MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Cumene Hydroperoxide (CAS # 80-15-9)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Cumene Hydroperoxide ITSL change in the averaging time from 24 hrs to annual

DATE: December 23, 2015

The current ITSL for Cumene Hydroperoxide (6 ug/m^3) was derived on March 17, 2006 (see attached justification memo). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). 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 being changed from 24 hours to annual at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

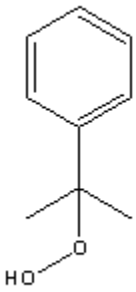
TO: Cumene Hydroperoxide File (CHP) [CAS #80-15-9]

FROM: Margaret M Sadoff, Toxics Unit, Air Quality Division (AQD)

DATE: March 17, 2006

SUBJECT: Initial Threshold Screening Level (ITSL) for cumene hydroperoxide

The ITSL for cumene hydroperoxide is 6 ug/m^3 with a 24 hr averaging time.



A search of the literature and the following databases was performed for health effects information regarding CHP: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, and CalEPA's Toxicity Values Database.

General Toxicity Information

Cumene hydroperoxide (CHP) is a colorless to pale, yellow liquid with a sharp, aromatic odor. It is slightly water soluble at < 0.01 g per 100 ml at 18C. CHP is produced via the oxidation of cumene in the presence of aqueous sodium carbonate as a catalyst. Over 95% of the CHP produced in the U.S. is used in the production of acetone and phenol. CHP is also used as a catalyst, a curing agent and a polymerization initiator (NTP Executive Summary for CHP, September 1998).

CHP is moderately toxic by inhalation, ingestion and skin absorption and is a known skin sensitizer. Like other peroxides, CHP is corrosive, causing burns and tissue damage upon prolonged or intense dermal contact or splashes to the eyes. The primary toxic effect is irritation of skin, eyes, and mucous membranes. (HSDB, Patty's Toxicology, 5th ed.)

Acute Toxicity

RTECS lists the following lethal values for rats and mice:

	4 hr LC 50 (ppm)	LD 50 Oral (mg/kg)	LD 50 Dermal (mg/kg)
Rats	220	382 800	500
Mice	200	342	490

Other ranges of LD50s have been reported between 800 and 1600 mg/kg/day. The dermal LD50 is > 200 mg/kg/day. An LC 50 of 700 mg/L was also reported from a 6 hour study. Inhalation experiments conducted in six female rats exposed 12 times to 16 ppm (100 mg/m^3) for 4-5 hours, produced salivation and nose irritation. All organs were normal at necropsy. When the concentration was increased to 31.5 ppm (196 mg/m^3) for six rats in seven exposures at 5 hrs each, respiratory difficulty was noted along with salivation, tremor, weight loss, and hyperemia of eyes and tail. The lungs were the target organ showing emphysema and thickening of the alveolar walls. Additionally, out of two rats that were exposed to 50 ppm (311 mg/m^3), one died of congested lungs and kidneys. (Patty's Toxicology, 5th ed.)

Carcinogenicity/Mutagenicity

CHP is hypothesized to be an active promoter in the initiation-promotion mouse epidermis model due to its ability to generate free radicals. It has also been shown to be genotoxic, inducing DNA damage and mutations in prokaryotic and eukaryotic systems (Ames test = 15 positive, 6 negative; E. coli test = 2 positive). Analysis of structure-activity relationships suggests that alkyl hydroperoxides, like CHP, are of moderate to high concern for carcinogenic potential because they are more stable than other peroxides and therefore more likely to remain active. There are currently no human or animal studies on the carcinogenicity of CHP. The NIEHS has recommended CHP for carcinogenicity testing. NTP has assigned a 2 year topical application study in rats and mice for this chemical. (NTP Executive Summary and CCRIS database).

Repro/Developmental Toxicity

Very limited data is available. One study (no detail available) reports CHP inhibition of progesterone biosynthesis which could potentially lead to pre-eclampsia (development of hypertension during pregnancy). It is not known whether this finding was *in vitro* or *in vivo* or in what species or concentrations the material was tested. (NTP Executive Summary for CHP, September 1998).

Occupational Health Standards and Human Data

There are no U.S occupational standards for CHP but there is a Russian STEL of 1 mg/m3. One case study reports that 5 workers were exposed to ambient concentrations of 0-60 mg/m3 CHP but no effects were reported. In a different occupational exposure case, a worker suffered chemical burns and subsequent recurring skin rashes from dermal exposure to CHP (exposure concentration unknown). (RTECS, HSDB).

Subchronic Inhalation Study by DOW

The only repeated exposure study available that provides sufficient data from which to derive an ITSL is a 90-day inhalation rat study obtained from a DOW Chemical TSCA 8(d) submission in 1979. The test material was a commercial-grade mixture that contained approximately 80% CHP, 18% cumene, and trace amounts of other impurities. In this study, groups of Fischer 344 rats, (10/sex/group) were exposed daily (6 hr/day, 5 days/week) to 0, 1*****, 6, or 31mg/m^3 of cumene hydroperoxide aerosol over a 3 month period (equates to 0, 0.16, 1 and 5 ppm vapor). Generation of an aerosol was necessary because CHP decomposes at elevated temperatures which precluded generation of a total vapor atmosphere at the

desired concentrations. The authors concluded that the aerosol concentrations generated represent true vapor concentrations of CHP based on particle size distribution data. A separate group of rats was exposed for 5 consecutive days to 124 mg/m^3 of CHP aerosol (20 ppm vapor). Exposure of this group was terminated after 5 days due to severe toxicity. All surviving rats from this group were sacrificed and examined on the 12th day of the study.

Body weights were recorded throughout the study and the rats were observed daily for general signs of toxicity. Hematology, urinalysis and clinical chemistry parameters were monitored. Gross and microscopic examinations were conducted at the termination of the study and on those rats that died or were terminated during the course of the study. The organs were weighed and organ to body weight ratios were calculated. Hematology, clinical chemistry, urine specific gravity, organ weight and body weight data were evaluated using an analysis of variance (ANOVA) and Dunnett's test. The level of significance for all cases was $p<0.05$.

Male and female rats exposed to 124 mg/m3 for five repeated daily exposures became extremely moribund, exhibiting cyanotic appearance of extremities, eye and nose irritation, breathing difficulties, and decreased body weights. 6/10 males and 3/10 females died by the 12^{th} day of the study. Treatment-related pathologic findings in rats in this high dose group included ulceration and inflammation of the cornea, nasal turbinates and lining of the stomach, consistent with primary tissue irritant effects. There were also significant decreases in body weight in both sexes in this group. Decreased WBC count was marked when compared to historical controls. Some immunologic effects were noted, but were believed to be secondary to stress during the time of the experiment.

***Note: The lowest dose group actually received 10 fewer exposures than the other two groups.**

From the remaining three groups, 10 animals per sex per group were autopsied at the end of the 3 month study. The authors report no treatment related effects on any of the parameters in male or female rats exposed to 1, 6 or 31 mg/m3 groups. Therefore, 31 mg/m3 was considered to be a NOAEL for rats in this study. Male rats in the 31 mg/m3 group showed statistically significant increased liver weights and relative heart weights as compared to controls. Similarly, female rats showed statistically significant increases in absolute and relative weights for heart (6 & 31 mg/m3), liver (1 and 31 mg/m3) and kidney (all dose groups). The authors conclude that these changes, in the absence of pathology or other indications of toxicity, are not biologically significant and therefore, 31 mg/m3 is a NOAEL rather than a LOAEL.

In determining whether 31 mg/m3 is a NOAEL or LOAEL for purposes of ITSL derivation, it would be helpful to know whether the increased organ weights observed in this study lie within normal parameters for rats. This information does not seem to be readily available. Also, if organ weight change is considered to be a LOAEL, then the lowest female dose group of 1 mg/m3 with statistically significant increased kidney weights could be the LOAEL. The authors note that the control group was held in an animal holding room. If the control animals were not subject to experimental conditions (i.e., not placed in experimental chambers under dynamic airflow conditions of ambient air), then the statistically significant differences between controls and dosed animals could be related to differences in experimental conditions other than CHP exposure.

Although statistical differences were noted between dose groups and controls, there does not seem to be a dose-response relationship. To verify this assumption, I performed a single-factor ANOVA analysis in Excel with the raw data from Appendix Tables 1 and 2. Female absolute heart, liver and kidney weights in the 1, 6 and 31 mg/m3 dose groups were not significantly different from each other at the 0.05 significance level. Only male rat relative heart weights between the 3 dose groups retained statistical significance. Therefore, this endpoint would be most appropriate for ITSL derivation. When considering all of the above factors, a LOAEL of 31 mg/m3 based on increased relative heart weights in male rats is appropriate for ITSL derivation.

Development of Screening Level

The ITSL was derived using EPA's, Methods for Derivation of Inhalation Reference Concentrations of Inhalation Dosimetry (1994). CHP is essentially insoluble in water but reactive in the respirative tract, therefore it could either be classified as a Category 2 or Category 3 gas. A Category 2 gas has potential for significant accumulation in the blood and thus for both respiratory and remote (extrarespiratory) toxicity. Category 3 gases, such as styrene and CHP's parent compound cumene, have little or no reactivity in the respiratory tract and exhibit extrarespiratory effects. These study results indicate that exposure to 124 mg/m3 CHP resulted in upper respiratory tract changes, including inflammation, erosion or ulcerations of the trachea and nasal turbinates, focal epithelial hyperplasia of tracheal mucosa and squamous metaplasia of the mucosa of the nasal turbinates; as well as histopathologic changes to the pancreatic acini, nonglandular stomach, spleen, thymus, eyes, and necrosis of extremities. However, since no respiratory tract effects were noted at the lower exposure levels and cumene hydroperoxide is essentially insoluble in water, a Category 3 gas classification is most appropriate.

Category 3 Approach for extrarespiratory effects with 31 mg/m3 as a LOAEL:

LOAEL[ADJ] = E (mg/m3) x D (h/24h) x W (days/7 days)
E = experimental concentration level
D = number of hours exposed/24 h; and
W = number of days of exposure/7 days

Dose[ADJ] = (31 mg/m^3) x 6hours/24hours x 5days/7days

Dose[ADJ] = 5.5 mg/m^3

$$LOAEL_{[HEC]} = Dose[ADJ] \times \frac{(Hb/g)A}{(Hb/g)H}$$

(Hb/g)A/(Hb/g)H = the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value. The value of 1.0 is used as a default when this ratio is unknown.

$LOAEL_{[HEC]}$ = 5.5 mg/m^3 x 1 = 5.5 mg/m3

$$RfC = \frac{NOAEL_{HEC}}{\text{Total UF}}$$

Where,
UF_1 is $10^{0.5}$ for animal and human differences (decreased from the full value of 10 because the toxicokinetic portion of interspecies variability is addressed by the dosimetric adjustment factor of 1.)
UF_2 is 10 to account for sensitive individuals.
UF_3 is 10 to account for subchronic to chronic exposure duration.
UF_4 is $10^{0.5}$ to account for LOAEL to NOAEL conversion (decreased from the full value of 10 because the critical effect of increased relative heart weights in male rats was not accompanied by pathology.)

$$RfC = \frac{5.5\ mg/m^3}{1{,}000}$$

RfC = 0.0055 mg/m^3

RfC = 5.5 ug/m^3 = **6 ug/m^3**

References:

1. TSCA 8(d) submittal. Dow Chemical USA. 1979. A 90-day repeated inhalation toxicity study of cumene hydroperoxide in rats. EPA/OTS; Doc #868600016.

2. Patty's Industrial Hygiene and Toxicology (5th ed.). 2001. Volume VI.

3. National Toxicology Program Executive Summary for CHP, September 1998.

MS:LH