MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2-Dichlorobenzene (CAS # 95-50-1)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: 1,2-Dichlorobenzene ITSL change in the averaging time from 24 hrs to annual

DATE: December 28, 2016

The current ITSL for 1,2-Dichlorobenzene is 300 ug/m^3, with annual averaging time (AT).

Previously, the ITSL was established on April 9, 2004 at 300 ug/m^3 with 24 hr averaging time (attached). 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 ITSL was based on an EPA (1989) Reference Dose (RfD) of 0.09 mg/kg-d, which EPA derived from a chronic (2-year) rat gavage bioassay. No adverse effects were observed in this key study, however EPA (1989) determined that 13-week supporting studies supported this NOAEL as an appropriate point-of-departure. EPA (1989) applied a total uncertainty factor (UF) = 1000, which consisted of a UF = 10 for each interspecies extrapolation and intraspecies variability, and UF_{db} = 10 for lack of studies assessing reproductive effects and adequate toxicity data in a second species. The current review notes that in utilizing this oral study for ITSL derivation, AQD also has route-to-route (oral to inhalation) conversion uncertainty which is also addressed with this UF_{db}. This concern is supported by EPA (1989) summarization of inhalation bioassays (for 7 months or during gestation) with NOAELs at estimated oral equivalent doses that were lower than that reported in the key study for RfD derivation (EPA, 1989). Therefore, this file review concludes that the EPA (1989) application of UF_{db} = 10 is appropriate to retain for this ITSL derivation. The current file review also concludes that the AT for the ITSL 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).

References:

EPA. 1989. Integrated Risk Information System (IRIS database). Chemical file for 1,2-Dichlorobenzene. Oral RfD assessment last revised 8/1/89. Retrieved on 12/28/16.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

APRIL 9, 2004

TO: File for 1,2-Dichlorobenzene (95-50-1)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The *final* initial threshold screening level (ITSL) for 1,2-dichlorobenzene is 300 $\mu g/m^3$ based on a 24 hr. averaging time. This compound was initially evaluated by AQD staff in 1993 using interim procedures* to derive 8 hr and 24 hr ambient impacts of 1500 ug/m^3 and 300 ug/m^3, respectively. In an effort to finalize all interim chemical screening levels, this chemical was re-reviewed to set a final Initial Threshold Screening Level.

The following references or databases were searched to identify data to determine the ITSL: IRIS-online, HEAST, NTP Management Status Report-online, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC-online, NIOSH Pocket Guide, and ACGIH Guide. Information to develop this chemical evaluation document was taken exclusively from the American Conference of Governmental Industrial Hygienists (ACGIH), supplemental documentation for o-dichlorobenzene, published in 1996. No other information has been published since that time to contradict this information. Therefore, the ACGIH document is still relevant to use as the main background document to describe the toxicity of this compound.

Ortho-dichlorobenzene (o-DCB) or 1,2-dichlorobenzene is a colorless to pale yellow liquid with a pleasant aromatic odor. An odor threshold of 0.3 ppm has been reported. The major use of o-DCB is as an intermediate in the synthesis of organic compounds such as 3,4-dichloroaniline and in the synthesis of herbicides. It is used as an industrial solvent, as a degreasing agent, as a heat exchange medium, as a deodorant for garbage and sewage, as a engine cleaner, and as an intermediate in dye manufacture. It is also used as an insecticide and a fumigant to control peach tree borers, bark beetles, grubs and termites.

Acute Studies

In acute studies o-DCB is classified as slightly toxic following oral administration of lethal doses of 2138 mg/kg in rats, 2000 mg/kg in mice, 1875 mg/kg in rabbits, and 3375 mg/kg in guinea pigs. Other investigators found the lowest dose producing mortality in the rat to be 3375 mg/kg. A single report on the dermal toxicity of o-DCB indicates that the substance is not well tolerated by rats. One animal died after five skin applications and another after nine applications. No skin response was detected; however, there was kidney damage. The dose applied and specific responses were not reported. Undiluted o-DCB applied to the eye of a

*Michigan Department of Environmental Quality – Air Quality Division Staff Activity Report, "Air Toxic Rules – Implementation Procedures", dated January 20, 1993.

rabbit caused pain and slight conjunctival irritation. There was no residual injury as the irritation cleared within 5 days.

Rats survived inhalation exposure for 2 hours at a concentration of 977 ppm but died after a 7-hour exposure. Rats that survived a 7-hour exposure at 539 ppm o-DCB showed liver necrosis and kidney tubule damage. Liver damage in rats was produced in another study at concentrations from 50 to 800 ppm, and exposures lasting between 0.5 and 1 hour at 390 ppm produced liver necrosis in three of six rats. Mice exposed for 1 hour to saturated o-DCB vapor (2000 to 3000 ppm) showed prompt narcosis followed by central nervous system depression and cyanosis (death in 24 hours). Rats and guinea pigs that survived this exposure were narcotized. No outward signs of response were seen in dogs exposed for 1 hour at 4000 ppm but 8000 ppm produced sedation.

Subchronic Studies
Rats exposed at a nominal concentration of 450 ppm, 6 hours/day for up to 13 days, survived the exposure but had pale, discolored kidneys at autopsy. No signs of adverse response were reported in a dog exposed 2 hours/day at 444 ppm. Two rats exposed at an average concentration of 322 ppm for 6 hours/day for 10 days showed weight loss but no histologic changes. In rats and guinea pigs exposed at 93 ppm, 7 hours/day for 6 to 7 months, the male guinea pigs had a decrease in spleen weight without any histopathologic changes. No other responses were detected and no adverse effects were seen at 49 ppm.

In separate 13-week studies conducted by the National Toxicology Program (NTP) in rats and mice, oral doses of 500 mg o-DCB/kg caused decreased survival (except in male rats). This dose produced necrosis and hepatocellular degeneration and depletion of lymphocytes in both the spleen and thymus and renal tubular degeneration in male rats. Multifocal mineralization of the myocardial fibers of the heart and skeletal muscle were seen in mice. At a dose of 250 mg/kg, necrosis of individual hepatocytes was evident except in the female mice. At a dose of 125 mg/kg, minimal hepatocellular necrosis was observed in a few rats.

No adverse effects were seen in rats following 138 gavage doses of 18.8 mg o-DCB/dose. At 188 mg/kg, a slight increase in liver and kidney weights without any histopathologic correlate was produced; 376 mg/kg produced slight liver damage and elevated liver and kidney weights but no effect on growth or other toxicologic end points.

Chronic/Carcinogenicity Studies
A 2-year NTP study was conducted in which rats and mice were treated 5 days/week with oral doses of either 60 or 120 mg/kg-DCB. Survival time of male rats receiving 120 mg/kg was reduced; however, aspiration of o-DCB may have been responsible for some deaths. Body weights of all treated animals were normal. An increase in the incidence of tubular regeneration in the male mouse kidney was the only compound-related, non-neoplastic, histological lesion observed, and no evidence of carcinogenicity was seen in the rats or mice receiving either the 60 or 120 mg/kg dosages.

Reproductive/Developmental Studies
Rats and rabbits were exposed 6 hours/day by inhalation at either 100, 200, or 400 ppm o-DCB, from gestation days 6 through 15 (rats) and days 6 through 18 (rabbits). Maternal toxicity was reflected by a reduced rate of bodyweight gain in all groups of the treated rats. Liver weights were increased at 400 ppm. No evidence of a fetal response was seen at any concentration. Female rabbits exposed at 400 ppm showed a decreased rate of weight gain over the first 3

exposure days without signs of a fetal response. Male rats given single intraperitoneal injections of either 50, 100, 250, 300, or 800 mg o-DCB/kg showed dose-related morphologic alterations in sperm consisting of misshapen head, acrosomal defects, and tail abnormalities.

Genotoxicity Studies
o-DCB was not mutagenic in Salmonella assays using several different strains both with and without metabolic activation. The chemical was considered toxic but not genetically active in two E. coli strains. Little or no recombinogenic activity was observed in Saccharomyces cerevisiae. An ether solution of o-DCB increased the frequency of back-mutations in Aspergillus nidulans.

Pharmacokinetic /Metabolism Studies
o-DCB is absorbed through the lungs, gastrointestinal tract, and intact skin. Relatively low water solubility and high lipid solubility favor penetration through most membranes by diffusion. Tissues showing this include pulmonary and gastrointestinal epithelia, the brain, hepatic parenchyma, renal tubules and the placenta. Following ten daily oral doses of 2 mg/kg to rats, o-DCB accumulation was most pronounced in the fat and was being stored in the liver, kidney, and heart. Sulfur conjugates of o-DCB were isolated from mouse urine following intraperitoneal injection. Oxidative hydroxylation and reductive dechlorination are the main routes of conversion for chlorinated benzenes. Hydroxylation is rapid and dechlorination appears limited with o-DCB. The extent of binding to cellular constituents and the effects of microsomal mixed-function oxidase enzyme on the rate of metabolism suggest that arene oxide intermediates may be the precursors of excreted metabolites.

Human Studies
o-DCB was found to be irritating when applied to the skin of human subjects for 15 to 60 minutes (amount not specified). A worker exposed to o-DCB following hand contact developed a dermatitis that was reportedly confirmed by a follow-up skin patch test as sensitization. A burning sensation was reported in two subjects following application of an unspecified amount of o-DCB liquid. The response became more intense during a 1-hour exposure and disappeared when the liquid was removed. A diffuse redness of the treated area developed and progressed to a darker red color with blister formation by 24 hours. A brown pigment formed at the site and was apparent 3 months post-exposure.

Intermittent exposure at 100 ppm in the workplace caused some irritation to the eyes and upper respiratory system. A definite odor of o-DCB was detected by those working around an inhalation chamber in which rats were being exposed at 50 ppm; however, no eye or nasal irritation was noted. Workers in a plant handling o-DCB with airborne concentrations ranging from 1 to 44 ppm (average concentration 15 ppm) showed no evidence of chemically induced injury attributable to o-DCB. The employees received periodic medical examinations including blood counts and urine analysis. Concentrations up to 100 ppm in a wool-handling operation induced sporadic irritation of the respiratory passages and eyes without any other ill effects.

Four cases involving cancer and exposure to o-DCB have been reported. In the first case, a 15-year-old girl died of peripheral leukoblastosis. She had frequently removed dirt and grease stains from her clothes with a product containing 37% o-DCB. A second report involved chronic lymphoid leukemia in a man who had worked with a solvent containing 80% o-DCB (and 15% p-DCB, 2% m-DCB) for ten years. Myeloblastic leukemia was reported in a 55-year-old woman who used o-DCB for an unspecified period to clean spots from clothing. Another case of myeloblastic leukemia was reported in a 40-year-old man who had been exposed for 22 years

to o-DCB in the preparation of dyestuffs. Data are insufficient for these cases to conclusively identify o-DCB as the causative agent for the reported leukemogenic effects.

Conclusion

Animal studies have shown that o-DCB is neither genotoxic nor carcinogenic. The compound has a low, acute oral toxicity while inhalation studies have resulted in moderate toxicity. Some of the inhalation studies reviewed during the chemical evaluation were of subchronic duration conducted over a period of six months; however, these studies used only one dose group. Data obtained from studies such as these would not provide enough information to derive an ITSL. The EPA also didn't consider these studies strong enough to develop an RfC, but instead developed an RfD from the NTP two-year rat bioassay. The bioassay showed that no adverse effects were seen in rats orally dosed at 120 mg/kg/day. The dose of 120 mg/kg/day was adjusted for the gavage schedule of 5 days/week, and 1000-fold uncertainty factor. The uncertainty factor accounted for animal to human extrapolation; sensitivity; and a lack of reproductive and adequate chronic toxicity in a second species. The EPA used this NOAEL to derive an RfD of 0.09 mg/kg/day. Since no new information has been published for o-DCB, and data do not indicate that use of oral data for inhalation risk assessment would be inappropriate, the RfD was used to derive an interim screening level.

The ITSL was determined as follows:

RfD = 0.09 mg/kg/day

$$0.09 \text{ mg/kg/day} \times \frac{70 \text{ kg}}{20 \text{ m}^3} = 0.315 \text{ mg/m}^3$$

$$0.3 \text{ mg/m}^3 \times 1000 \frac{\text{ug}}{\text{mg}} = 300 \text{ ug/m}^3$$

The ITSL for 1,2-dichlorobenzene = 300 ug/m^3 based on 24 hr. averaging.

References:

1. Documentation of Threshold Limit Values and Biological Exposure Indices. 1996. *Supplement: 1,2-dichlorobenzene.* American Conference of Governmental Industrial Hygienists (ACGIH), 6th Edition.

2. U.S. Department of Health and Human Services. 1985. Toxicology and Carcinogenesis Studies of 1,2-Diclorobenzene (o-Dichlorobenzene) (CAS No. 95-50-1) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Carcinogenesis Testing Program; National Cancer Institute; National Toxicology Program. NIH Publication No. 86-2511. [NTP-1985; TR-255].