MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Cumene [CAS# 98-82-8]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 20, 2017

SUBJECT: Cumene [CAS# 98-82-8] ITSL change in the averaging time from 24 hours to annual

The current initial threshold screening level (ITSL) for cumene is 400 µg/m^3 based on an annual averaging time. The ITSL established on 5/16/2014 based on an EPA reference concentration (RfC) of 400 µg/m^3 based on two rat inhalation studies by Cushman et al. (1995). The first study was a 13-week rat inhalation study, the second study was a 13-week inhalation study with a 4-week recovery period. The critical effects observed were increased in kidney weights in female rats and increased adrenal weights in male and female rats. When the screening level was derived in 2014 the averaging time was set at 24 hours. As the basis for the screening level used two studies with a minimum of 13 weeks, the averaging time may appropriately be set at annual. Therefore, the averaging time is being changed from 24 hours to annual at this time.

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).

Cushman JR, Norris JC, Dodd DE, Darmer KI, and Morris CR. 1995. Subchronic inhalation toxicity assessment of cumene in Fischer 344 rats. J. Am. Coll. Toxicol. 14(2):129-147.

EPA. 1997. Integrated Risk Information System. Cumene (CASRN 98-82-8). Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=306

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Cumene File (CAS # 98-82-8)

FROM: Doreen Lehner

SUBJECT: Initial Threshold Screening level for Cumene (CAS # 98-82-8)

DATE: May 16, 2014

The Initial Threshold Screening Level (ITSL) for cumene (CAS # 98-82-8) is 400 µg/m^3 based on a 24-hour averaging time.

This ITSL is based on the EPA 1997 Reference Concentration for Chronic Inhalation Exposure (RfC) for cumene of 400 µg/m^3. The EPA derived the RfC from two successive rat inhalation studies performed by Cushman et al., (1995). "Two successive subchronic inhalation toxicity studies with cumene vapor (>99.9% pure) were conducted on Fischer 344 rats. In the first study, groups (21/sex) were exposed to 0, 100, 496, or 1202 ppm (0, 492, 2438, or 5909 mg/cu.m, respectively) cumene vapor for 6 hours/day, 5 days/week, for 13 weeks (duration adjusted to 0, 88, 435, and 1055 mg/cu.m). In the second study, the group size was decreased to 15/sex, an additional group (50 ppm, duration adjusted to 44 mg/cu.m) was added, and a 4-week post-exposure recovery period was incorporated at the end of the experiment. Animals were sacrificed a few days after the last exposure in the first study and after the 4-week post-exposure period in the second study. Parameters monitored included clinical signs of toxicity, body weight, food and water consumption, hematology and serum chemistry, organ weights, gross and histopathology (including examination of all respiratory tract tissues, including three sections of the lungs and four sections of the nasal turbinates). Extensive neurotoxicity (including motor activity tests and neurohistopathology) and auditory brain stem responses were assessed in the second study. Some quantitative and morphologic evaluations of spermato-genesis also were examined in the first study (epididymal tissue was taken from 15 rats/group in the first study, and the left testis was taken from each male) in an effort to judge the potential of cumene to cause reproductive toxicity" (EPA, 1997).

"Both absolute and relative weights were increased significantly (>10%, p</= 0.05) in the kidneys and adrenal glands of both sexes at the highest concentration in the first study. The results of the second study, with a 4-week post-exposure period, indicated limited reversibility to these alterations. In this second study, significant mean weight increases were present 4 weeks post-exposure in adrenals from females exposed to the highest concentration. These alterations are considered toxicologically significant and adverse, because such persistence indicates limited reversibility and uncertainty about the progression and fate of these alterations under chronic exposures. No reproducible or dose-related neurotoxicological effects or neurohisto-pathology were noted. Morphological evaluation of epididymal and testicular sperm showed no cumene-related differences in count, morphology, or stages of spermatogenesis, although one high-dose rat did have diffuse testicular atrophy. The only microscopic effect associated with

these organ weight changes was increased incidence of kidney lesions at the two highest exposure concentrations in male rats only. The renal histopathology reported in this study fulfill several criteria for assignation to male specific renal nephropathy caused by chemicals that induce excessive accumulation of alpha-2µ-globulin (EPA, 1991; Hard et al., 1993): lesions were limited to males; hyaline droplet formation was noted, which increased in severity in a dose-related fashion; and lesions associated with the pathologic sequence of alpha-2µ-globulin nephropathy were noted, including tubular proteinosis (presumably from exfoliation of epithelial cells into the proximal tubular lumen) and tubular epithelial cell hyperplasia/hypertrophy (presumed to be regenerative from tubular necrosis). Although one criterion is not met within the study, positive identification of the accumulating protein in the hyaline droplets as alpha-2µ-globulin, the pattern described strongly suggests male rat specific nephropathy. The U.S. EPA does not consider nephropathy associated with accumulation of alpha-2µ-globulin as an appropriate endpoint to determine noncancer toxicity. Chronic progressive nephropathy, which also occurs predominately in male rats, also is characterized by tubular hyperplasia and proteinosis (Montgomery and Seely, 1990), and this condition also may contribute to these renal lesions. These lesions, as well as the renal weight increases in males, which may be confounded by this species and sex-specific nephropathy, thus are not used in this assessment. The critical effects in this subchronic study are increased relative and absolute kidney weights in females and increased relative and absolute adrenal weights in both sexes at the highest concentration tested, 1202 ppm, the LOAEL. The next lower concentration, 496 ppm, is the NOAEL" (EPA, 1997).

The EPA used the critical effect of increased kidney weights in female rats and adrenal weights in male and female rats NOAEL of 496 ppm from the Cushman et al. (1995) studies. The conversion factors and assumptions include: cumene molecular weight at 120.2 g/mol and assuming 25 °C and 760 mmHg, the NOAEL and adjusted NOAEL is calculated below:

$$NOAEL\ \left({}^{mg}/_{m^3}\right) = 496\ ppm\ \times \frac{120.2\ {}^{g}/_{mol}}{24.45} = 2438\ {}^{mg}/_{m^3}$$

$$NOAEL_{[adj]} = 2438\ {}^{mg}/_{m^3}\ \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 435\ {}^{mg}/_{m^3}$$

The $NOAEL_{[HEC]}$ was calculated for a gas: extrarespiratory (systemic) effect assuming periodicity was obtained. Because the b:a lambda values are unknown for the experimental animals species and humans, a default value of 1 is used for this ratio.

$$NOAEL_{[HEC]} = \frac{b{:}\ a\ lambda_{animal}}{b{:}\ a\ lambda_{human}} = 435\ {}^{mg}/_{m^3}$$

The EPA used an uncertainty factor of 1,000 that are applied to the $NOAEL_{[HEC]}$: "10 for subchronic-to-chronic extrapolation and 10 for consideration of intraspecies variation. Partial uncertainty factors also are applied to this effect level for consideration of interspecies extrapolation (which already has been addressed partially through the calculation of an HEC) and for database deficiencies (lack of reproductive studies). The total UF = 10 x 10 x 3 x 3,

which is rounded to 1,000" (EPA, 1997). This gives an RfC of 400 µg/m^3. According to Rule 232(1)(a) an inhalation RfC can be used for an ITSL. Rule 232(2)(b) states that the averaging time for an ITSL derived from an inhalation RfC is set at a 24-hour averaging time.

Therefore, the Initial Threshold Screening Level (ITSL) for cumene (CAS# 98-82-8) is 400 µg/m^3 based on a 24-hour averaging time.

Reference:

Act 451 of 1994. Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Cushman JR, Norris JC, Dodd DE, Darmer KI, and Morris CR. 1995. Subchronic inhalation toxicity assessment of cumene in Fischer 344 rats. J. Am. Coll. Toxicol. 14(2):129-147.

EPA. 1991. Alpha-2 microglobulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Rat. EPA/625/3-91/019F. September.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

EPA. 1997. Integrated Risk Information System. Cumene (CASRN 98-82-8). Retrieved data on 5/15/2014. Available online at: http://www.epa.gov/iris/subst/0306.htm

Hard GC, Rodgers IS, Baetcke KP, Richards WL, McGaughty RE, and Valcovic LR. 1993. Hazard evaluation of chemicals that cause accumulation of alpha2-microglobulin, hyaline droplet nephropathy, and tubular neoplasia in the kidneys of male rats. Environ. Health Perspect. 99:313-349.

Montgomery CA Jr., and Seely JC. 1990. Chapter 10. Kidney. In: Pathology of the Fischer Rat, Reference and Atlas, Boorman GA, Eustis SL, Elwell MR, Montgomery CA Jr., MacKenzie WF (eds). Academic Press, New York, pp 127-153.

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