MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dichlorobenzidine (CAS # 91-94-1)

FROM: Doreen Lehner

SUBJECT: Screening level for Dichlorobenzidine (CAS # 91-94-1)

DATE: April 11, 2014

The Initial Risk Screening Level (IRSL) for dichlorobenzidine (CAS # 91-94-1) is 0.002 µg/m^3 based on an annual averaging time. The IRSL was established on 10/4/1983 and is based on a study of female Beagle dogs by Stula et al. 1978. The dogs developed urinary bladder transitional cell carcinomas (5/5). The oral potency of 8.57 E-2 (mg/kg)-1 was converted to a human inhalation carcinogenicity slope factor of 0.00048 (µg/m3)-1.

Dichlorobenzidine (CAS # 91-94-1), also known as 4-(4-amino-3-chlorophenyl)-2-chloroaniline, dichloro-4,4-biphenyldiamine, and 3,3'-dichlorobenzidine, is a pale yellow liquid with a molecular weight of 253.13 g/mol. Dichlorobenzidine "is widely used in the production of diarylide dyes and diarylide yellow pigments used in the production of printing inks" (Wikipedia, 2014).

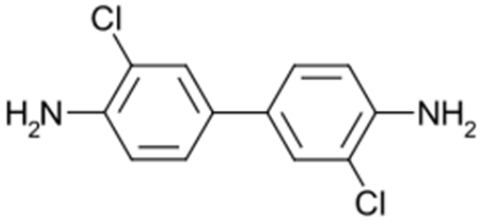

Figure 1. Chemical structure of dichlorobenzidine.

In 1993, the U.S. EPA established a carcinogenic oral risk slope factor of 4.5 x 10^{-1} (mg/kg-day)$^{-1}$ based "on statistically significantly increased tumor incidences in rats, mice, and dogs. Additional support is provided by positive evidence of genotoxicity and structural relationship to the known human bladder carcinogen benzidine" (EPA, 1993). The key study used by the EPA is Stula et al. (1975) where 50 male and 50 female ChR-CD rats were fed 1,000 ppm (50 mg/kg/day) 3,3'-dichlorobenzidine in the diet. "The compound was administered for the duration of the study, which had been intended to last 2 years. The average length of time on test was 349 days (range of 143 to 488) for females and 353 (range 118 to 486) [days] for males. The reason for the early mortality was not stated. Male and female control animals (range of 118 to 486) [days] (50/group) were fed the standard diet and observed for up to 2 years. An interim sacrifice of 6 rats/group was conducted at 12 months and was not included in the final tumor analysis. In males, statistically significant increases in tumor incidences were observed at three sites: granulocytic leukemia (9/44 treated vs. 2/44 control), mammary adenocarcinoma (7/44 vs.

0/44) and zymbal gland carcinoma (8/44 vs. 0/44). In female rats, mammary adenocarcinomas were the only tumors showing a significant increase in incidence (26/44 vs. 3/44)" (EPA, 1993). EPA used the mammary adenocarcinoma tumor type in female ChR-CD rats as the most sensitive endpoint.

Administered (ppm)	Dose Animal Transformed (mg/kg/day)	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	0	3/44
1000	50	8.5	26/44

"The slope factor incorporates an increase by a factor of (730/488)**3, the ratio of the lifetime of the rat to the survival period for the rat, because of the greatly reduced survival in the exposed group. The animal transformed dose was determined by assuming a 5% food consumption value for rats. Human equivalent doses were derived by multiplying the animal transformed dose by (wt. animal/wt. human)**3, assuming the body weight of the rat is 0.35 kg and body weight of an adult human is 70 kg" (EPA, 1993).

The EPA used a second study by Stula (1978) as a support for the discussion of the confidence of the slope factor. In the Stula et al. (1978) study, "6 female beagle dogs were given 100 mg 3,3'-dichlorobenzidine by capsule 3 times/week for 6 weeks and then 100 mg 5 times/week for 7 years. The total duration of the study was 7.1 years. Two animals died during the course of the study. No tumors were found in the animal that died after 3.5 years while the animal that died after 6.6 years had both an undifferentiated liver carcinoma and a papillary transitional cell carcinoma of the bladder. Of the 4 animals remaining at the end of the study, 3 had liver carcinoma and all 4 had bladder papillary transitional cell carcinoma. Six untreated control animals, observed for 8 to 9 years, had no liver or bladder neoplasms" (EPA, 1993). EPA observed that with "one exposed group, response cannot reflect any curvature in the underlying dise-response relationship. Thus, the model could be far above or below true risk" (EPA, 1993). A slope factor of 1.7 $(mg/kg/day)^{-1}$ was derived from the data from the Stula et al. (1978) study using the incidence of hepatic carcinomas (4/5 treated vs. 0/6 control) in female beagles (EPA, 1993).

Rule 231(1) was used to develop a potential IRSL using the value derived by EPA for dichlorobenzidine. The equation is below:

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

The EPA carcinogenic risk oral slope factor of 4.5×10^{-1} is converted to an inhalation cancer value using the equation in Rule 231(3)(f) below:

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

$$q_1^* \left({}^{\mu g}/_{m^3}\right)^{-1} = 4.5 \times 10^{-1} \left({}^{mg}/_{kg/day}\right)^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1}$$
$$= 0.000128571 \left({}^{\mu g}/_{m^3}\right)^{-1}$$

Using this value for the unit risk gives:

$$potential\ IRSL = \frac{1 \times 10^{-6}}{0.000128571} = 0.007777804\ {}^{\mu g}/_{m^3} = 0.0078\ {}^{\mu g}/_{m^3}$$

In 1995, the MDEQ Water Resources Division (WRD) performed a literature review and derivation of a human oral carcinogenicity slope factor of 1.7 (mg/kg/day)$^{-1}$. This oral carcinogenicity slope factor is based on a 100% incidence of bladder tumors (5/5) and a 80% incidence of liver carcinomas (4/5) in female Beagle dogs exposed to dichlorobenzidine in gelatin capsules 3 times per week for 6 weeks and then 5 times per week for up to 7.1 years (Stula et al., 1978).

Rule 231(1) was used to develop a potential IRSL using the value derived by WRD for dichlorobenzidine. The equation is below:

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

The WRD human oral cancer value of 1.7 (mg/kg/day)$^{-1}$ found in the justification in Appendix A is converted to an inhalation cancer value using the equation in Rule 231(3)(f) below:

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

$$q_1^* \left({}^{\mu g}/_{m^3}\right)^{-1} = 1.7 \left({}^{mg}/_{kg/day}\right)^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1} = 0.0004857 \left({}^{\mu g}/_{m^3}\right)^{-1}$$

Using this value for the unit risk gives:

$$potential\ IRSL = \frac{1 \times 10^{-6}}{0.0004857} = 0.0020588417\ {}^{\mu g}/_{m^3} = 0.0021\ {}^{\mu g}/_{m^3}$$

Rounded to 0.002 µg/m^3; the potential IRSL for dichlorobenzidine is 0.002 µg/m^3 using the WRD derived value based on the Stula et al. (1978) study on dogs. The potential IRSL for dichlorobenzidine is 0.0078 µg/m3 using the EPA derived value was largely based on the Stula et al. (1975) study on rats. It is interesting that EPA acknowledges that the rat study having only one dose level and one control is not adequate by itself, but used the dog study to increase the confidence of the rat study findings. One should also note that the dog study only had one dose level and one control as well. In the rat study the dose was 1,000 ppm (50 mg/kg/day) for up to

2 years and in the dog study the dose was lower at 100 mg/per capsule 3 times a week for 6 weeks then 5 times per week for up to 7.1 years. The authors estimated that the dogs received a daily dose of 9.1 to 12.8 mg/kg. The average lifespan of Beagle dogs is between 13 and 17 years (therefore 7.1 years is only 42 to 55% of the total lifespan); this may be compared to the rat study (using EPAs calculation of 730 days for a 2-year lifespan, 488 days of study = 67% of the total lifespan). The lower dose given to the Beagles still produced significant carcinogenic tumors. There is a discussion in Appendix A on why WRD chose the Beagle study over the rat study. "The decision as to which study and which potency to use is a difficult one. Jim Cogliano of EPA believes that the rat data are preferable because a greater number of animals were used thus generating a more statistically meaningful potency (Cogliano, 1987 [see Appendix A]). Biological significance is associated with the dogs, however, since they appear to be the most sensitive species. I am basing my decision on biological rather than statistical grounds and choose the dog data over the rat data. In my opinion, the dog liver data is preferable over the dog bladder tumor data because manipulation of the bladder tumor data to lower the 100% incidence rate adds greater uncertainty to a process already fraught with uncertainties" (see Appendix A).

Based on the information above, the Initial Risk Screening Level (IRSL) for dichlorobenzidine (CAS# 91-94-1) established in 1993 is 0.002 µg/m^3 and the SRSL is 0.02 µg/m^3 based on an annual averaging time.

References:

APCR, 1994. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994. Act 451, as amended (NREPA).

EPA. 1993. Integrated Risk Information System. 3,3'-Dichlorobenzidine (CASRN 91-94-1). Retrieved data on 4/10/2014. Carcinogenicity assessment last revised 7/01/1993. Available online at: http://www.epa.gov/iris/subst/0504.htm

Stula EF, Sherman H, Zapp JA, and Clayton JW. 1975. Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylanaline). Toxicol. Appl. Pharmacol. 31:159-176.

Stula EF, Barnes JR, Sherman H, Reinhardt CF, and Zapp JA. 1978. Liver and urinary bladder tumors in dogs from 3,3'-dichlorobenzidine. J. Environ. Pathol. Toxicol. 1(4):475-490.

Wikipedia. 2014. 3,3'-Dichlorobenzidine. Available online at: http://en.wikipedia.org/wiki/3,3'-Dichlorobenzidine

Appendix A:

Cancer Risk Justification
3,3'-Dichlorobenzidine
CAS #91-94-1

Several studies have been conducted to determine the carcinogenic potential of 3,3'-dichlorobenzidine (3,3'-DCB). When administered to rats at 300 ppm in the diet for 40 weeks, 3,3'-DCB did not induce an increase in tumors (Tsuda, 1977). Hamsters receiving 1000 ppm 3,3'-DCB in the diet for life did not develop tumors either (Saffioti, et al. 1967), but in a later study done with similar groups of animals, 3000 ppm 3,3'-DCB produced 4 bladder carcinomas (Sellakumar, et al. 1969). A Russian study by Pliss (1958) reports a variety of tumors in rats resulting from the administration of 3,3'-DCB in their food at a dose of 10-20 mg/day for 12 months. The rats were observed for life and 23 of the 50 rats tested developed tumors (zymbal gland, skin, mammary gland, bladder and others).

A group of 50 male and 50 female rats were given diets containing 1000 ppm 3,3'-DCB for up to 16 months (Stula et al., 1975). Male rats exhibited a statistically significant increase in granulocytic leukemia (9/44), mammary adenocarcinomas (7/44) and zymbal gland carcinomas (8/44). Female rats developed mammary adenocarcinomas only (26/44).

Six female Beagle dogs were used in a second study by Stula et al. (1978). The dogs were administered 100 mg of 3,3'-DCB in gelatin capsules 3 times per week for 6 weeks then 5 times per week for up to 7.1 years. One dog died after 3.5 years on study and did not develop any tumors. A second dog that died after 6.6 years on study had an undifferentiated bladder carcinoma. Of the remaining 4 dogs killed at 7.1 years, 4 out of 4 had hepatocellular carcinomas and papillary transitional-cell carcinomas of the bladder. The authors estimated that the dogs received a daily dose of 9.1 to 12.8 mg/kg. None of the control dogs, which were killed at 8-9 years of age, developed tumors.

The two studies conducted by Stula et al. (1975 and 1978) are the only studies adequate for determining a potency. The dog study reports a 100% incidence of bladder tumors (5/5) and an 80% incidence of liver carcinomas (4/5). Utilizing the bladder tumor data requires some manipulation of the data since it does not provide enough information for the multistage model to perform. An option is to choose some value between 4 and 5 for the number of animals with bladder tumors. A value of 4.5 was previously determined and used upon recommendation from CAG and by previous staff members who determined that as the value approaches the number 5, i.e., 4.9 or 4.99, the potency (q_1^*) becomes artificially inflated. The potency generated using 4.5 is 2.7 $(mg/kg/day)^{-1}$. Utilization of the liver carcinoma dog data (0/6, 4/5), as was done in the Ambient Water Quality Criteria Document for 3,3-Dichlorobenzidine (EPA, 1980), generates a potency of 1.7 $(mg/kg/day)^{-1}$.

The incidence rate of mammary adenocarcinomas is the highest tumor incidence produced in the rat study. Stula et al. (1975) utilized 50 male and 50 female rats for the control and experimental groups. The resulting potency using this data (3/44, control group; 26/44, treated group) is 0.79 $(mg/kg/day)^{-1}$.

The decision as to which study and which potency to use is a difficult one. Jim Cogliano of EPA believes that the rat data are preferable because a greater number of animals were used thus generating a more statistically meaningful potency (Cogliano, 1987). Biological significance is associated with the dogs, however, since they appear to be the most sensitive species. I am basing my decision on biological rather than statistical grounds and choose the dog data over the rat data. In my opinion, the dog liver data is preferable over the dog bladder tumor data because manipulation of the bladder tumor data to lower the 100% incidence rate adds greater uncertainty to a process already fraught with uncertainties. In conclusion, the potency used to generate the surface water recommendations is 1.7 $(mg/kg/day)^{-1}$.

REFERENCES

1. Cogliano, J. November 9, 1987. Personal Communication.

2. EPA. 1980. Ambient Water Quality Criteria for Dichlorobenzidine. EPA 440/5-80-040.

3. Pliss, C.B. 1958. Experimental tumors induced in rats by dichlorobenzidine. Byul. Eksperim. Biol. Med. 46:1238-40.

4. Saffioti, U. et al. 1967. Induction of bladder cancer in hamsters fed aromatic amines. In: Deichmann, W. and Lampe, K.F., eds., Bladder Cancer. A symposium. Birmingham, Alabama p. 129.

5. Sellakumar, A.R. et al. 1969. Aromatic amines carcinogenicity in hamsters. Proc. Am. Assoc. Cancer Res. 10:78. Abstract No. 309.

6. Stula, E.F. et al. 1975. Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis-(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). Toxicol. Applied Pharmacol. 31:159-176.

7. Stula, E.F. et al. 1978. Liver and urinary bladder tumors in dogs from 3,3'-dichlorobenzidine. J. Env. Pathol. Toxicol. 1:475-490.

8. Tsuda, H. et al. 1977. Synergistic effect of urinary bladder carcinogenesis in rats treated with N-butyl-N-(4-hydroxybutyl)-nitrosamine, N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide-N-2-fluorenyl-acetamide and 3,3-dichlorobenzidine. Gann 68:183-192.

HUMAN CANCER VALUE WORKSHEET

Chemical Name: 3,3'- dichlorobenzidine · CAS No. 91-94-1
Developed By: C. Summers
Reviewed By: D. Bush Verification Date: 9/5/97

Key Study: Stula et al. (1975) dosed 9 beagle dogs w/ 100 mg 3,3'- DCB 5d/wk for the first 6 wks, then 5d/wk for the remaining 304 wks (total exposure duration = 7.1 yrs). Five of six dogs survived @ least 6.6 yrs. 9 mos., 4/5 developed hepatocellular carcinomas and all 5 developed papillary & urothelial cell carcinomas of the bladder. The incidence of hepatocellular carcinoma generated the highest potency by the linear, multistage model.

Average dose = $\left(10.5 \text{ mg/kg/treatment}\right)\left(\frac{1078 \text{ days}}{2572 \text{ days}}\right) = 7.4 \text{ mg/kg/d}$

Average BW of controls = 11.4 kg

SSF = $\sqrt[4]{\frac{7025}{11.4 \text{ kg}}} = 1.574$

GLOBAL 82 $q_{1\,animal}^{*} = \frac{95\% \text{ upper 11}}{\text{MLE.}}$ w/ R = 1×10^{-5} = $\frac{2.836579\times10^{-5}}{4.5979015029\times10^{-5}} = 0.5051837787$

$q_{1\,human}^{*} = q_{1\,animal}^{*} \times SSF. = 0.5051837787 \times 1.574 = 0.7951837787 \cong 0.80 (mg/kg/d)^{-1}$

RAD = $\frac{1\times10^{-5}}{0.80 (mg/kg/d)^{-1}} = 1.25\times10^{-5} \text{ mg/kg/d}$.

HCV drinking water = $\frac{(1.25\times10^{-5} \text{ mg/kg/d})(70 \text{ kg})}{2.0 \text{ l/d} + \left[(.1032 \text{ kg/l} \times 198 \text{ l/kg}) + (.0114 \text{ kg/l} \times 314 \text{ l/kg})\right]} = .0001391 \text{ mg/l} \cong 0.14 \text{ ug/l}$

HCV non-drinking water = $\frac{(1.25\times10^{-5} \text{ mg/kg/d})(70 \text{ kg})}{.01 \text{ l/d} + \left[(.1032 \text{ kg/l} \times 198 \text{ l/kg}) + (.0114 \text{ kg/l} \times 314 \text{ l/kg})\right]} = .0002034 \text{ mg/l} \cong 0.20 \text{ ug/l}$

DATE: 08-14-89
TIME: 13:18:15

DATA FILENAME : a:33dchben.dat

CAS# 91-94-1

GLOBAL (MAY 1982)

K.S. CRUMP & COMPANY, INC.
1201 GAINES STREET
RUSTON, LA 71270
(318) 255-4800

0

GLOBAL82 - DATA TITLE:33dichlorobenzidene,Stula-dog liver

GROUP 1 HAS 0 RESPONSES OUT OF 6 MEMBERS FOR A DOSE OF .000000

GROUP 2 HAS 4 RESPONSES OUT OF 5 MEMBERS FOR A DOSE OF 7.40000

PREDICTED AND OBSERVED RESPONSE PR(:LITIES

GROUP= 1 PREDICTED= .000000 OBSERVED= .000000
GROUP= 2 PREDICTED= .800000 OBSERVED= .800000

THE CHI-SQUARE GOODNESS OF FIT STATISTIC IS 1.386670E-31

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0)= .000000000000

Q(1)= .217491609788

THE MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -2.50201211769

CALCULATIONS ARE BASED UPON EXTRA RISK

0 LINEARIZED MULTISTAGE CONFIDENCE LIMITS

CONFIDENCE LIMITS FOR A RISK OF .100000 M.L.E. DOSE= .4844348514

UPPER CONFIDENCE LIMITS ON RISK

90%	95%	97.5%	99%
.186210	.218222	.248890	.287649

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
.247704	.207325	.178336	.150355

CONFIDENCE LIMITS FOR A RISK OF 1.000000E-02 M.L.E. DOSE= 4.6210223297E-02

UPPER CONFIDENCE LIMITS ON RISK

90%	95%	97.5%	99%
1.946350E-02	2.320996E-02	2.693165E-02	3.186290E-02

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.362852E-02	1.977674E-02	1.701143E-02	1.434236E-02

CONFIDENCE LIMITS FOR A RISK OF 1.000000E-03 M.L.E. DOSE= 4.60017898888E-03

UPPER CONFIDENCE LIMITS ON RISK

90%	95%	97.5%	99%
1.954762E-03	2.335033E-	).714091E-03	3.218361E-03

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.352195E-03	1.968754E-03	1.693470E-03	1.427767E-03

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CONFIDENCE LIMITS FOR A RISK OF 1.000000E-04 M.L.E. DOSE= 4.5981084250E-04

UPPER CONFIDENCE LIMITS ON RISK

90%	95%	97.5%	99%
1.955603E-04	2.336438E-04	2.716189E-04	3.221581E-04

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.351136E-04	1.967868E-04	1.692708E-04	1.427125E-04

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CONFIDENCE LIMITS FOR A RISK OF 1.000000E-05 M.L.E. DOSE= 4.5979015029E-05

UPPER CONFIDENCE LIMITS ON RISK

90%	95%	97.5%	99%
1.955687E-05	2.336579E-05	2.716398E-05	3.221903E-05

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.351030E-05	1.967779E-05	1.692632E-05	1.427060E-05

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CONFIDENCE LIMITS FOR A RISK OF 1.000000E-06 M.L.E. DOSE= 4.5978808266E-06

UPPER CONFIDENCE LIMITS ON RISK

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1.955696E-06	2.336593E-06	2.716419E-06	3.221936E-06

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.351019E-06	1.967770E-06	1.692624E-06	1.427054E-06

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CONFIDENCE LIMITS FOR A RISK OF 1.000000E-07 M.L.E. DOSE= 4.5978783788E-07

UPPER CONFIDENCE LIMITS ON RISK

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LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.351018E-07	1.967769E-07	1.692623E-07	1.427053E-07

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CONFIDENCE LIMITS FOR A RISK OF 1.000000E-08 M.L.E. DOSE= 4.5978807524E-08

UPPER CONFIDENCE LIMITS ON RISK

90%	95%	97.5%	99%
1.955698E-08	2.336595E-08	2.716423E-08	3.221941E-08

LOWER CONFIDENCE LIMITS ON SAFE DOSE

90%	95%	97.5%	99%
2.351019E-08	1.967769E-08	1.692624E-08	1.427054E-08

0 GLOBAL 82 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK

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CONFIDENCE LIMIT FOR A RISK OF 1.000000E-02. THE MLE ESTIMATE OF DOSE IS 4.621022E-02
THE 95.0 PERCENT LOWER LIMIT ON DOSE IS 1.977674E-02
THE COEFFICIENTS CORRESPONDING TO THE 95.0 PERCENT BOUND ARE:
Q(0)= .000000000000

Q(1)= .508189630819

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CONFIDENCE LIMIT FOR A RISK OF 1.000000E-05. THE MLE ESTIMATE OF DOSE IS 4.597902E-05
THE 95.0 PERCENT LOWER LIMIT ON DOSE IS 1.967779E-05
THE COEFFICIENTS CORRESPONDING TO THE 95.0 PERCENT BOUND ARE:
Q(0)= .000000000000

Q(1)= .508189630819

****

CONFIDENCE LIMIT FOR A RISK OF 1.000000E-06. THE MLE ESTIMATE OF DOSE IS 4.597881E-06
THE 95.0 PERCENT LOWER LIMIT ON DOSE IS 1.967770E-06
THE COEFFICIENTS CORRESPONDING TO THE 95.0 PERCENT BOUND ARE:
Q(0)= .000000000000

Q(1)= .508189630819