal skin irritation and moderately severe corneal necrosis.

Subsequent to the early toxicity studies mentioned above, the BRRC conducted additional toxicity studies on 1P2P for TSCA (Toxic Substance Control Act) requirements. These have included a series of 9-day inhalation studies, acute and primary irritancy studies, 2-week inhalation studies, and a 14-week inhalation study.

In one of the 9-day inhalation studies (BRRC Report #49-120, 1987), four groups of ten F-344 rats/sex were exposed 6 hrs/day to mean 1P2P vapor concentrations of 0, 503, 983, or 2000

ppm. The results suggested that the eye was the primary target organ for whole-body exposure to 1P2P vapor. Rats exposed to 2000 ppm had histopathological lesions which included keratitis, superficial ulceration, vascularization and stromal mineralization. Rats exposed to 503 or 983 ppm of 1P2P vapor also developed histological eye lesions, but the lesions were not as severe as those observed in the 2000 ppm group. Decreased body weight gains and increased liver and kidney weights were observed in both sexes of the 2000 ppm group. Males of the 983 ppm group had increased liver and kidney weights, while males of the 503 ppm group had an increased kidney/body weight value. No histopathology was observed in the kidneys or liver for the 2000 ppm group.

In addition to the 9-day inhalation study mentioned above, Union Carbide conducted three more 9-day inhalation studies to further assess the acute toxicity and primary irritancy of 1P2P (BRRC Report #s 49-179, 1986; 50-8, 1987; 52-28, 1989). One study (BRRC #49-179) showed that exposure of Sprague-Dawley rats to a dynamically-generated, substantially saturated vapor produced no mortalities during a 6-hour exposure. While another 9-day inhalation study (BRRC #50-8) conducted with male Fischer-344 and Sprague-Dawley rats, male New Zealand white rabbits, and Hartley guinea pigs were exposed 6 hrs/day at a mean vapor concentration of 105, 486, or 1824 ppm. The results of this study indicated that there was not only a biological difference in species susceptibility to toxicity from 1P2P vapor, but there were obvious differences between the rat strains as well, as described below.

Exposure to 1824 ppm 1P2P produced ocular irritation, eye lesions, and central nervous system depression (ataxia, prostration, narcosis) in both strains of rats and in rabbits. Three of six rabbits died at this exposure. F-344 rats were the most sensitive species for eye lesions, and developed conjunctivitis, keratitis, and corneal opacities. Histologically, the eyes of the F-344 rats showed necrosis of the conical epithelium, stromal mineralization and fibrosis, and conical vascularization. The severity of these lesions was related to both the number of exposures and the exposure concentration. Moreover, these ocular lesions persisted throughout a 4-week recovery period. In comparison, Sprague-Dawley rats exposed to 1824 ppm 1P2P had opacities and keratitis, but no eye lesions were considered to be permanent in nature (e.g., mineralization, stromal fibrosis, or corneal vascularization). Eye lesions in this same dose group of rabbits consisted of conjunctivitis, keratitis, transient opacities, and corneal epitheial degeneration. Guinea pigs exposed to the high dose exhibited neither central nervous system depression nor ocular lesions. Exposure to 486 and 105 ppm 1P2P produced eye lesions similar to those described in the 1824 ppm group for all test species (except the guinea pig), although at a much lower incidence. Only in the F-344 rat were lesions produced not considered to be reversible.

An additional 9-day study was conducted to determine a NOEL for the ocular effects of F-344 rats (BRRC Report #52-28, 1989). Male F-344 and Sprague-Dawley rats were exposed 6 hrs/day to mean concentrations of 5, 48, or 99 ppm 1P2P. There were no ocular changes associated with 1P2P exposure for either strain at any concentration. This was in contrast to the previous study (BRRC #50-8) in which low incidence of nonreversible eye lesions was produced in F-344 rats exposed to 105 ppm. The explanation for this difference was attributed to the pre-existing condition of conical dystrophy in the animal supplier's rat colonies. BRRC's animal supplier worked to eliminate the cases of conical dystrophy from their colonies in preparation for subsequent studies. In addition, BRRC eliminated all but the most minimally

affected rats from being placed on the study by having a veterinary ophthalmologist examine pre-test animals with more sensitive instrumentation.

Union Carbide finally detemined a NOAEL from a fourteen-week vapor inhalation study (BRRC Report #53-44, 1990), using F-344 and Sprague-Dawley rats. Four groups of F-344 and Sprague-Dawley rats, each containing 20 males and 20 females, received whole-body exposures of either filtered air or vapor of 1P2P for 6 hours/day, 5 days/week for 14 weeks; target concentrations were 0, 30, 100, or 300 ppm. Half of the animals (10/sex/strain/group) were kept for an additional 3-month recovery period. Monitors for toxic effects included clinical observations, ophthalmic examinations, body and organ weights, clinical pathology (hematology, serum chemistry, and urinalysis), and macro- and microscopic evaluations. There were no exposure related clinical signs during the study. For all groups of animals, eyes appeared normal during ophthalmic examinations.

There was a slight decrease in total leukocyte count for female F-344 rats (300 and 30 ppm groups) associated with a decrease in lymphocytes (300 ppm group). These effects were absent at the end of the recovery period. Other statistically significant differences were neither consistent nor concentration related and were considered to be spurious.

There were statistically significant decreased body weight and body weight gains for female F-344 rats of the 300 ppm group. The weight gains were lower for most of the exposure period and for 4 weeks following the end of the exposure regimen. At the end of the last full week of 1P2P exposures (Week 13), the body weight gain for the 300 ppm group females was 84% of that of controls. Female F-344 rats of the 100 ppm group had a statistically significantly lower body weight gain at the end of the second exposure week, after which no further effects occurred during the 1P2P exposure regimen. There were no significant exposure-related effects on the body weight or body weight gain for female F-344 rats of the 30 ppm group, any of the groups of male F-344 rats or either sex of the SD rats.

All other testing parameters appeared normal. No exposure-related gross or microscopic lesions were identified at necropsy or during pathologic examination. Corneal dystrophy was observed in rats of all groups, including the control group.

The authors suggested 300 ppm as a LOAEL, or marginal-effects concentration; and 100 ppm a no-observable-adverse-effect-concentration, or NOAEL. The Scientific Advisory Panel (SAP) concurred with this outcome at its February 28, 1995 meeting. According to the Panel, the data did not show that a true dose-response relationship existed for 1P2P and its effect on body weights in F-344 female rats. When determining if a dose-response relationship does exist, there must be consistent change in the measured parameter with a corresponding change in dose e.g., body weights; and that a clearly adverse effect should be consistent and congruent with increasing dose. The Panel agreed that data presented in this study did not follow this criteria. Additionally, Panel members questioned the type of statistics that was used to account for multiple comparisons to controls. They stated that if the proper statistical analysis was used, significant data points at the 30 ppm dose level would not have been observed. Therefore, a motion was made and approved by the panel to set 100 ppm as a NOAEL, and 300 ppm as a LOAEL for this study.

The ITSL was derived as follows using Rule 232(1)(a); RfC Methodology

Molecular weight of 1P2P = 118.2g
NOAEL = 100 ppm

Conversion of NOAEL ppm to NOAEL mg/m³:

$mg/m^3 = ppm \times MW/(24.45)$
$mg/m^3 = 100 \text{ ppm} \times 118.2/24.45 = 483.4 \text{ mg/m}^3$

To calculate the duration-adjusted exposure levels in mg/m³ for experimental animals:

E = experimental exposure level
D = number of (hours exposed/day)/24 hours, and
W = number of (days of exposure/week)/7 days.

$NOAEL_{[ADJ]} (mg/m^3) = E(mg/m^3) \times D(\text{hours/day/24 hours}) \times W(\text{days/7 days})$
$NOAEL_{[ADJ]} (mg/m^3) = 483.4 \text{ mg/m}^3 \times 6/24 \times 5/7 = 86.3 \text{ mg/m}^3$

To calculate the NOAEL human equivalent concentration:

The exposure related effects observed in the test animals were extrarespiratory effects (e.g., decrease in body weight gain, and hematologic effects). For gases and vapors that exhibit their toxic effects outside of the respiratory tract, an approach for the scenario when the arterial concentration (leaving the lung) of the gas in the animal is periodic with respect to time is to use the following equation:

$NOAEL_{[HEC]}$ = the NOAEL human equivalent concentration,
$NOAEL_{[ADJ]}$ = the NOAEL adjusted for duration, and
λ_A/λ_H = the ratio of the blood to air partition coefficient of the chemical for the animal species to the human value. In the case where λ values are unknown, the default value of $\lambda_A/\lambda_H = 1$.

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} (mg/m^3) \times \lambda_A/\lambda_H$
$NOAEL_{[HEC]} (mg/m^3) = 86.3 \text{ mg/m}^3 \times 1/1 = 86.3 \text{ mg/m}^3$

Using this equation is based on the fact that the internal concentration of the inhaled agent achieved a consistent pattern over the 14 weeks of exposure, or periodicity. The conditions of periodicity are assumed to have been met with a 6 hr/day, 5 days/week for 14 weeks.

To calculate the RfC:

UF = an uncertainty factor of 1000 is based on 10 for sensitive individuals, 10 for extrapolating animal data to humans, and 10 for extrapolating subchronic data to chronic data.
MF = modifying factor (equal to 1)

$RfC = [NOAEL_{[HEC]} (mg/m^3)]/[UF \times MF]$
$RfC = (86.3 \text{ mg/m}^3)/(10x10x10) = 0.0863 \text{ mg/m}^3$

mg/m^3 to $\mu g/m^3$ conversion:
$0.0863 \text{ mg/m}^3 \times 1000 = 86.3 \text{ } \mu g/m^3$

ITSL for 1-propoxy-2-propanol = 86 $\mu g/m^3$ for 24 hr. averaging.

References:

1. Ballantyne et al., 1988. The acute toxicity and primary irritancy of 1-propoxy-2-propanol. Vet Human Toxicol 30:126-129.
2. Gingell, R. et al., 1994. Glycol Ethers and Other Selected Glycol Derivatives. Patty's Industrial Hygiene and Toxicology, 4th cd., Volume II; Part D. George and Florence Clayton, editors. John Wiley & Sons, Inc. New York. pgs. 2761-2966.
3. Bushy Run Research Center, Project Report # 49-120. Propasol® Solvent P: Nine-Day Vapor Exposure Study on Rats. January 15, 1987. TSCA §8(e) Compliance Audit Program (8ECAP-01 10). EPA-OTS (88- 920002627).
4. Bushy Run Research Center, Project Report # 49-179. Propasol® Solvent P: Acute Toxicity and Primary Irritancy Studies. December 23, 1986. TSCA §8(e) Compliance Audit Program (8ECAP-01 10). EPA-OTS (88-920002627).
5. Bushy Run Research Center, Project Report # 40. Propasol® Solvent P: Solvent P: Nine-Day Vapor Exposure Study on Male Rats, Rabbits, and Guinea Pigs with Particular Reference to Ocular Effects. September 30, 1987. TSCA §8(e) Compliance Audit Program (8ECAP-01 10). EPA-OTS (88-920002627).
6. Bushy Run Research Center, Project Report # 52-28. Propasol® Solvent P: Solvent P: Additional Two-Week Vapor Exposure Study with Male Fischer 344 and Sprague-Dawley Rats. April 4, 1989. TSCA §8(e) Compliance Audit Program (8ECAP-0110). EPA-OTS (89-090000150).
7. Bushy Run Research Center, Project Report # 53-44. Propasol® Solvent P: Solvent P: Fourteen-Week Vapor Inhalation Study with Male Fischer 344 and Sprague-Dawley Rats. July 19, 1990, TSCA §8(e) Compliance Audit Program (8ECAP-01 10). EPA-OTS (89-900000372).