MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Chlorobenzene (CAS No. 108-90-7)

FROM: Cathy Simon, Air Quality Division

DATE: February 27, 2013

SUBJECT: Update of the Initial Threshold Screening Level

The initial threshold screening level (ITSL) for chlorobenzene has been changed from 70 µg/m^3 (24-hour averaging time) to 50 µg/m^3 (annual averaging time). This ITSL is designed to be protective of effects from chronic exposure to chlorobenzene. In addition, an acute based ITSL of 4,400 µg/m^3 (8-hour averaging time) has also been established. Background information, supporting data, and the basis for these screening levels are provided below.

Background

In 1993, the Air Quality Division (AQD) of the Michigan Department of Natural Resources (MDNR) established interim ITSLs for chlorobenzene of 460 µg/m^3 (8-hour averaging time) and 70 µg/m^3 (24 hour averaging time) (MDNR, 1993). The scientific data and interim ITSLs for chlorobenzene were re-evaluated in 1996 by the AQD, and a final ITSL of 70 µg/m^3 (24-hour averaging time) was established for this compound (MDEQ, 1996).

The US Environmental Protection Agency (EPA), Office of Air Quality Planning and Standards (OAQPS) has adopted a chronic toxicity value of 1000 µg/m^3 for chlorobenzene (EPA, 2012a). This value is based upon the chronic reference exposure level (REL) for chlorobenzene derived by the California Environmental Protection Agency (Cal/EPA, 2000). The US EPA's Superfund Health Risk Technical Support Center has developed a provisional inhalation reference concentration (RfC) of 50 µg/m^3 for chlorobenzene (EPA, 2006). This provisional RfC is considered a provisional peer reviewed toxicity value (PPRTV), which is a toxicity value derived for use in the US EPA's Superfund Program when such a value is not available in the EPA's Integrated Risk Information System (IRIS) database.

A review was undertaken to evaluate the basis for the different health benchmark values for chlorobenzene used by the AQD and the US EPA, and update the existing ITSL as appropriate. This evaluation did not include an independent review of all relevant scientific literature, but relied primarily on reviews done by various organizations such as the Agency for Toxics Substances and Disease Registry (ATSDR), US EPA, and Cal/EPA. Information from these and other sources, as well as the findings of the evaluation are presented below.

Review of the ITSL

The previous ITSL of 70 µg/m^3 (24-hour averaging time) established by the Michigan Department of Environmental Quality (MDEQ) in 1996, was derived from a US EPA oral reference dose (RfD) value of 0.02 mg/kg/day (MDEQ, 1996). The oral RfD was selected as the basis for deriving the ITSL as no inhalation RfC was available.

The American Conference of Governmental Industrial Hygienists (ACGIH) adopted a Threshold Limit Value (TLV) of 10 ppm (46 mg/m^3) in 1991 (ACGIH, 2001). This TLV remains unchanged as of the present date (ACGIH, 2012). The National Institute of Occupational Safety and Health (NIOSH) has not established any recommended exposure levels for chlorobenzene, but have stated that the 1989 Occupational Safety and Health Administration (OSHA) permissible exposure level (PEL) of 75 ppm (350 mg/m^3) may not be protective to workers (NIOSH, 2013).

The Agency for Toxics Substances and Disease Registry (ATSDR) has established an intermediate oral minimal risk level (MRL) of 0.4 mg/kg/day, but no inhalation MRLs (ATSDR, 1990). The US EPA has established an oral RfD in its Integrated Risk Information System (IRIS) data base, but no inhalation RfC (EPA, 2013).

Both the Cal/EPA chronic reference exposure level of 1000 ug/m^3 and the US EPA PPRTV of 50 ug/m^3 were derived from a two generation reproductive study by Nair et al (1987; as reviewed by US EPA, 2006 and Cal/EPA, 2000) in which Sprague Dawley rats (30/sex/group) were exposed to 0, 50, 150, and 450 ppm (0, 230, 691, and 2072 mg/m^3) chlorobenzene in air for 6 hours/day and 7 days/week. The F_0 animals were exposed for 10 weeks before mating, and during mating, gestation, and lactation, after which they were sacrificed. The F_1 rats were exposed for 11 weeks before mating, and during mating, gestation, and lactation, after which they were also sacrificed. The F_2 rats were sacrificed after weaning.

The results of this study showed the liver and kidney were target organs in both sexes of rats, as well as the testes in male rats. The absolute and relative liver weights were significantly increased in F_0 and F_1 male rats exposed to the two highest dose levels (150 and 450 ppm). Histopathology effects in the liver showed that the incidence of centrilobular hepatocellular hypertrophy was significantly increased in F_0 males in the 150 and 450 ppm dose groups, and marginally increased in the 450 ppm F_1 males. The relative liver weight was also significantly increased in the F_0 and F_1 female rats exposed to 450 ppm of chlorobenzene. Kidney effects observed included a statistically significant increased incidence of tubular dilation, chronic interstitial nephritis, and foci of regenerative epithelium in F_0 males exposed to 150 and 450 ppm of chlorobenzene. The incidence of small and flaccid testes was significantly increased in the F_1 males in the 450 ppm dose group. Degeneration of the germinal epithelium in the testes was not significantly increased in any dose group, but was considered treatment related in the two highest dose groups based on the severity of observed lesions. No adverse effects on reproductive performance or fertility were observed at any dose level (Nair et al, 1987; as reviewed by US EPA, 2006 and Cal/EPA, 2000).

In deriving a chronic REL, Cal/EPA (2000) identified a NOAEL of 50 ppm and a LOAEL of 150 ppm from the Nair et al (1987) study. Critical effects identified included increased liver weight, hepatocellular hypertrophy, renal degeneration and inflammation, and testicular degeneration. The NOAEL of 50 ppm was adjusted by a factor of 6 hours/24 hours to get an average daily exposure concentration of 13 ppm. Cal/EPA derived a human equivalent concentration (HEC) of 26 ppm by multiplying the average daily concentration of 13 ppm by a regional gas dose ratio (RGDR) of 2.0. The REL was then determined as follows:

$$\text{REL} = \frac{NOAEL_{(HEC)}}{UF_A \; X \; UF_S \; X \; UF_H} = \frac{26\ ppm}{3\ x\ 3\ x\ 10} = 0.3 \text{ ppm} = 300 \text{ ppb} = 1000\ \mu g/m^3$$

Where:
UF_A = Interspecies uncertainty factor = 3
UF_S = Subchronic uncertainty factor = 3
UF_H = Intraspecies uncertainty factor = 10

In deriving a provisional RfC, the US EPA also utilized the study by Nair et al (1987) and also identified a NOAEL of 50 ppm and a LOAEL of 150 ppm. The US EPA, however, used the benchmark dose methodology to derive the LED_{10} as a point of departure for derivation of the provisional RfC, instead of the NOAEL. Incidence data for kidney and liver treatment related effects were modeled, and the lesion that resulted in the lowest LED_{10} was chosen as the point of departure for the provisional RfC. Modeling showed that renal tubular dilation resulted in the lowest LED_{10}. The EPA (2006) selected a LED_{10} of 39.7 ppm as the point of departure for the provisional RfC as stated below:

> The dichotomous models estimated concentrations between 17 and 125 ppm associated with a 10% extra risk (ED_{10}) for tubular dilation (Table 8). As assessed by Akaike's Information Criterion (AIC), the best fitting models were the gamma, quantal linear, and Weibull models. Each of these models calculated ED_{10} values of 53.8 ppm and a lower 95% confidence interval (LED_{10}) of 39.7 ppm. Therefore, 39.7 ppm was selected as the point of departure to derive the p-RfC (EPA, 2006, p. 23).

The LED_{10} of 39.7 ppm (183 mg/m^3) was adjusted by a factor of 6 hours/24 hours to account for exposure duration, resulting in an $LED_{10\ ADJ}$ of 46 mg/m^3. The US EPA used a default rat to human blood:air partition coefficient ratio (L_R/L_H) of 1 to derive a LED_{10HEC} of 46 mg/m^3. The $LED_{10\ HEC}$ was then divided by a total uncertainty factor of 1000 (3 to account for interspecies extrapolation, 10 to protect sensitive subpopulations, 10 for subchronic to chronic extrapolation, and 3 for database uncertainties), resulting in a provisional RfC of 50 µg/m^3.

The US EPA's basis for use of a database uncertainty factor of 3 included the lack of a study in which the entire respiratory tract was examined. None of the available animal inhalation studies identified by the US EPA examined the upper respiratory tract. In one acute exposure human study cited by EPA (2006), none of the subjects reported eye or nose irritation, although one subject did complain of a sore throat. The US EPA also identifies the lack of neurological testing as further basis for the 3 fold database uncertainty factor, and cites two acute human studies and three occupational studies that are suggestive of this concern. In the same study mentioned above in which one subject complained of a sore throat, headaches and drowsiness were reported by subjects exposed to 60.2 ppm of chlorobenzene. In another acute human study, changes in electroencephalographic (EEG) patterns were observed in 2/4 humans exposed to 0.2 mg/m^3, although the US EPA stated that the toxicological relevance of this effect was not clear, and the reliability of the data was uncertain (EPA, 2006). The reliability of the occupational studies that have reported potential neurological effects was also questioned by the US EPA because workers were exposed to other chemicals in addition to chlorobenzene and/or exposure concentrations were not reported (EPA, 2006). Lastly, the US EPA cites a Russian study of potential neurological effects in rats exposed at 0.2 ppm (1 mg/m^3), but states, "the toxicological significance of the reported effect (changes in the conduction speeds of nerve impulses to sets of flexor and extensor muscles on Day 39) is not clear, and these results have not been confirmed by other studies." (EPA, 2006).

The provisional RfC derived by the US EPA (2006) provides the most scientifically justified health benchmark value to use for development of the ITSL. While both the US EPA and

Cal/EPA start with the same study (Nair et al, 1987) in their risk assessment approach, the US EPA utilizes the benchmark dose methodology instead of the NOAEL/LOAEL approach. The use of the benchmark dose methodology is a more current health risk assessment methodology, and it addresses several of the limitations inherent in the NOAEL/LOAEL approach (EPA, 2012b; 1995). Additionally, the provisional RfC has gone through a fairly extensive peer review process as part of the process for developing a PPRTV as described in EPA (2006):

> PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided by IRIS values. (EPA, 2006).

As described above, the provisional RfC of 50 µg/m^3 derived by the US EPA (2006) includes a database uncertainty factor of three. RfCs that include a database uncertainty factor are examined on a case-by-case basis to determine the appropriateness of including this uncertainty factor in derivation of the ITSL. The lack of any inhalation toxicity studies that evaluate the upper respiratory tract is a shortcoming of the database identified by the US EPA (2006). Further concern is raised with regards to this issue from recent *in vitro* studies using human lung epithelial cells, which show that exposure to chlorobenzene causes an inflammatory response. Fischader et al (2008) exposed human lung epithelial cells (A549) that had been stimulated with tumor necrosis factor alpha (TNF-α) to chlorobenzene at concentrations of 1 ng/m^3 to 100 g/m^3 via the gas phase. After 20 hours of exposure, the release of the chemokine, monocyte chemoattractant protein-1 (MCP-1), was significantly increased at exposure concentrations of 10 – 100 µg/m^3. Feltens et al (2010) found that expression of several markers for oxidative stress were increased after human lung epithelial cells (A549) were exposed to chlorobenzene at concentrations between 100 µg/m^3 and 10 mg/m^3 using an air-liquid cell culture system. In addition to the concerns for potential neurological effects due to chlorobenzene discussed by EPA (2006), Kunimoto et al (2003) found that chlorobenzene, like methylmercury, inhibited neurite extension in an *in vitro* assay using cultured human neuronal cells. Considering the data deficiencies identified by the US EPA (2006), and the *in vitro* studies discussed above, the use of the database uncertainty factor of three is justified for inclusion in the derivation of the ITSL from the provisional RfC.

Rule 232(1)(a) of the Michigan Air Pollution Control Rules specifies that when an inhalation RfC is available, the ITSL equals the RfC, and Rule 232(2)(b) specifies that the averaging time for an ITSL based on an inhalation RfC is 24 hours. Rule 229(2)(b), however, allows for the use of alternative methods for deriving an ITSL from those specified in Rule 232, provided those methods are more appropriate based on toxicological grounds and supported by the scientific data. The provisional RfC of 50 µg/m^3 provides the best scientific basis for derivation of the ITSL. While use of a 24-hour averaging time coupled with this value should be protective of both acute and chronic effects of chlorobenzene, it is likely over conservative, and a more appropriate approach would be to set separate acute and chronic based ITSLs if adequate data are available. An evaluation of the data has been done and an acute based ITSL derived as discussed in the section below. Therefore, pursuant to Rule 229(2)(b), the ITSL for chlorobenzene is 50 µg/m^3 based on an annual averaging time. This ITSL should provide adequate protection from chronic exposures to chlorobenzene.

Development of an Acute ITSL

The National Research Council (NRC) has established various Acute Exposure Guideline Levels (AEGLs) for chlorobenzene (NRC, 2012). No other acute health based benchmark established by a federal or a state agency was identified to evaluate for purposes of establishing an acute based ITSL, however, as previously mentioned, the ACGIH has also established a TLV of 10 ppm (46 mg/m^3) for chlorobenzene. Both the AEGLs and the ACGIH TLV of 10 ppm were evaluated for consideration of establishing an acute based ITSL for chlorobenzene.

As mentioned above, the NRC has developed various AEGLs for chlorobenzene. The AEGL-1 value for chlorobenzene is 10 ppm for the 10-minute, 30-minute, 1-hour, 4-hour, and 8-hour time periods. An AEGL-1 is defined as below, according to the NRC (2001):

> AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter (ppm or mg/m^3)) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure (NRC, 2001, p. 35).

Two key studies were identified by the NRC (2012) for deriving the AEGL-1 values. Both involved exposing healthy volunteers to chlorobenzene via inhalation for up to eight hours per day.

In the first study, by Ogata et al (1991), five healthy adult male volunteers with a mean age of 42 years (range of 30 – 63 years), were exposed to either 11.8 or 60.2 ppm of chlorobenzene for a total of 7 hours, consisting of three hours exposure in the morning, followed by a one hour break, and ending with four hours exposure in the afternoon. Although the primary purpose of this study dealt with quantification of urinary metabolites and blood levels of chlorobenzene, along with establishing relationships between chlorobenzene concentrations in air and blood levels, the authors also provided data on some effects of exposure to chlorobenzene. Effects evaluated included complaints, flicker-fusion values, pulse rates and blood pressure.

Effects of exposure were only provided for volunteers exposed to 60.2 ppm, and although five subjects were exposed to this concentration of chlorobenzene, data were provided on only four subjects. Complaints reported included a sensation of disagreeable odor and of drowsiness in 4/4 subjects, a heavy feeling in the head and/or headache in 3/4 subjects, throbbing pain in the eyes in 2/4 subjects, and sore throat in 1/4 subjects. The mean flicker fusion value in the four exposed volunteers was significantly decreased after the three hour morning exposure. No consistent changes in pulse rate or blood pressure were observed in the exposed volunteers. The 60.2 ppm exposure concentration in this study may be considered a LOAEL.

In the second study by Knecht and Woitowitz (2000), eight healthy volunteers (six male and two female), with an average age of 29 years (range of 22 – 56 years), were exposed to chloro-benzene at a concentration of 9.6 ppm for 8 hours per day for a total of 5 days. The exposure was interrupted after 4 hours for a 45 minute break, before continuing to the end of the day. Five of the subjects performed physical activity at a level of 75 W for 10 minutes per hour on a bicycle ergometer, two subjects performed physical activity at 50 W in a similar manner, and one subject remained at rest during the exposure period. The primary purpose of this study was to obtain toxicokinetic data on the absorption and elimination of chlorobenzene and various metabolites. No data or information was reported regarding any effects to the volunteers from exposure to chlorobenzene. Although no data regarding effects were reported in the study, the

NRC (2012) used it to develop an AEGL for chlorobenzene and stated that, “none of the subjects complained of irritant or CNS effects.” The basis for this finding was a personal communication with U. Knecht, one of the authors of the study (NRC, 2012).

A third study in which human subjects were exposed to chlorobenzene on an acute basis includes a Russian study summarized by the US EPA (2006) in the document, *Provisional Peer Reviewed Toxicity Values for Chlorobenzene*. In this Russian study by Tarkhova (1965), four subjects were exposed to 0.1, 0.2, and 0.3 mg/m^3 of chlorobenzene for 2 ½ minutes. The study measured changes in electroencephalographic (EEG) patterns in response to light flashes. The results showed that no effects on EEG patterns occurred at the lowest dose level; however, effects were observed in 50% (2/4) of the subjects exposed to 0.2 mg/m^3 and in 75% (3/4) subjects exposed to 0.3 mg/m^3. The NRC (2012) also mentioned this study as “supplementary information” to deriving an AEGL, since they did not have access to the original publications and instead relied on a summary.

To derive the AEGL-1, the NRC utilized the study by Knecht and Woitowitz (2000), identifying a concentration of 10 ppm as a no adverse effect level after eight hours exposure. This concentration was selected as the point of departure to derive the AEGL-1. Uncertainty factors of one for both interspecies and intraspecies differences were then applied to this point of departure value, resulting in an AEGL-1 concentration of 10 ppm. The concentration of 10 ppm was applied to all AEGL-1 time periods. The NRC provided the following rationale for these decisions:

> Despite the fact that only a few subjects were tested, an uncertainty factor of 1 for intraspecies variability was considered appropriate because of the conservatism of the point of departure already provides a margin of safety. (The point of departure of 10 ppm was obtained from a repeated-exposure study, and effects observed at 60 ppm were rather slight.) No information about the time dependency of the effects at 10 or 60 ppm is available. Because of the effects at 60 ppm include irritation and CNS effects (drowsiness, heavy feeling in the head, and headache), the 8-h AEGL-1 value of 10 ppm is considered appropriate for all time points. Furthermore, Knecht and Woitowitz (2000) reported that chlorobenzene concentrations in blood reached a steady-state level within 1 h. (NRC, 2012, pages 102-103).

The AEGL-1 of 10 ppm was not considered appropriate to use as an acute based ITSL for chlorobenzene. The primary purpose of the AEGL program is to develop guideline levels for once-in-a-lifetime, short-term exposures to airborne concentrations of chemicals. AEGLs were developed to be used in emergency planning and accident situations where exposure to the chemical of concern does not occur on a regular basis. Exposure to concentrations of a chemical below the AEGL-1 may result in some effects:

> Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects (NRC, 2001, p. 35).
>
> Thus, below the AEGL-1 values, there may be specific effects, such as the perception of a disagreeable odor, taste, or other sensations (mild sensory irritation). In some people, that exposure level could result in mild lacrimation or coughing (NRC, 2001, p. 41).

The ITSLs are designed for permitting of air toxic chemicals, where the general public can be exposed continuously or on a repeated basis to the chemicals emitted from a facility. The use of

an intraspecies factor of 1 to derive the AEGL-1 is of special concern in considering the appropriateness of use of this value to derive an acute based ITSL for chlorobenzene.

The two key studies used in deriving the AEGL-1 are also the best data available to consider for derivation of an acute based ITSL. Considering both studies together, however, there are still limitations to the data. Neither study was specifically designed to measure the acute toxic effects of chlorobenzene exposure. While the study by Ogata (1991) did report limited data on complaints and a few measured endpoints, the Knecht and Woitowitz (2000) study provided no data on the effects of exposure to chlorobenzene. The only information available as to these impacts comes from a personal communication with the authors as cited in the NRC (2012) documentation of the derivation of the AEGLs for chlorobenzene. It is not clear from this documentation as to whether the subjects in the Knecht and Woitowitz (2000) study were specifically asked at the time of the study to identify any adverse effects they were experiencing, or whether it was the authors after the fact recollection that no one complained at this time. Additionally, the number of subjects tested was very small and consisted only of healthy workers. Furthermore, only male volunteers were used in the Ogata et al (1991) study, and in the Knecht and Woitowitz (2000) study, only two of eight subjects were female.

With regards to the Tarkhova (1965) study, the US EPA considered the changes in the EEG pattern in response to rapid light flashes in human subjects exposed to chlorobenzene to be of unknown toxicological significance (EPA, 2006). The US EPA also concluded this study was not adequate to use for risk assessment purposes.

The ACGIH TLV of 10 ppm was also evaluated with regards to use in derivation of an acute ITSL for chlorobenzene. The primary basis for the TLV comes from two rat inhalation studies cited by the ACGIH, in which liver effects were observed in rats exposed repeatedly to chloro-benzene at 75 ppm, and slight liver weight increases were “seen in one of two generations of males exposed at 50 ppm” (ACGIH, 2001). As the TLV was based upon chronic animal data, the acute human data from the studies by Ogata (1991) and Knect and Woitowitz (2000) were considered more appropriate to use in deriving an acute ITSL.

Considering the above information, an acute ITSL may be derived from the Knect and Woitowitz (2000) study as follows:

$$ITSL_{(acute)} = NOAEL/UF_H$$

$$ITSL_{(acute)} = \frac{44\ mg/m^3}{10} = 4.4\ mg/m^3 = 4{,}400\ \mu g/m^3$$

Where:
NOAEL = 9.6 ppm (44 mg/m^3).
UF_H = Uncertainty factor to account for variation in sensitivity of human population (UF_H = 10).

For comparison purposes, an acute based ITSL could be derived from the Ogata (1991) study as follows:

$$ITSL_{(acute)} = LOAEL/UF_H \times UF_L$$

Where:
LOAEL = 60.2 ppm (277 mg/m^3).
UF_H = Uncertainty factor to account for variation in sensitivity of human population (UF_H = 10).
UF_L = Uncertainty factor for extrapolation from LOAEL to NOAEL (UF_L = 3 - 10).

Using an UF_L of 10 in the algorithm above would result in an acute ITSL of 2,800 µg/m^3, and use of an UF_L of 3 would result in an acute ITSL of 9,200 µg/m^3. The range between these two values encompass the acute ITSL of 4,400 µg/m^3 derived from the study by Knect and Woitowitz (2000).

The final acute ITSL is 4,400 µg/m^3 based on an 8-hour averaging time. The study by Knect and Woitowitz (2000) was selected over that by Ogata (1991) because it was based on the preferred point of departure of a NOAEL instead of a LOAEL, and included a larger number of subjects, as well as both males and females. The acute ITSL of 4,400 µg/m^3 (8-hour averaging time) was derived pursuant to Rule 229(2)(b) of the Michigan Air Pollution Control Rules.

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