**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

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**INTEROFFICE COMMUNICATION**

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TO: File for 1,4-Dichlorobenzene (CAS # 106-46-7)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for 1,4-Dichlorobenzene (CAS # 106-46-7)

DATE: December 1, 2016

The initial threshold screening level (ITSL) for 1,4-dichlorobenzene is 800 µg/m³ based on an annual averaging time. The ITSL was established on 11/1/1996 based on EPA's reference concentration (RfC) of 800 µg/$m^3$. The ITSL averaging time is being changed from 24 hours to annual at this time. The initial risk screening level (IRSL) for 1,4-dichlorobenzene is 0.25 µg/$m^3$ and the secondary risk screening level (SRSL) is 2.5 µg/$m^3$ based on an annual averaging time.

1,4-Dichlorobenzene (1,4-DCB) [CAS # 106-46-7], also known as para-dichlorobenzene and PDB, is an organic compound composed of two chlorine atoms substituted for hydrogen at opposing sides on a benzene ring. 1,4-DCB is a colorless to white, crystalline solid with a strong odor, a melting point of 53.1°C, a boiling point at 174°C, and a molecular weight of 147.01 g/mol. The vapor pressure of 1,4-DCB at 54.8°C is 10 mmHg. It is practically insoluble in water, but is soluble in organic solvents including ether, chloroform, carbon disulfide, and benzene and highly soluble in ethanol and acetone. 1,4-DCB is noncorrosive, volatile, and combustible. When heated to decomposition, it can produce hydrochloric acid and carbon monoxide. 1,4-DCB is used: as a soil insecticidal fumigant to control moths, fruit borers, and ants; a deodorant to control moths (mostly in mothballs in which it is a replacement for naphthalene); to control mold and mildew growth on tobacco seeds, leather, and fabrics; as an extreme pressure lubricant; as a disinfectant in waste containers and restrooms (it is the characteristic smell associated with urinal cakes); as a germicide or disinfectant; as a chemical intermediate in dyes, pharmaceuticals, and resin-bonded abrasives; and as a precursor in the production of polyphenylene sulfide (a plastic used in electronics applications) (NTP, 2011; Cal EPA, 1997). 1,4-DCB is not known to occur naturally in the environment. 1,4-DCB can also be released when lindane degrades. Environmental releases of 1,4-DCB from chemical dumps, manufacturing effluents, and from its use as a deodorant may result in volatilization of 1,4-DCB causing exposure mainly via inhalation, but potential exposure through ingestion and dermal contact is possible (Cal EPA, 1997; NTP, 2011). 1,4-DCB "has been detected in meat and eggs from exposed animals and in fish from contaminated waters" (NTP, 2011).

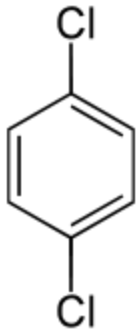


**Figure 1.** Structure of 1,4-Dichlorobenzene.

A literature review was conducted to determine an initial risk screening level (IRSL) for 1,4-dichlorobenzene. The following references and databases were searched to derive the screening level: Chemical Criteria Database (CCD), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2012 Guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 7/15/14), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, and EPA Toxic Substance Control Act Test Submission Database (TSCATS).

**ITSL Derivation:**

The ITSL was based on the EPA RfC of the same value. EPA (1996) used a study by the Chlorobenzene Producers Association (1986) to derive an RfC of 0.8 mg/m$^3$ based on increased liver weights in P1 males during a rat multi-generation reproductive study. This RfC and basis were still current in IRIS as of 7/7/2014. “In a two generation reproductive study Sprague-Dawley rats (P1) {28/sex/group} were exposed to 1,4-dichlorobenzene (1,4-DCB) vapor at concentrations of 0, 50, 150, or 450 ppm (0, 301, 902, 2705 mg/cu.m) for 10 weeks, 6 hours/day, 7 days/week, then the rats were mated for 3 weeks. For exposure of the next generation, selected F1 weanlings were exposed to 1,4-DCB for 11 weeks then mated. Adult males in the 150 ppm group exhibited reduced body weights and weight gain, reduced food consumption, increased incidence of tremors, unkempt appearance and nasal and ocular discharges. A statistically significant (p=0.01) increase in liver weights was noted at necropsy in the 150 and 450 ppm groups (16 and 38%, respectively). In addition, there was a statistically significant (p=0.01) increase in kidney weight for both parental males and females. At 450 ppm there was a statistically significant (p=0.01) decrease in live births, a decrease in pup weights, and decreased pup survival at day 4 of lactation for both the F1 and F2 generations. In addition, histological observations showed significant increases in incidence of hepatocellular hypertrophy in F0 and F1 males and females. No developmental abnormalities were observed in the pups examined. All dose levels caused hyaline droplet nephrosis in post-pubertal males; this change was associated with the formation of alpha-2μ-globulin but is recognized as an abnormality specific for male rats and does not have significance relative to human health (EPA, 1991). The lesions observed in the male rats treated with 1,4-DCB met the criteria for alpha-2μ-globulin nephropathy, that is, excessive accumulation of hyaline droplets in the P2 segment of the proximal tubule, single cell necrosis, accumulation of granular casts, increased cellular proliferation in the P2 segment and linear mineralization of tubules” (EPA, 1996).

"The NOAEL established from this study was 50 ppm (301 mg/cu.m) and the LOAEL is 150 ppm (902 mg/cu.m); the critical effect was the significant increase in liver weights of P1, parental males" (EPA, 1996). A total uncertainty factor of 100 was used. "An uncertainty factor of 10 was used to account for sensitive subpopulations among humans. An uncertainty factor of 3 rather than 10 was used to account for interspecies differences since dosimetry adjustments were applied. An additional factor of 3 was used since the NOAEL was based on a subchronic rather than chronic study" (EPA, 1996).

According to Rule 232(1)(a) an ITSL can be determined to be equal to an EPA inhalation RfC. Therefore, the ITSL for 1,4-dichlorobenzene is 800 µg/m³. An averaging time of annual, rather than 24-hours, is more appropriate in this case because the study duration was over multiple generations, reproduction and development were evaluated, and a 3-fold subchronic-to-chronic uncertainty factor was applied.

**IRSL Derivation:**

EPA (IRIS) has not reviewed 1,4-dichlorobenzene for carcinogenicity and there are no EPA provisional peer reviewed toxicity values (PPRTV). ATSDR "(minimal risk levels) MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects" (ATSDR, 2006). ATSDR (2006) did use the Aiso et al., (2005) study to derive the chronic inhalation MRL although they did not use a carcinogenic endpoint for their derivation. Instead ATSDR used changes in the nasal olfactory epithelium to derive their chronic inhalation MRL of 0.02 ppm. California EPA derived an inhalation unit risk of 0.000011 $(ug/m^3)^{-1}$ and a slope factor of 0.04 $(mg/kg\text{-}day)^{-1}$ based on the NTP (1987) study using male mouse hepatocarcinoma and adenoma data. The Texas Commission on Environmental Quality does not have a carcinogenic Effects Screening Level (ESL), but does have a long-term ESL for p-dichlorobenzene of 106 $\mu g/m^3$ based on the Aiso et al., (2005) study, which found an increase in nasal olfactory epithelial lesions as the critical health effect.

NTP (1987) conducted a bioassay in which groups of 50 male and female F344/N rats and $B6C3F_1$ mice were exposed in corn oil by gavage to 1,4-DCB 5 days/week at doses of 0, 150, or 300 mg/kg-day [time-weighted average doses of 0, 107, or 214 mg/kg/day] (male rats) and 0, 300, or 600 mg/kg-day [time-weighted average doses of 0, 214, or 428 mg/kg/day] (female rats and mice of both sexes) for two years. "Among male rats, a dose-dependent increase in renal tubular cell adenocarcinoma and a marginal increase in mononuclear cell leukemia were observed (Table 1). NTP concluded that there was clear evidence of carcinogenicity of 1,4-DCB for male rats, but no evidence of carcinogenicity for female rats. Liver tumor incidence was significantly increased among both male and female mice (Table 2)" (OEHHA, 1997). There was a marginal trend toward increased follicular cell adenomas of the thyroid among female mice (0/48 control; 0/45 at 300 mg/kg-day; 3/46 at 600 mg/kg-day) and a marginal but significant increase in the incidence of pheochromocytoma among male mice (0/47 control; 2/48 at 300 mg/kg-day; 4/49 at 600 mg/kg-day). NTP concluded that there was clear evidence of carcinogenicity of 1,4-DCB for both male and female $B6C3F_1$ mice.

Table 1. Tumor Incidence in 1,4-DCB Treated Male F344/N Rats (NTP, 1987)

| Dose [time-weighted average dose] (mg/kg-day) | Renal Tubular Cell Adenocarcinoma | Mononuclear Cell Leukemia |
|---|---|---|
| 0 [0] | 1/50 | 5/50 |
| 150 [107] | 3/50 | 7/50 |
| 300 [214] | 7/50 | 11/50 |

Table 2. Tumor Incidence in 1,4-DCB Treated $B6C3F_1$ Mice (NTP, 1987)

| Dose [time-weighted average dose] (mg/kg-day) | Hepatocellular Carcinoma | | Hepatocellular Adenoma | | Combined Hepatocellular Adenoma or Carcinoma | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| 0 [0] | 14/50 | 5/50 | 5/50 | 10/50 | 17/50 [17/43] | 15/50 [15/46] |
| 300 [214] | 11/49 | 5/48 | 13/49* | 6/48 | 22/49 [22/40] | 10/48 [10/45] |
| 600 [428] | 32/50* | 19/50* | 16/50* | 21/50* | 40/50* [40/42] | 36/50* [36/45] |

* Statistically significant increase in incidence ($p<0.05$).
[The premature mortality of animals without tumors was subtracted from the sample groups.]

"The appearance of renal tubule tumors in male rats raises the possibility that the tumors were induced by a mechanism involving the hyperplastic response mediated by the binding of the test compound to $\alpha_{2\mu}$-globulin. This binding leads to accumulation in the renal proximal tubules which results in nephrotoxicity, hyperplasia and a subsequent carcinogenic response, a mechanism hypothesized for certain strains of male rats (including Fisher 344/N) but determined to be irrelevant to humans for the purposes of risk assessment because of the absence of significant amounts of $\alpha_{2\mu}$-globulin in humans (EPA, 1991). There is evidence that the development of kidney tumors observed in the male F344 rats exposed to 1,4-DCB by oral gavage is subsequent to the nephrotoxic action of 1,4-DCB from its (or a metabolite's) binding to $\alpha_{2\mu}$-globulin and accumulation in the tubules. The evidence comes from several observations:

1. 1,4-DCB induces renal tumors only in male rats and not in female rats or mice.
2. 1,4-DCB produces renal toxicity and cell proliferation only in male rats and in the proximal tubules in the P2 segment and there are associated hyaline droplets which contain $\alpha_{2\mu}$-globulin (Bomhard *et al*., 1988; Charbonneau *et al*., 1989).
3. A rat strain lacking $\alpha_{2\mu}$-globulin did not develop nephropathy or hyaline droplet accumulation in response to 1,4-DCB exposure (Dietrich and Swenberg, 1991).
4. 1,4-DCB and its primary metabolite (2,5-dichlorophenol) have been shown to reversibly bind to $\alpha_{2\mu}$-globulin both in vitro and in vivo (Charbonneau *et al*., 1989).

From this evidence it appears plausible that the $\alpha_{2\mu}$-globulin mechanism may play a role in the etiology of the renal tumors in male rats" (OEHHA, 1997). Because this mechanism may be irrelevant to humans, the nephropathy and carcinogenesis at this site have not been used for risk assessment to determine an IRSL for 1,4-DCB.

In a study by Aiso *et al*., (2005), groups of 50 male and female $BDF_1$ mice and 50 F344 rats were exposed to 1,4-DCB vapor at concentrations of 0 (control), 20, 75, or 300 ppm (0, 120, 450, or 1800 mg/m$^3$ respectively) for 6 hours/day, 5 days/week for 2 years. "Centrilobular hypertrophy of hepatocytes, papillary mineralization, and pelvic urothelial hyperplasia of the

kidney were noted in the 300 ppm-exposed male rats. Treatment and age-related increases in incidences of the eosinophilic globules of the respiratory and olfactory epithelia in female rats and incidences of the respiratory metaplasia of the nasal gland epithelium in mice and rats and the olfactory epithelium in mice were noted. The nasal lesion was the most sensitive endpoint of chronic inhalation toxicity" (Aiso *et al*., 2005).

Table 3. Incidences of selected lesions in the liver and kidneys of mice exposed by inhalation to *p*-DCB for 2 years (Aiso *et al*., 2005)

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| **p-DCB concentration** | **0 ppm [0 mg/m$^3$]** | **20 ppm [120 mg/m$^3$]** | **75 ppm [450 mg/m$^3$]** | **300 ppm [1800 mg/m$^3$]** | **0 ppm [0 mg/m$^3$]** | **20 ppm [120 mg/m$^3$]** | **75 ppm [450 mg/m$^3$]** | **300 ppm [1800 mg/m$^3$]** |
| **Mice** | | | | | | | | |
| Number of animals examined | 49 | 49 | 50 | 49 | 50 | 50 | 49 | 50 |
| Hepatocellular adenoma | 13 | 9 | 7 | 13 | 2 | 10 | 6 | 20 |
| Hepatocellular carcinoma | 12 | 17 | 16 | 38 | 2 | 4 | 2 | 41 |
| Hepatoblastoma | 0 | 2 | 0 | 8 | 0 | 0 | 0 | 6 |
| Histiocytic sarcoma | 0 | 3 | 1 | 6 | 2 | 1 | 1 | 0 |

"Case reports of chronic lymphoid leukemia (two cases), acute myeloblastic leukemia (two cases) and myeloproliferative syndrome (one case) were observed in individuals exposed to 1,2- and 1,4-DCB from repeated use of a mixture of the compounds as a solvent/cleaning fluid (NTP, 1987). There was no indication of exposure to benzene. In its evaluation of this study, IARC reported that it 'suggested an association between leukemia and exposure to dichlorobenzenes' (IARC, 1982)" (OEHHA, 1997).

Potential IRSL Derivation using the NTP (1987) Two-year Gavage Study Data

The cancer potency for 1,4-DCB was calculated from the male mouse hepatocarcinoma and adenoma data of NTP (1987) using EPAs benchmark dose software. The adjusted 1,4-DCB doses were calculated at 0, 214, or 428 mg/kg/day (see table 2). The premature mortality of animals without tumors was subtracted from the sample groups. The 95% upper confidence bound on the dose-response slope was used to derive the cancer potency factor ($q_1^*$). The equation for converting an animal $q_1^*$ to a human equivalent $q_1^*$ using Rule 231(3)(f)(ii) equation gives:

$$q_1^*({}^{\mu g}/_{m^3})^{-1} = q_1^* ({}^{mg}/_{kg/day})^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{a}{b}$$

Where:
a = absorption efficiency by the inhalation route of exposure.
b = absorption efficiency by the oral route of exposure.

In the absence of absorption efficiency data, the value for a/b = 1. After performing the benchmark dose calculations based on male mouse hepatocarcinoma and adenoma, the cancer slope factor ($q_1^*$) is 0.00217111 $(mg/kg/day)^{-1}$.

The equation listed under Rule 336.1231 on part 3(c) was used to calculate the equivalent human dose from animal data, assuming that milligram/surface area/day is an equivalent dose between species. To make this adjustment, the multistage cancer slope factor in units of $(milligram/kilogram/day)^{-1}$, is multiplied by factor (T). Using the most current EPA method for using this calculation, the EPA now uses ¾ power in their calculation, so this equation's exponent has been changed to the ¼ power to reflect this update.

$$T = \left(\frac{W_H}{W_A}\right)^{1/4}$$

Where $W_H$ = Average weight of an adult human (assumed to be 70 kg).
$W_A$ = Body weight of the male $B6C3F_1$ mouse (control group at 85 weeks).

$$T = \left(\frac{70\ kg}{0.0428\ kg}\right)^{1/4} = 6.359362297$$

The multistage cancer slope factor of 0.00217111 $(mg/kg)^{-1}$ for the male mouse needs to be converted to a human cancer slope factor by multiplying by the T factor above.

Human cancer slope factor = male mouse cancer slope factor x 6.359362297
Human cancer slope factor = 0.00217111 $(mg/kg/day)^{-1}$ x 6.35936227 = 0.013806875 $(mg/kg/day)^{-1}$

The oral human cancer slope factor is in $(mg/kg/day)^{-1}$ units, which needs to be converted to $(ug/m^3)^{-1}$. Imputing this value into the above equation gives:

$$q_1^*\left(^{\mu g}/_{m^3}\right)^{-1} = 0.013806875\ \left(^{mg}/_{kg}\right)^{-1} \times \frac{20m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1} = 0.000003945\left(^{\mu g}/_{m^3}\right)^{-1}$$
$$= 3.945\ E^{-6}\ \left(^{\mu g}/_{m^3}\right)^{-1}$$

The potential IRSL can be calculated via Rule 231(1) using the human cancer slope factor as the unit risk value using equation below:

$$Potential\ IRSL = \frac{1 \times 10^{-6}}{Unit\ Risk}$$

Where:
Unit risk = Additional lifetime cancer risk occurring in a population in which all individuals are exposed continuously for life to a concentration of 1 microgram per cubic meter of the chemical in the air they breathe. The IRSL is determined as an estimated lifetime cancer risk of 1 in 1 million. $q_1^*$ is used as the unit risk in this equation. Using the $q_1^*$ from the above equation gives:

$$Potential\ IRSL = \frac{1 \times 10^{-6}}{3.945 \times 10^{-6}} = 0.253485425\ {}^{\mu g}/_{m^3}$$

OEHHA (2009) has an inhalation unit risk = 1.1 $E^{-5}$ $(ug/m^3)^{-1}$, which was determined using a linearized multistage procedure developed by Crump et al., (1982). The program used for that calculation was not specified. The calculation utilized in the present assessment is the EPAs Benchmark Dose Software using the cancer multistage model. Also, OEHHA (2009) calculated their scaling factor as $q_{human}$ x $q_{animal}$ x $(bw_h/bw_a)^{1/3}$, where the present assessment utilized the current EPA method which uses an exponent of ($^1/_4$) in the calculation. These differing methods may account for the differences between OEHHA (2009) inhalation unit risk of 1.1 $E^{-5}$ $(ug/m^3)^{-1}$ and the current calculated inhalation unit risk 3.945 $E^{-6}$ $(ug/m^3)^{-1}$.

Potential IRSL Derivation using the Aiso et al., (2005) Two-year Inhalation Study Data

1,4-DCB is fairly water soluble and was found to be reactive in both the respiratory tract, where 1,4-DCB caused nasal olfactory epithelial lesions, and in the liver. According to EPA (1994), 1,4-DCB can be classified as a category 2 gas, as it has the potential for significant accumulation in the blood and has a higher potential for both respiratory and remote toxicity. Due to EPA's documentation of problems with derivation of Category 2 gas equations, 1,4-DCB should be treated as a category 3 gas when working with the gas equations. Therefore, the EPA (1994) regional gas ratio ($RGDR_{PU}$) for a category 3 gas as the adjustment for animal exposure to human exposure was evaluated. The blood:air partition coefficients are not known for either mice or humans. Therefore, the $RGDR_{PU}$ is the default value of 1. Thus, the animal adjusted concentrations are the same as the human equivalent concentrations.

The data from the Aiso et al., (2005) study found in Table 3 were run in the EPA Benchmark Dose Software (BMDS) version 2.5.0 using the dichotomous data utilizing the multistage cancer model. The results were reviewed to determine whether the data were within acceptable limits. Four of the tumor types in the table above did not have acceptable values. The male mouse histiocytic sarcoma, the female mouse hepatocellular adenoma, and the female mouse hepatocellular carcinoma had p-values less than 0.1. The female mouse hepatocellular adenoma also had scaled residuals greater than 2. The female mouse histiocytic sarcoma plot showed no response and the cancer slope factor calculation failed, which is consistent with the data shown (as the control mice had higher incidence of histiocytic sarcoma tumors than the highest dose). The other tumor incidence data are shown in table 4.

Table 4. Model predictions for tumors in $BDF_1$ mice exposed to 1,4-dichlorobenzene vapors for 6 hours/day, 5 days/week for two years.

| Animal | Tumor Type | p-Value | $Chi^2$ | AIC | Cancer unit risk $(mg/m^3)^{-1}$ |
|---|---|---|---|---|---|
| Male mouse | Hepatocellular adenoma | 0.2620 | 2.68 | 207.298 | 0.000110231 |
| Male mouse | Hepatocellular carcinoma | 0.2669 | 1.23 | 239.907 | 0.000684447 |

EPA (2012) states the benchmark dose model p-value must be greater than 0.1. Of the remaining models, the model with the lowest AIC may be used to calculate the point of departure. "This criterion is intended to help arrive at a single BMDL value in an objective, reproducible manner" (EPA, 2012). The multistage model adequately fits both of these data sets. Although the male mouse hepatocellular adenoma data fit the model, the slope generated a graph that was of poor quality, which is consistent with the lack of a dose response effect of p-DCB in the study data in table 3. Therefore, the resulting unit risk for the male mouse hepatocellular adenoma was less reliable than the male mouse hepatocellular carcinoma unit

risk. The male mouse hepatocellular carcinoma showed a clear dose response with increasing p-DCB dosing seen in table 3 and yielded a greater unit risk (more potent), which will be used for calculation of the potential screening level (per Rule 231(3)(b)) with the unit risk of 0.000684447 $(mg/m^3)^{-1}$ which is converted using the following equation:

$$0.00068447\,{}^{m^3}/_{mg} \times \frac{1\,mg}{1000\,\mu g} = 0.00000068447\,({}^{\mu g}/_{m^3})^{-1}\ or\ 6.8447\,E^{-7}({}^{\mu g}/_{m^3})^{-1}$$

Using this value as the $q_1^*$, which is considered the unit risk value for determining the IRSL in Rule 231(1) equation below:

$$Potential\ IRSL = \frac{1 \times 10^{-6}}{unit\ risk} = \frac{1 \times 10^{-6}}{6.8447 \times 10^{-7}\ {}^{ug}/_{m^3}} = 1.462\ {}^{\mu g}/_{m^3}$$

According to Rule 231(4) an annual averaging time is used for the IRSL and SRSL.

Therefore, if using the NTP (1987) two-year oral study to derive the unit risk value the initial risk screening level (IRSL) for 1,4-dichlorobenzene is 0.25 µg/m$^3$ and the secondary risk screening level (SRSL) is 2.5 µg/m$^3$ based on an annual averaging time. If using the Aiso et al. (2005) two-year inhalation study to derive the unit risk value, the IRSL for 1,4-dichlorobenzene is 1.5 µg/m$^3$ and the SRSL is 15 µg/m$^3$ based on an annual averaging time.

Both the NTP (1987) study and the Aiso et al., (2005) study found elevated liver tumors in mice and rats. Both are well conducted studies. It was not possible to derive a unit risk value for combined male mouse hepatocellular adenoma and carcinoma results with the available data in the Aiso et al. (2005) study. This is a significant limitation of the Aiso et al. (2005) study given that the NTP study shows that the combined effects of 1,4-DCB in mice showed a statistically significant increase in combined hepatocellular adenoma or carcinomas. This inability to account for the combined hepatocellular adenoma or carcinoma effects with the Aiso et al., (2005) study results in a potential underestimation of the potential risk when extrapolated to humans. Even though inhalation is the primary route of human exposure for ITSL and SRSL derivation, it is more appropriate to use the NTP (1987) study for derivation of the IRSL and SRSL as the unit risk value derived using the NTP (1987) study accounts for combined hepatocellular adenomas or carcinomas and better ensures health protectiveness.

After reviewing the available data, the initial risk screening level (IRSL) for 1,4-dichlorobenzene is 0.25 µg/m$^3$ and the SRSL is 2.5 µg/m$^3$ based on an annual averaging time.

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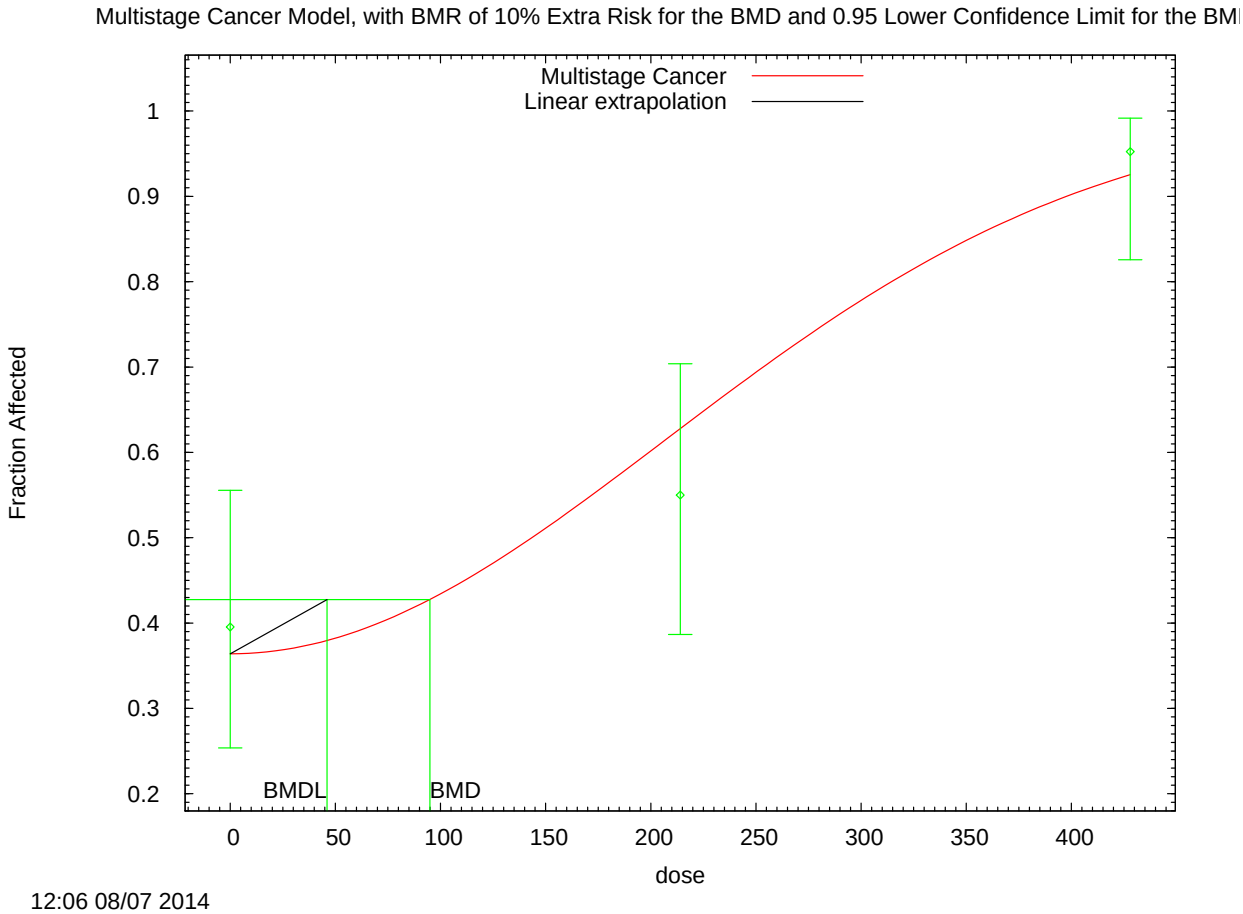
DL:lh

**Appendix A.**

NTP (1987)


Multistage Cancer Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM
Multistage Cancer
Linear extrapolation
Fraction Affected
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
BMDL
BMD
0
50
100
150
200
250
300
350
400
dose
12:06 08/07 2014

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        Input Data File: C:/USEPA/BMDS250/Data/msc_1-4-DCB_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS250/Data/msc_1-4-DCB_Opt.plt
                                              Thu Sep 25 15:43:37 2014
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 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Hepato_Aden_or_Carc
   Independent variable = Dose_mg-kg-day

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.292631
                        Beta(1) =            0
                        Beta(2) = 1.44446e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.47

   Beta(2)        -0.47            1
```

Parameter Estimates

| Variable | Estimate | Std. Err. | 95.0% Wald Confidence Interval Lower Conf. Limit | Upper Conf. Limit |
|---|---|---|---|---|
| Background | 0.363983 | * | * | * |
| Beta(1) | 0 | * | * | * |
| Beta(2) | 1.16825e-005 | * | * | * |

* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---|---|---|---|---|---|
| Full model | -64.4227 | 3 | | | |
| Fitted model | -65.2706 | 2 | 1.69592 | 1 | 0.1928 |
| Reduced model | -82.2353 | 1 | 35.6253 | 2 | <.0001 |

AIC: 134.541

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.3640 | 15.651 | 17.000 | 43.000 | 0.427 |
| 214.0000 | 0.6275 | 25.100 | 22.000 | 40.000 | -1.014 |
| 428.0000 | 0.9252 | 38.857 | 40.000 | 42.000 | 0.670 |

Chi^2 = 1.66 d.f. = 1 P-value = 0.1976

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

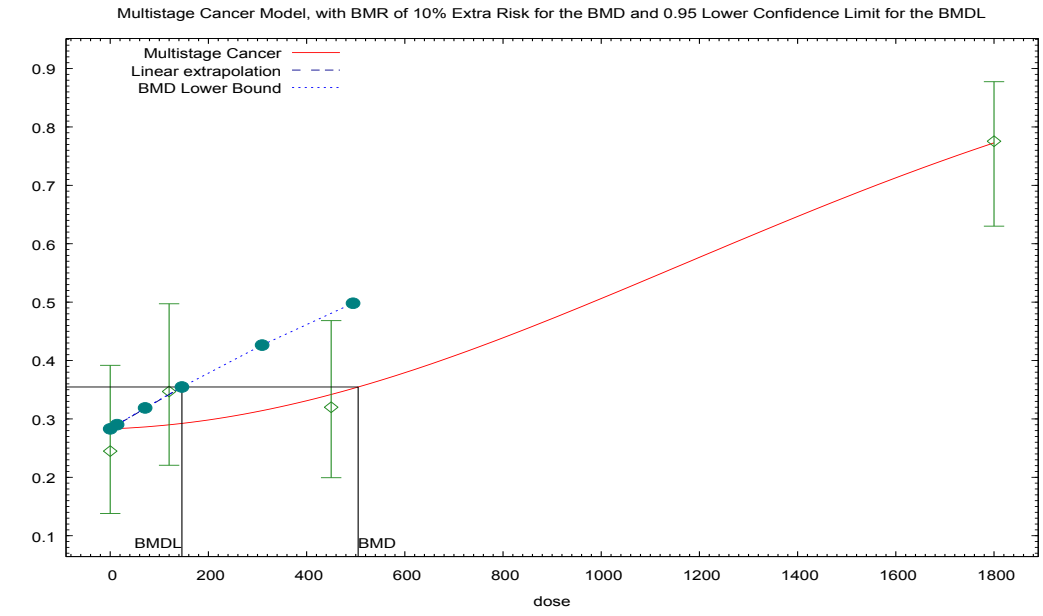
BMD = 94.9668

BMDL = 46.0594

BMDU = 117.276

Taken together, (46.0594, 117.276) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.00217111


Multistage Cancer Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Multistage Cancer
Linear extrapolation
BMD Lower Bound
Fraction Affected
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
BMDL
BMD
0
200
400
600
800
1000
1200
1400
1600
1800
dose
14:01 11/02 2016

```
 ================================================================
          Multistage Model. (Version: 3.4;  Date: 05/02/2014)
          Input Data File: C:/USEPA/BMDS2601/Data/msc_1-4-dichlorobenzene male mice_1-4-dichlorobenzene
male mice.(d)
          Gnuplot Plotting File:  C:/USEPA/BMDS2601/Data/msc_1-4-dichlorobenzene male
mice_1-4-dichlorobenzene male mice.plt
                                                    Wed Nov 02 14:01:03 2016
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = hepat_carc
   Independent variable = Dose_mg-m3

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.286333
                        Beta(1) = 1.03238e-005
                        Beta(2) = 3.50821e-007
```

BMDS Analysis of Aiso el al (2005)

Asymptotic Correlation Matrix of Parameter Estimates

| | Background | Beta(1) | Beta(2) |
|---|---|---|---|
| Background | 1 | -0.7 | 0.59 |
| Beta(1) | -0.7 | 1 | -0.94 |
| Beta(2) | 0.59 | -0.94 | 1 |

Parameter Estimates

| Variable | Estimate | Std. Err. | 95.0% Wald Confidence Interval Lower Conf. Limit | Upper Conf. Limit |
|---|---|---|---|---|
| Background | 0.283 | 0.0558967 | 0.173444 | 0.392555 |
| Beta(1) | 4.08363e-005 | 0.000410122 | -0.000762989 | 0.000844661 |
| Beta(2) | 3.32334e-007 | 2.36333e-007 | -1.30869e-007 | 7.95537e-007 |

Analysis of Deviance Table

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---|---|---|---|---|---|
| Full model | -116.345 | 4 | | | |
| Fitted model | -116.954 | 3 | 1.21761 | 1 | 0.2698 |
| Reduced model | -134.101 | 1 | 35.5116 | 3 | <.0001 |

AIC: 239.907

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.2830 | 13.867 | 12.000 | 49.000 | -0.592 |
| 120.0000 | 0.2899 | 14.206 | 17.000 | 49.000 | 0.880 |
| 450.0000 | 0.3419 | 17.094 | 16.000 | 50.000 | -0.326 |
| 1800.0000 | 0.7730 | 37.879 | 38.000 | 49.000 | 0.041 |

Chi^2 = 1.23 d.f. = 1 P-value = 0.2669

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 504.959

BMDL = 146.103

BMDU = 677.272

Taken together, (146.103, 677.272) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.000684447