MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Bis(2-chloroisopropyl) ether (CAS# 108-60-1)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 25, 2017

SUBJECT: Bis(2-chloroisopropyl) ether (CAS# 108-60-1) ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for bis(2-chloroisopropyl) ether is 140 µg/m^3 based on an annual averaging time. The ITSL was originally established on 6/9/2006 and is based on an EPA oral reference dose (RfD) of 0.04 mg/kg/day derived from a Mitsumori et al., (1979) 24-month oral mouse study. The current file review concludes that the averaging time may appropriately be set at annual, as the key study is a 24-month oral mouse study. Therefore, the averaging time is being changed from 24 hours to annual.

References:

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

EPA. 1990. Integrated Risk Information System. Bis(2-chloroisopropyl) ether (CASRN 108-60-1). Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=407

Mitsumori K, Usui T, Takahashi K, and Shirasu Y. 1979. Twenty-four month chronic toxicity studies of dichlorodiisopropyl ether in mice. J. Pesticide Sci. 4:323-335.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Bis(2-chloroisopropyl)ether, CAS# 108-60-1
(also known as dichlorodiisopropyl ether or DCIP)

FROM: Margaret M. Sadoff, Air Toxics Unit

SUBJECT: Development of Screening Level

DATE: June 9, 2006

The ITSL for Bis(2-chloroisopropyl)ether is 140 ug/m3 with a 24-hour average.

A search of the literature and the following databases was performed for information regarding DCIP: 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.

DCIP MW = 171

Description
(Sources: IARC Monographs Volume 41, p.149-159, NTP Technical Report. No. 239)

DCIP is a colorless to yellowish-brown liquid with a boiling point of 187C and a vapor pressure of 1mmHg. If released to air, DCIP will exist solely as a vapor in ambient air. It has been used historically in paint and varnish removers, spotting agents, and cleaning solutions. It is formed in large quantities as a by-product in some propylene oxide, propylene glycol and chlorohydrin production processes although some manufacturers have since modified their processes to eliminate formation of DCIP as a by-product. This chemical is no longer commercially produced in the US or western Europe and is not known to occur naturally. It is the active ingredient of a nematocide developed and used on field crops in Japan.

Human Toxicity
(Source: Toxline, HSDB)

The toxicity of DCIP is somewhat less than that of the dichloroethyl ethers. Toxicity has been observed primarily in the liver, kidneys and lungs. DCIP causes no primary irritation of the skin but may penetrate the skin sufficiently to cause death. No cases of injury to health of humans have been reported. Exposure in the workplace is likely to be from inhalation and dermal exposures whereas the general population is predominantly exposed via contaminated drinking water.

Experimental Animal Toxicity
(Source: The following are secondary sources as summarized on Toxline, HSDB except as noted).

Note: Except where explicitly stated, for most of these experiments it is not known whether the exposures were to pure or technical grade chemical.

Acute & Intermittent Inhalation Exposure

A rat LC50 from an 8-hour inhalation exposure was reported as 350 ppm (2,448 mg/m3).

A 4-hour inhalation exposure to mice and rats reported an LC50 of 12,800 mg/m3.

One of four rats died after a 3-hour exposure at 175 ppm (1,224 mg/m3) In a separate exposure, one of four animals (species not identified) died after an 8-hour exposure to 175 ppm.

Ten rats survived a 6-hour exposure to 350 ppm, but two of five died after an 8-hour exposure. These animals exhibited moderate lung congestion and some liver necrosis. When rats were exposed to 700 ppm, deaths occurred after 6 hours of exposure. Autopsy revealed slight lung irritation and moderate to severe liver damage.

Rats exposed to a saturated atmosphere of DCIP exhibited signs of immediate eye irritation and some uncoordination. The maximum exposure time causing no death at saturated concentrations was 1 hour.

Effects on 2 male and 2 female rats which were exposed to vapor concentrations of 700 ppm DCIP for 5 hours were irritation of nose and eyes, respiratory difficulty, and death of two animals. At autopsy congested liver and kidney were observed.

Four male and four female rats exposed to vapor concentrations of 350 ppm on eight separate occasions for 5 hours at a time exhibited lethargy, respiratory difficulty, and retarded weight gain. At autopsy, congested liver and kidney were observed.

Four male and 4 female rats exposed to vapor concentrations of 70 ppm on 20 separate occasions for 6 hours at a time exhibited lethargy and retarded weight gain. Autopsy revealed normal organs.

Four male and four female rats exposed to vapor concentrations of 2 ppm on 20 separate occasions for 6 hours at a time showed no symptoms of toxicity and normal organs at autopsy.

Oral Exposure

One LD50 value of 240 mg/kg has been reported in rats of unspecified species and sex. In a separate study, gavage doses of 250 mg/kg produced no deaths when administered to male and female F344/N rats 5 times per week for 13 weeks (NTP Technical Report No. 239).

Rats fed 22 doses of 0.01 g/kg DCIP in olive oil by stomach tube during a period of 31 days exhibited a decrease in growth rate. Rats fed 0.20 g/kg on this same dosing schedule exhibited increases in liver, kidney and spleen weights. (Patty's Industrial Hygiene and Toxicology, 4th ed.)

Mice fed 10,000 ppm 98.5% pure DCIP exhibited decreased body weight gain, decreased food consumption, mild anemia, and other changes in blood chemistry. At 2,000 ppm, exposure inhibited body weight gain and caused anemia in female mice. No increase in the frequency of age-related lesions & tumors was observed. The maximum NOELS in male & female mice were 2,000 & 400 ppm, respectively. (See RfD critical study for more detail).

Dermal Exposure

No primary irritation of the skin was noted after 20 applications to the ear of rabbits. Scaliness was reported after the same number of applications to the skin of rabbit abdomen.

Genotoxicity

Salmonella mutagenicity tests have been largely positive as have mouse lymphoma tests and *in vitro* tests for chromosome aberrations and exchanges. Drosophila tests were inconclusive. It is difficult to draw conclusions from these assays which have used various commercial grades of test material rather than pure chemical.

EPA RfD Critical Study
(Source: EPA, IRIS. Key study by Mitsumori et al., 1979)

The RfD of 0.04 mg/kg/day is based on a 104 week study in which mice were exposed to 98.5% pure chemical in the diet. ICR mice (56/sex/group) were fed DCIP at levels of 0, 80, 400, 2000 or 10,000 ppm in the diet for 104 weeks. Comprehensive blood hematology, chemistry and urinalysis determinations were performed on seven mice/sex/group at 13, 26 and 52 weeks and on 6 mice/sex/group at 78 weeks. The remaining mice were examined at 104 weeks. Findings indicate a treatment related increase in erythrocyte destruction. The females were considered to be more sensitive and therefore a NOAEL of 400 ppm (35.8 mg/kg/day) was considered appropriate for basis of an RfD. A LOAEL of 2,000 ppm (198 mg/kg/day) was also reported. Histopathology results on all major organs and tissues did not show any significant increase in incidence of any tumor type.

EPA reported medium confidence in the study due to an acceptable number of animals, dose groups, and test parameters measured. The database confidence was low, however, because there were no supporting studies available. Other studies conducted using an isopropyl isomer mixture that contained only 70% DCIP were evaluated but not included in the RfD supporting document. Therefore, confidence in the resulting RfD is also low. A total uncertainty factor of 1,000 was applied – 10 for interspecies variability, 10 for interhuman variability, and 10 for data gaps. A literature review last updated in 2002 did not find any new relevant studies.

Carcinogenicity Data
(Sources: Toxline HSDB and IARC Monographs Volume 41, p.149-159 and NTP Technical Report Nos. 191 & 239 unless otherwise noted).

This chemical is not listed as a human or animal carcinogen in IARC or IRIS. IARC Monograph Vol. 41 concluded there was limited evidence in experimental animals and therefore DCIP is not classifiable as to its carcinogenicity in humans (Group 3).

In the same study on which the RfD is based, ICR mice of both sexes were fed diets containing 98.5% pure DCIP at 0, 80, 400, 2000, or 10,000 ppm for 104 wks. (Mitsumori et al., 1979). Histopathology was performed on all major organs and tissues but no increased incidence of tumors were found in treated vs. control groups. The authors conclude that dietary dose levels of up to 10,000 ppm in mice did not present evidence of carcinogenicity under experimental conditions. They note, however, that other related haloethers such as bis (chloromethyl)ether have shown high potential for carginogenicity in several species. They hypothesize that higher homologs of this chemical class may be less active as carcinogens.

NTP Testing: Carcinogenicity of technical grade DCIP (containing approximately 70% DCIP and 30% 2-chloro-1-methylethyl-(2-chloropropyl)ether) was evaluated by oral gavage of test material in corn oil to 50/sex/group F344 rats (1979) and 50/sex/group B6C3F1 mice (1982). The test material was not carcinogenic in rats of either sex but there were positive results in mice. Doses evaluated in mice were 0, 100 and 200 mg/kg. Male and female mice exhibited alveolar/bronchiolar (A/B) adenoma/carcinoma (lung cancer) and males also exhibited hepatocellular carcinomas. In addition, the occurrence of a low incidence of squamous cell papillomas or carcinomas in the stomach or forestomach of females (a rare tumor in B6C3F1 mice) was probably associated with the administration of test chemical. (NTP Technical Report Nos. 191 & 239).

An NTP working group concluded that the negative Mitsumori study had limited sensitivity to detect cancer effects. They questioned the stability of the chemical in feed, which was not reported by Mitsumori. If the chemical were unstable in the feed, then the amount of chemical available would be considerably less than the stated doses. NTP notes that mice fed 10,000 ppm in the Mitsumori study consumed 60 to 80% less than controls and weight gain was depressed in this dose group by more than 50%. (Note: Presumably, NTP had some rationale for the chemical being unstable or unpalatable in the diet and therefore chose to go with the gavage route for their own studies in rats and mice). Differences in the strains of mice used by Mitsumori (ICR mice) and NTP (B6C3F1 mice) could also account for the differences in reported results. (NTP Technical Report No. 239)

Human Data on the Carcinogenicity of Related Compounds: No human data is available on the pure chemical or technical grade DICP. The following information is based on two structurally related chemicals. The incidence of lung cancer in workers exposed to chloromethyl methyl ether and its associated impurity, bis (chloromethyl) ether in a chemical manufacturing plant was eight times higher than expected. Of 14 men (33 to 55 years old) who developed lung cancer, 12 were confirmed by histopathology as oat cell carcinoma. The duration of exposure ranged from 3 to 14 years. A total of 34 incidences of lung cancer have been associated with occupational exposure to these two chemicals in the U.S. Potential confounding lifestyle factors or multiple chemical exposure scenarios are not reported in the NTP summary.

Metabolites identified from animal studies are 1-chloro-2-propanol, propylene oxide, and 2 (1-methyl-2-chloroethoxy) propionic acid. Propylene oxide is an animal carcinogen with an IRSL of 0.3 ug/m3. The cancer endpoints for B6C3F1 mice exposed to propylene oxide via inhalation exposure were increased incidence of hemangiomas or hemangiosarcomas of the nasal turbinates. Other animal experiments involving structurally related haloethers show association with lung tumors. The weight of evidence is suggestive of carcinogenicity for the pure chemical DICP, although there is considerable uncertainty with regard to any quantitative assessment of this chemical for cancer effects.

Screening Level Rationale

There are no chronic or subchronic animal inhalation data from which to derive a screening level. Based on the rules hierarchy, an RfD-based ITSL is appropriate. The calculation pursuant to R232(1)b is as follows:

$$\text{ITSL} = \text{Oral Rfd} \times \frac{70\ \text{kg}}{20\ \text{m3}}$$

$$= 0.04\ \text{mg/kg/day} \times (70\ \text{kg}/20\text{m3})$$

$$= 0.14\ \text{mg/m3}$$ or **140 ug/m3, 24 hour average**

There is insufficient data on pure bis(2-chloroisopropyl)ether from which to derive a quantitative risk value for carcinogenicity. Since the RfD NOAEL of 35.8 mg/kg/day and the resulting RfD-based ITSL are below the testing doses selected in carcinogenicity bioassays, it is unclear what margin of safety may be provided for potential cancer effects of DICP. Since there are no supporting studies to the positive NTP bioassay in mice and no positive studies on pure DICP, an IRSL cannot be developed at this time. This chemical should be re-evaluated on a periodic basis for data on carcinogenicity from which an IRSL could be developed.

Primary References:

Mitsumori K, Usui T, Takahashi K & Shirasu Y. (1979). Twenty-four month chronic toxicity studies of dichlorodiisopropyl ether in mice. J. Pesticide Sci. 4: 323-335.

Bioassay of Technical Grade bis(2-chloro-1methylethyl)ether for possible carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series, No. 191, 1979.

Carcinogenesis Bioassay of bis(2-chloro-1-methylethyl)ether (70%) containing 2-chloro-1-methylethyl-(2-chloropropyl)ether (30%) in B6C3F1 Mice (Gavage Study). National Toxicology Program Technical Report Series, No. 239, December 1982.

IARC Monograph Volume 41, p.149-159.

MS:lh