MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 1,2-Dibromo-3-Chloropropane [CAS# 96-12-8]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 18, 2017

SUBJECT: 1,2-Dibromo-3-Chloropropane [CAS# 96-12-8] remaining at 24 hours

The current initial threshold screening level (ITSL) for 1,2-dibromo-3-chloropropane (DBCP) is 0.2 µg/m^3 based on a 24-hour averaging time. The ITSL established on 8/15/1991 is based on an Environmental Protection Agency (EPA) reference concentration (RfC) of 0.2 µg/m^3 published in the EPA's Integrated Risk Information System (IRIS) database in 1991. The EPA derived the RfC from Rao et al. (1982) 14-week rabbit inhalation study. Male New Zealand white rabbits (10/group) were exposed to either 0, 0.1, 1, or 10 ppm (0, 0.94, 9.4, or 94 mg/m^3) DBCP vapors for 6 hours/day, 5 days/week (duration-adjusted to 0, 0.17, 1.7, and 17 mg/m^3) for 14-weeks. The rabbits receiving the highest dose were exposed for only 8 weeks due to high mortality (pneumonia). Rabbits showed reduced sperm counts at 1 ppm. The NOAEL for the study was 0.1 ppm (0.17 mg/m^3 $NOAEL_{(HEC)}$). When the screening level was derived in 1991 the averaging time was set at 24 hours. As 1,2-dibromo-3-chloropropane is a reproductive toxicant it is appropriate for the ITSL to remain at a 24-hour averaging time

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MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2-Dibromo-3-Chloropropane (CAS No. 96-12-8)

FROM: Cathy Simon, Toxics Unit, Air Quality Division

DATE: June 11, 2012

SUBJECT: Development of Cancer Risk Screening Levels for 1,2-Dibromo-3-Chloropropane

The initial risk screening level (IRSL) for 1,2-dibromo-3-chloropropane (dibromochoropropane; DBCP) is $1x10^{-4}$ µg/m^3, and the secondary risk screening level (SRSL) is $1x10^{-3}$ µg/m^3.

Background

The Air Quality Division (AQD) established an initial threshold screening level (ITSL) of 0.2 µg/m^3 (24-hour averaging time) for DBCP in 1991. This ITSL was based on the United States Environmental Protection Agency (US EPA) reference concentration of 0.2 µg/m^3 published in the EPA's Integrated Risk Information System (IRIS) database that same year. At that time, no IRSL or SRSL were established by the AQD as no carcinogenic risk assessment for DBCP was available on IRIS, nor did the AQD do an independent review of the carcinogenicity data.

Since the AQD established an ITSL for DBCP, the California Environmental Protection Agency (Cal/EPA) and the US EPA have both determined that this compound may cause cancer in exposed humans, and have developed cancer risk values to evaluate this potential risk. An evaluation of the risk assessments done by these two agencies was undertaken to determine the most appropriate cancer risk values to use by the AQD to establish the IRSL and SRSL. This evaluation focused only on review of information related to the cancer risk assessment for DBCP, and did not include any update of the existing ITSL. Furthermore, 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 International Agency for Research on Cancer (IARC), the Agency for Toxics Substances and Disease Registry (ATSDR), the US EPA, and the Cal/EPA. Information from these and other sources, as well as the result of the risk assessment evaluation are presented below.

Dibromochloropropane has been used in the past as a pesticide, and was previously registered by the US EPA as a soil fumigant to control nematodes in a large number of crops. In 1997, the US EPA suspended registration for uses on nineteen fruits and vegetables. Further suspensions followed, and by 1999 the US EPA had cancelled registration for all pesticide uses, except for use as a soil fumigant on nematodes for pineapples in Hawaii. This use was subsequently cancelled in 1985 (EPA, 1995; NTP, 1982; NTP, 2011). DBCP has also been used in the past as an intermediate in the synthesis of organic chemicals, such as the brominated flame retardant, tris[(2,3-dibromopropyl) phosphate]. DBCP is no longer commercially manufactured in the United States. It has been reported that as of 2009, DBCP was not produced for sale by any manufacturing plant worldwide; however, another source

identified 21 suppliers worldwide in 2009, including 13 US suppliers (NTP, 2011). It is unclear where these suppliers would be obtaining the DBCP, considering the lack of manufacturers.

Carcinogenicity Data

Human epidemiologic data to evaluate the carcinogenic potential of DBCP are very limited. These studies, including four cohort studies and one population based case-control study have been evaluated by the IARC (1999). IARC concluded that an excess of lung cancer was found in two of the four cohort studies, an excess of liver and biliary tract cancer was observed in another cohort study, and in the fourth cohort study an excess of cervical cancer and a non-significant excess of melanoma and leukemia were observed. Shortcomings associated with these studies included such things as small number of cases, uncertain exposure levels, and exposure to other chemicals. The case-control study involved evaluation of the relationship between gastric cancer and leukemia and DBCP contamination of drinking water in Fresno County, California. IARC's review of this study indicated that there was a non-significant association of leukemia and gastric cancer with exposure to DBCP in groundwater. Due to the short comings of this limited data base, IARC concluded that there was inadequate evidence in humans for the carcinogenicity of DBCP (IARC, 1999).

Dibromochloropropane has been found to be carcinogenic in rats and mice by both oral and inhalation exposures. Two studies were available that evaluated the carcinogenicity of DBCP by oral administration, one a study by the National Cancer Institute (NCI, 1978) in which animals were administered the compound by gavage, and the other an unpublished feeding study done by Hazelton Laboratories (EPA, 2006). In the NCI study, administration of DBCP by gavage caused squamous cell carcinomas of the forestomach in male and female Osborn-Mendel rats, and male and female B6C3F1 mice. Additionally, statistically significant increased incidences of mammary gland adenocarcinomas were also found in exposed female rats (NCI, 1978). In the Hazelton Laboratory study, DBCP administered in the diet to male and female Charles River rats and HaM/ICR Swiss mice produced tumors of the stomach in both species and sexes. Increased incidences of tumors of the kidney and liver were also observed in the exposed rats (EPA, 2006).

The only inhalation carcinogenicity bioassay available was done by the National Toxicology Program (NTP, 1982). In this study, groups of 50 male and 50 female F344 rats and B6C3F1 mice were exposed to DBCP at concentrations of 0.6 or 3.0 ppm for 6 hours per day, 5 days per week for 76 – 103 weeks. In rats, inhalation exposure to DBCP was associated with an increased incidence of nasal cavity tumors and tumors of the tongue in both sexes, and cortical adenomas in the adrenal gland of females. In addition, mammary gland tumors in the low dose female rats were significantly increased above the control group. DBCP was also carcinogenic in both male and female mice, causing an increased incidence of nasal cavity tumors and lung tumors. Tables 1 and 2 provide a summary of the incidence rates for each tumor type.

Table 1. Rat Tumor Incidences from NTP (1982) Inhalation Bioassay

Tumor Type	Male Dose (ppm)			Female Dose (ppm)		
	0	0.6	3.0	0	0.6	3.0
Nasal cavity[a]	0/50	32/50[b]	39/49[b]	1/50	21/50[b]	42/50[b]
Tongue – squamous cell papilloma and/or carcinoma	0/50	1/50	11/49[b]	0/50	4/50	9/50[b]
Adrenal – cortical adenoma	1/49	6/49	3/48	0/50	7/50[b]	5/48[b]
Mammary gland – fibroadenoma	0/50	0/50	0/49	4/50	13/50[b]	4/50

[a] Includes – squamous cell carcinoma, squamous cell papilloma, adenomatous polyp, adenoma (NOS), carcinoma (NOS), adenocarcinoma (NOS) in the nasal cavity and/or turbinates.
[b] Significantly greater than control group

Table 2. Mouse Tumor Incidence from NTP (1982) Inhalation Bioassay

Tumor Type	Male Dose (ppm)			Female Dose (ppm)		
	0	0.6	3.0	0	0.6	3.0
Nasal cavity[a]	0/45	1/42	21/48[b]	0/50	11/50[b]	38/50[b]
Lung	0/41	3/40	11/45[b]	4/50	12/50[b]	18/50[b]

[a] Includes – squamous cell carcinoma, squamous cell papilloma, adenomatous polyp, adenoma (NOS), carcinoma (NOS), adenocarcinoma (NOS), neoplasm (NOS), carcinosarcoma, fibrosarcoma, sarcoma (NOS), keranthoacanthoma, hemangiosarcoma
[b] Significantly greater than control group

Genotoxicity Data

Dibromochloropropane has been tested in a number of *in vitro* and *in vivo* mutagenicity assays. The preponderance of this data has shown positive results. EPA (2006) has summarized this data:

> *"In vitro* genotoxicity studies found that DBCP induced mutations in bacteria in the presence of metabolic activation, as well as mutation, DNA strand breaks, sister chromatid exchanges, chromosomal aberrations and neoplastic transformation in mammalian cells (IARC, 1999). The metabolites of DBCP induce reverse and forward mutations in bacterial assays suggesting DBCP is a proximate carcinogen. *In vivo* genotoxicity studies showed that DBCP induced sex-linked recessive lethal mutations and other effects in *Drosophila*, as well as various effects in mammals, including DNA strand breaks in testicular and other tissues, unscheduled DNA synthesis in rat spermatocytes, micronuclei in bone marrow cells of rats and mice and forestomach cells of rats, and dominant lethal effect in orally-dosed rats (IARC, 1999)." (EPA, 2006).

Carcinogenicity Summary

The overall carcinogenic potential of DBCP has been evaluated by a number of organizations, including the IARC, the US EPA, and the ATSDR. These groups have reviewed the available data related to the carcinogenicity of DBCP, including, but not limited to the information cited above. The IARC's (1999) overall evaluation of DBCP was that it is possibly carcinogenic to humans (Group 2B). This evaluation was based on the finding that there was inadequate evidence of carcinogenicity in humans, but sufficient evidence in experimental animals. The ATSDR (1992) concluded that based on evidence in animals, DBCP is "reasonably anticipated to be carcinogenic in humans who are exposed to sufficient doses for long enough periods." EPA (2006) found that DPCP is "considered likely to be carcinogenic to humans." DBCP meets the definition of carcinogen found in Rule 103(c) of the Michigan Air Pollution Control Rules.

Review and Evaluation of Existing Cancer Risk Assessments

Utilizing the data from animal bioassays, inhalation unit risk values have been developed by the Cal/EPA and the US EPA. The Cal/EPA developed an inhalation unit risk value of $2x10^{-3}$ $(\mu g/m^3)^{-1}$ which was used for their Air Toxics Hot Spots program (Cal/EPA, 2009). This unit risk value is also used by the US EPA's Office of Air Quality Planning and Standards (OAQPS) for risk assessments of hazardous air pollutants (EPA, 2012a). The Cal/EPA unit risk value was used by the US EPA OAQPS to characterize the cancer risk for exposure to DBCP based on data from the 2005 National Air Toxics Assessment program (EPA, 2011), and in their school air toxics initiative (EPA, 2009a).

The first inhalation unit risk value derived by the US EPA was reported in the 1997 Health Effects Assessment Summary Tables (HEAST). This value was reported as $6.9x10^{-7}$ $(\mu g/m^3)^{-1}$ (EPA, 1997). More recently, the US EPA has developed an inhalation unit risk value of $6x10^{-3}$ $(\mu g/m^3)^{-1}$ under the Superfund program (EPA, 2006). Along with this inhalation unit risk value, the US EPA has also determined that DBCP causes cancer by a mutagenic mode of action (EPA, 2006). The US EPA's IRIS database does not include an evaluation of the carcinogenicity of DBCP. Table 3 provides a listing of the unit risk values derived by the US EPA and Cal/EPA.

Table 3. Unit Risk Values for DBCP as Determined by the US EPA and Cal/EPA

Unit Risk $(\mu g/m^3)^{-1}$	Source
$2x10^{-3}$	Cal/EPA, 2009[a]
$6.9x10^{-7}$	EPA, 1997
$6x10^{-3}$	EPA, 2006

[a] This unit risk value has also been used by the US EPA OAQPS for risk assessment of hazardous air pollutants.

The California unit risk value of $2x10^{-3}$ $(\mu g/m^3)^{-1}$ was derived from the unpublished study conducted by Hazelton Laboratories, utilizing the incidence of forestomach squamous cell carcinomas in female mice administered DBCP in the diet (Cal/EPA, 2009). In this study, no tumors were observed in the control group, whereas 19/50 of the high dose group developed tumors. No histopathological examination was done of the low and mid dose groups, so these groups were not included in the risk assessment for DBCP. The Cal/EPA (2009) stated that the potency factor based on the Hazelton study was "consistent with the incidence of stomach carcinomas in the female mice in the NCI gavage study." The Cal/EPA (2009) did not utilize the NTP inhalation study to derive their final cancer potency factor but indicated that using this

study resulted in a potency value that was "close to, but slightly lower than the potency based on the Hazelton Laboratory study." Considering the above information, the Cal/EPA concluded that the Hazelton Laboratory study was the most appropriate animal data to use for deriving the cancer potency value.

The Cal/EPA (2009) used the linearized multistage model, with the 95% upper confidence bound on the dose response slope, to derive their cancer potency value with the following adjustments:

> "The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)$, were T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse)." (Cal/EPA, 2009).

The oral potency value of 6.6 $(mg/kg/day)^{-1}$ was then transformed to an inhalation unit risk value of $2x10^{-3}$ $(\mu g/m^3)^{-1}$ using a default human body weight and breathing rate of 70 kg and 20 m^3/day, respectively (Cal/EPA, 2009).

The US EPA's unit risk value of $6.9x10^{-7}$ $(\mu g/m^3)^{-1}$ reported in HEAST (EPA, 1997) was derived from the incidence of nasal cavity tumors in rats and mice from the NTP bioassay (NTP, 1982). Unfortunately, no details were available to document how this value was determined.

The US EPA (2006) unit risk value of $6x10^{-3}$ $(\mu g/m^3)^{-1}$ developed for the Superfund program, was also based upon the NTP inhalation cancer bioassay. Seven different unit risk values were derived by EPA from this study, using species, sex, and tumor specific data. These seven different unit risk values included those based on tumors of the nasal cavity in male rats, female rats, male mice, and female mice, adrenal cortex tumors in female rats, as well as lung tumors in male and female mice. The unit risk values ranged from a low of 2.3×10^{-7} $(\mu g/m^3)^{-1}$ based on lung tumors in male mice, to a high of 5.6×10^{-3} $(\mu g/m^3)^{-1}$ based on tumors of the nasal cavity in male rats.

In developing the unit risk values for DBCP, the US EPA utilized the methodology in their *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a). Following these guidelines, the US EPA utilized the benchmark dose methodology to determine the $BMCL_{10}$, followed by linear extrapolation to the origin determined by dividing the $BMCL_{10}$ into 0.1 (10%). Exposure concentrations used in the NTP inhalation study were first converted to human equivalent concentrations (HEC) prior to modeling. Nasal cavity tumors were considered an extrathoracic region effect and lung tumors a pulmonary region effect. DBCP was considered a category 1 (reactive) gas for these effects. The adrenal tumors were considered an extrarespiratory effect, and HECs were calculated treating DBCP as a category 3 gas.

The inhalation unit risk values for each tumor type are shown below in Table 4 which is adapted from Table 14 in EPA (2006).

Table 4. Inhalation Unit Risk Values Determined by the US EPA (2006)

Tumor Type, Species and Sex	HEC (mg/m3) and Incidence			Unit Risk Value $(\mu g/m^3)^{-1}$
Nasal Cavity, Male Rats	0 mg/m^3 0/50	0.23 mg/m^3 32/50	1.13 mg/m^3 39/49	5.6×10^{-3} [a]
Nasal Cavity, Female Rats	0 mg/m^3 1/50	0.17 mg/m^3 21/50	0.83 mg/m^3 42/50	2.9×10^{-3}
Nasal Cavity, Male Mice	0 mg/m^3 0/45	0.21 mg/m^3 1/42	1.06 mg/m^3 21/48	6.3×10^{-4}
Nasal Cavity, Female Mice	0 mg/m^3 0/50	0.18 mg/m^3 11/50	0.91 mg/m^3 38/50	1.8×10^{-3}
Lung, Male Mice	0 mg/m^3 0/41	3.64 mg/m^3 3/40	18.22 mg/m^3 11/45	2.3×10^{-5}
Lung, Female Mice	0 mg/m^3 4/50	3.01 mg/m^3 12/50	15.07 mg/m^3 18/50	3.8×10^{-5}
Adrenal Cortex, Female Rats	0 mg/m^3 0/50	1.04 mg/m^3 7/50	5.2 mg/m^3 5/48	2.4×10^{-4} [a]

[a] To obtain an adequate fit to the data for male rat nasal tumors and female mouse adrenal tumors, the high dose groups were dropped, leaving only controls and one dose group for each of these endpoints.

The largest unit risk value, 5.6×10^{-3} $(\mu g/m^3)^{-1}$, based on the incidence of nasal cavity tumors in male rats, was selected by the US EPA (2006) to derive the provisional peer-reviewed toxicity value (PPRTV) for DBCP. This unit risk value was also considered to be the most appropriate value to use for determining the IRSL and SRSL. This unit risk value was selected because it was derived from the NTP inhalation bioassay which was a high quality study utilizing the most appropriate route of exposure. Furthermore, the dose equivalency between humans and laboratory animals was determined using EPA's methodology for deriving reference concentrations (EPA, 1994) which currently provides the best state of the science for inhalation dosimetry. Additionally, this value was derived using the most updated US EPA carcinogen risk assessment guidelines (EPA, 2005a) which underwent extensive scientific peer review, and provide the best state of the science in this area. Lastly, this unit risk value 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)

The Cal/EPA unit risk value, although used by the US EPA OAQPS programs, was not selected for use in developing the IRSL or SRSL. Shortcomings of this risk assessment included use of an oral cancer bioassay instead of the NTP (1982) inhalation bioassay to develop an inhalation unit risk value; use of older risk assessment guidelines instead of the most current EPA methodology (EPA, 2005a); and animal to human extrapolation methodology in which the dose of the compound is normalized by the 2/3 power of body weight per day, instead of 3/4 power, as supported by the most current science.

The HEAST unit risk value of 6.9×10^{-7} $(\mu g/m^3)^{-1}$ (EPA, 1997) was also not selected for use in developing the IRSL and SRSL. HEAST values are a compilation of health assessment values that have been developed in the past by various EPA offices. These values have not been submitted to EPA for consensus, and were last updated in 1997. Furthermore, although the HEAST value for DBCP was based on data from the NTP (1982) inhalation bioassay, no details on methodologies used in the derivation were available to assess its validity.

The US EPA (2006) has also determined that DBCP acts by a mutagenic mode of action. The discussion is limited regarding the basis of this determination, but focuses on the finding of a significant number of positive results in several different mutagenicity assays, and that DBCP is metabolized to reactive products that can bind to cellular DNA and proteins, with the principal adduct being S-[1-(hydroxymethyl)-2-(N^7-guanyl)ethyl]-glutathione. While the cancer risk assessment for DBCP has not under gone the extensive peer review process of an IRIS based chemical, 1,2,3-trichloropropane (TCP), a structurally similar compound to DBCP, has under gone this process and been determined to act by a mutagenic mode of action. The supporting documentation for the IRIS summary for TCP (EPA, 2009b) provides a detailed discussion of the finding of a mutagenic mode of action, with similar supporting data and rationale as for DBCP. EPA (2012b) also states in the IRIS documentation for TCP that "DBCP also forms the same major DNA adduct, S-[1-(hydroxymethyl)-2-(N^7-guanyl)ethyl]-glutathione, as 1,2,3-trichloropropane (Humphreys et al., 1991)." Considering the above information, a mutagenic mode of action for DBCP is supported and should be used in deriving the IRSL and SRSL.

Derivation of the IRSL and SRSL

The unit risk value of 5.6×10^{-3} $(\mu g/m^3)^{-1}$, based on nasal cavity tumors in male rats, was used to derive the IRSL. Since DBCP has been found to act by a mutagenic mode of action, derivation of the IRSL requires the use of age dependent adjustment factors (ADAF) to account for the increased susceptibility for early life stages. The use of ADAFs is consistent with the methodology specified in the US EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (2005b), to account for the increased susceptibility of children from ages 0 -16 years old. The IRSL is derived as follows:

$$IRSL = \frac{Target\ risk\ value}{Unit\ risk\ value\ x\ ADAF}$$

Where:

Target risk value = 1×10^{-6}

Unit risk value = 5.6×10^{-3} $(\mu g/m^3)^{-1}$

ADAF = a cumulative age dependent adjustment factor that assumes a 70 year lifetime, and takes into account a 10 fold increased susceptibility for ages 0 – 2 years, a 3 fold increased susceptibility from 2 – 16 years old, and no adjustment for susceptibility for ages 16 – 70 years. This factor is derived as follows:

$$ADAF = \frac{(2\ years\ x\ 10) + (14\ years\ x\ 3) + (54\ years\ x\ 1)}{70\ years} = 1.66 \cong 1.7$$

Using the above equation, the IRSL is determined as follows:

$$IRSL = \frac{1x10^{-6}}{5.6x10^{-3}\left(\mu g / m^3\right)^{-1} x\, 1.7} = 1x10^{-4}\ \mu g / m^3$$

The SRSL is derived using the same equations as above, except a target risk value of $1x10^{-5}$ is substituted for the target risk value of $1x10^{-6}$. Making this substitution, results in a SRSL of $1x10^{-3}$ µg/m^3.

The above derivation of the IRSL and SRSL for 1,2-dibromo-3-chloropropane is based upon the methodology specified in Rule 229(1)(c) of the Michigan Air Pollution Control Rules.

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