MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 3,3'-Dimethoxybenzidine (CAS # 119-90-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: August 18, 2016

SUBJECT: Screening Level for 3,3'-Dimethoxybenzidine (CAS # 119-90-4)

The initial threshold screening level (ITSL) for 3,3'-dimethoxybenzidine (CAS# 119-90-4) is 9.8 µg/m^3 based on an annual averaging time. The initial risk screening level (IRSL) is 0.039 µg/m^3 with an annual averaging time, and the secondary risk screening level (SRSL) is 0.39 µg/m^3 with an annual averaging time.

"3,3'-Dimethoxybenzidine is an aromatic amine that is initially a colorless crystal but turns violet upon standing at room temperature (HSDB, 2009)….It is stable at normal temperatures and pressures" (NTP, 2014a) with a molecular weight of 244.28904 g/mol. 3,3'-Dimethoxybenzidine is used: as a chemical intermediate for producing dyes and pigments; a chemical intermediate in the production *o*-dianisidine diisocyanate (used in adhesives and as a component of polyurethanes); as a dye for paper, plastics; rubber, textiles, and leather; as a test substance for the detection of metals, thiocyanates, and nitrites; and for detection of blood, and in the quantitation of chlorine in water, and glucose by the glucose oxidase method (Morgan et al., 1990; NTP, 2014a).

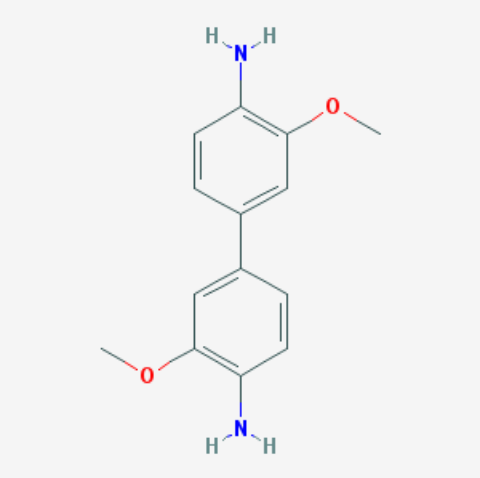

Figure 1. Structure of 3,3'-dimethoxybenzidine.

A literature review was conducted to determine the screening levels for 3,3'-dimethoxy-benzidine. The following references and databases were searched to derive the above screening levels: 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) 2014 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 10/26/15), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, U.S. EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

IRSL Derivation:

3,3'-Dimethoxybenzidine is listed on the EPA's HAPs list. EPA has listed 3,3'-dimethoxy-benzidine as a Group B2, probable human carcinogen (EPA, 2016). NTP (2014a) has listed 3,3'-dimethoxybenzidine as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. "Oral exposure to 3,3'-dimethyoxybenzidine caused tumors in two rodent species and at several different tissue sites. Administration of 3,3'-dimethoxybenzidine by stomach tube caused cancer (carcinoma) of the Zymbal gland, skin, and intestine and benign urinary-bladder tumors (papilloma) in rats of both sexes, and dietary exposure to 3,3'-dimethoxybenzidine caused benign forestomach tumors (papilloma) in hamsters (IARC 1974, 1982)" (NTP 2014a). "Administration of the dihydrochloride salt of 3,3'-dimethoxybenzidine in the drinking water increased the combined incidence of benign and malignant tumors of the Zymbal gland (adenoma and carcinoma), liver (hepatocellular adenoma and carcinoma), large intestine (adenomatous polyps and adenocarcinoma), skin (basal-cell or sebaceous gland adenoma and carcinoma), and oral cavity (squamous-cell papilloma and carcinoma) in both sexes. In males, it also caused cancer of the preputial gland (carcinoma), small intestine (adenocarcinoma), and mesothelium of the testes (metastatic mesothelioma), and in females, it also caused cancer of the clitoral gland (carcinoma) and mammary gland (adenocarcinoma) and increased the combined incidence of benign and malignant tumors of the uterus and cervix (adenoma and carcinoma) (NTP, 1990)" (NTP, 2014a).

3,3'-Dimethoxybenzidine dihydrochloride (DMOB) was evaluated as part of the National Toxicology Program's Benzidine Dye Initiative. "The Benzidine Dye Initiative is a collaborative effort of the National Institute of Environmental Health Sciences, the National Center for Toxicological Research, the National Institute of Occupational Safety and Health, the U.S. Environmental Protection Agency, the Consumer Product Safety Commission, and the Occupational Safety and Health Administration under the aegis of the National Toxicology Program (NTP). The objective of this initiative is to develop an integrated body of scientific data concerning the metabolism and pharmacokinetics, genetic toxicology *in vivo* carcinogenicity of dyes derived from benzidine, DMOB, and 3,3'-dimethoxybenzidine. Because studying each of the hundreds of benzidine-based dyes was considered to be impractical, the research program is designed to evaluate representative benzidine cogeners, benzidine cogener-derived, and benzidine-derived dyes" (Morgan et al., 1990). 3,3'-Dimethoxybenzidine-based dyes have been shown to be metabolized to 3,3'-dimethoxybenzidine dihydrochloride (DMOB) in dogs, rats, and humans; and were evaluated for chronic toxicity and carcinogenicity as part of the National Toxicology Program's Benzidine Dye Initiative (Morgan et al., 1990). DMOB was evaluated because benzidine is a structurally related chemical, is also a known human carcinogen, and because humans are exposed to DMOB during production of bisazobiphenyl dyes (Morgan et al., 1990). In a study by Morgan et al., (1990), seventy F344/N rats of each sex were used in the control group, 45 rats of each sex were in the low-dose group, 75 rats of each sex were in the mid-dose group, and 70 rats of each sex were in the high-dose group and were

administered either 0, 80, 170, or 330 ppm (an estimated dose of 0, 6, 12, and 21 mg/kg/day for males and 0, 7, 14, and 23 mg/kg/day for females) of DMOB respectively in drinking water. "3,3'-Dimethoxybenzidine dihydrochloride/water solutions were stable for at least 2 weeks when stored in the dark at room temperature, and for at least 48 hours under simulated dosing conditions. Drinking water solutions were prepared two times per week and were used or stored for up to 7 days before being used" (Morgan et al., 1990).

Table 1. Incidence of Neoplastic Lesions in F344 Rats Exposed to 3,3'-Dimethoxybenzidine for 21 Months.

	Male Rats				Female Rats			
3,3'-Dimethoxybenzidine concentration	**0 ppm**	**80 ppm**	**170 ppm**	**330 ppm**	**0 ppm**	**80 ppm**	**170 ppm**	**330 ppm**
Large intestine combined polyp (adenomatous) and adenocarcinoma	0/60	1/45	8/75	8/60	0/60	1/45	1/75	3/60
Liver combined neoplastic nodule and carcinoma	1/60	4/45	7/74	8/60	0/60	1/44	0/75	3/60
Mammary gland adenocarcinoma	0/60	0/45	0/75	0/60	1/60	2/45	14/75	20/60
Preputal/clitoral gland adenoma	14/60	6/43	19/73	12/59	5/58	13/44	13/74	16/55
Preputal/clitoral gland carcinoma	2/60	6/43	15/73	19/59	2/58	17/44	41/74	30/55
Skin squamous cell papilloma	0/60	5/45	7/75	5/60	0/60	0/45	3/75	0/60
Skin squamous cell carcinoma	0/60	9/45	24/75	21/60	0/60	0/45	0/75	0/60
Zymbal gland adenoma	0/59	4/45	11/75	9/60	0/60	3/45	4/75	3/60
Zymbal gland carcinoma	0/59	7/45	14/75	21/60	1/60	10/45	17/75	13/60

Table 1 data were taken from Morgan et al., (1990).

"The 21-month study was originally designed for 24 months, but was terminated early because of rapidly declining animal survival due to neoplasia" (Morgan et al., 1990). "The mean body weights of dosed rats began to decrease relative to those of controls after about 1 year of exposure at 170 or 330 ppm. During the course of the study, body weight decreases ranged from 6 to 22% for males and 7 to 17% for females; however, decreases of 22% in males and 17% in females were observed only in the last week of the study and were based on a small number of surviving animals" (Morgan et al., 1990). "Ductular ectasia and glandular hyperplasia occurred at increased incidences in dosed male rats but not in female rats. The incidence of carcinomas of the preputial gland occurred with significantly positive trends; the incidences in the mid- and high-dose groups were significantly greater than those in the controls. In female rats, the incidences of adenomas and carcinomas were significantly greater in almost all dosed groups than in controls. Bilateral neoplasms of the preputial or clitoral glands occurred in 11 exposed male and 29 exposed female rats" (Morgan et al., 1990). "3,3'-Dimethoxybenzidine had a profound effect on the preputial and clitoral glands in treated male and female rats, giving rise to a high incidence of adenomas and/or carcinomas, nearly 7 to 10 times higher than in untreated historical control F344/N rats" (Morgan et al., 1990).

"3,3'-Dimethoxybenzidine exposure led to development of uncommon epithelial neoplasms of the small and large intestine in male rats. Neoplasms were principally cystic mucinous

adenocarcinomas of the small intestine and adenomatous polyps of the large intestine. Polyps in the colon were first observed at week 48, whereas adenocarcinomas in the small intestine first occurred after 39 weeks of chemical exposure. Adenocarcinomas in the large intestine were also observed in the low-, mid-, and high-dose groups of exposed female rats. Although not as numerous as in males, these neoplasms were considered to be related to DMOB (dimethoxybenzidine dihydrochloride) exposure because no adenocarcinomas or adenomatous polyps of the large intestine have been observed in over 1600 control female rats" (Morgan et al., 1990).

"3,3'-Dimethoxybenzidine intake led to a high incidence of adenocarcinomas in the mammary gland of females receiving the mid and high doses. The incidence of adenocarcinomas in the high-dose group (33%) was four times greater than the highest observed historical incidence in untreated control female F344/N rats. The first neoplasm was observed in a high-dose female at week 41, whereas in the female controls, one adenocarcinoma was observed at termination at week 93. The incidence of fibroadenomas decreased as the DMOB dose and incidence of adenocarcinomas increased, suggesting an increased progression of fibroadenomas to adenocarcinomas with increased dose of DMOB" (Morgan et al., 1990).

"3,3'-Dimethoxybenzidine was clearly carcinogenic for male and female F344/N rats as indicated by increased incidences of malignant and benign tumors at a variety of tissue and organ sites" (Morgan et al., 1990).

The results in Table 1 were run through EPA's Benchmark Dose Software (BMDS) version 2.6.0.1 (build 88) and were run using dichotomous data with the best statistical fit using the multistage cancer model was for male rat skin squamous cell carcinoma. The 95% upper confidence bound on the dose-response slope was used to derive the cancer slope factor (animal) of 0.0317044 $(mg/kg/day)^{-1}$. Rule 231(1) states that the IRSL is calculated using the following equation:

$$IRSL = \frac{1 \times 10^{-6}}{unit\ risk}$$

Where the unit risk is (q_1^*), the equation for calculating q_1^* is below:

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

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. The cancer slope factor for male rat skin squamous cell carcinoma is 0.0317044. Since the study was performed using the 3,3'-dimethoxybenzidine metabolite DMOB, the molecular weights of these compounds differ and an adjustment needs to be made to determine the equivalent exposure of 3,3'-dimethoxybenzidine using the following equation:

$$DMOB\ ({}^{mg}/_{kg/day})^{-1} \times \frac{MW\ 3{,}3' - dimethoxybenzidine}{MW\ 3{,}3' - dimethoxybenzidine\ dihydrochloride} = 3{,}3' - dimethoxybenzidine\ ({}^{mg}/_{kg/day})^{-1}$$

Where the molecular weight of 3,3'-dimethoxybenzidine is 244.28904 g/mol and the molecular weight of DMOB is 317.21 g/mol. Adding this information to the equation above:

$$0.0317044\ ({}^{mg}/_{kg/day})^{-1} \times \frac{244.28904\ {}^{g}/_{mol}}{317.21\ {}^{g}/_{mol}} = 0.02441612\ ({}^{mg}/_{kg/day})^{-1}$$

The q_1^* equation is for a human unit risk, therefore, the following interspecies scaling factor equation from Rule 231(3)(c) is needed:

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

Where:
W_H = Average weight of an adult human (assumed to be 70 kg).
W_A = Body weight of F344/N rat (0.373 kg).

$$T = \left(\frac{70\ kg}{0.373\ kg}\right)^{1/4} = 3.701240469$$

The human cancer slope factor = male rat cancer slope factor adjusted for 3,3'-dimethoxybenzidine x interspecies scaling factor (T)
Human cancer slope factor (q_1^*) = 0.02441612 (mg/kg/day)$^{-1}$ x 3.701240469 = 0.090369932 (mg/kg/day)$^{-1}$

The oral human cancer slope factor is in (mg/kg/day)$^{-1}$ units which needs to be converted to (µg/m^3)$^{-1}$. Imputing the human cancer slope factor (q_1^*) to the equation above gives:

$$q_1^*\ ({}^{\mu g}/_{m^3})^{-1} = 0.090369932\ ({}^{mg}/_{kg/day})^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1} = 0.00002582\ ({}^{\mu g}/_{m^3})^{-1}$$

Using Rule 231(1) equation above to derive the IRSL:

$$IRSL = \frac{1 \times 10^{-6}}{0.00002582\ ({}^{\mu g}/_{m^3})^{-1}} = 0.038729667\ {}^{\mu g}/_{m^3} \approx 0.039\ {}^{\mu g}/_{m^3}$$

According to Rule 231(4) the averaging time for an IRSL or SRSL is annual. Therefore, the IRSL for 3,3'-dimethoxybenzidine is 0.039 µg/m^3 with an annual averaging time and the SRSL is 0.39 µg/m^3 with an annual averaging time.

ITSL Derivation:

The Environmental Protection Agency does not have a reference concentration for chronic inhalation exposure (RfC) or a reference dose for chronic oral exposure (oral RfD). The literature review determined that the best available toxicity study for noncancer risk assessment and ITSL derivation is Morgan et al., (1990). In the Morgan et al., (1990) study seventy F344/N rats of each sex were used in the control group, 45 rats of each sex were in the low-dose group, 75 rats of each sex were in the mid-dose group, and 70 rats of each sex were in the high-dose group and were administered either 0, 80, 170, or 330 ppm (an estimated dose of 0, 6, 12, and 21 mg/kg/day for males and 0, 7, 14, and 23 mg/kg/day for females) of DMOB respectively in drinking water. The Morgan et al., (1990) study detected non-neoplastic lesions when exposed to 3,3'-dimethoxybenzidine in drinking water for 21 months in rats.

Table 2. Incidence of Non-neoplastic Liver Lesions in F344 Rats Exposed to 3,3'-Dimethoxybenzidine for 21 Months.

	Males				Females			
3,3'-Dimethoxybenzidine concentration	**0 ppm**	**80 ppm**	**170 ppm**	**330 ppm**	**0 ppm**	**80 ppm**	**170 ppm**	**330 ppm**
Centrilobular degeneration	0	4	9	10	1	3	8	5
Clear cell focus	19	11	16	28	7	11	18	15
Cystic degeneration	13	23	34	28	1	2	1	5
Eosinophilic focus	6	15	35	38	5	7	20	28
Hematopoietic cell proliferation	2	15	39	41	1	18	43	41
Necrosis	4	15	18	17	1	3	13	18

The non-neoplastic liver lesions were analyzed using the Benchmark Dose Software (BMDS) version 2.6.0.1 (build 88) and was run using dichotomous data utilizing the following statistical models at the default settings: gamma, logistic, loglogistic, logprobit, multistage, probit, weibull, and quantal-linear. Appendix 1 shows some of the results from the BMDS calculations for eosinophilic focus and hematopoietic cell proliferation.

It was determined that the most critical effect from exposure to 3,3'-dimethoxybenzidine was eosinophilic focus in male rats using the loglogistic model, which gave a p-value of 0.8148, a chi-square of 0.05, and a BMDL of 0.27939. "Foci are presumptive preneoplastic lesions that can vary from barely perceptible to cytomorphologically and tinctorially discrete lesions. Foci typically blend imperceptibly with, and do not compress, surrounding hepatic parenchyma, though minimal compression may occur….Eosinophilic foci typically stain more eosinophilic than surrounding hepatocytes and often consist of hepatocytes that are larger than the adjacent normal parenchyma" (NTP, 2014b).

Rule 232(1)(b) an ITSL can be determined using an oral reference dose. According to the EPA dose response assessment (EPA, 1993), an RfD can be determined using the following equation:

$$RfD\left(mg/\frac{kg}{day}\right) = \frac{NOAEL\ (or\ LOAEL\ or\ BMDL)}{UFs\ (UF_A \times UF_H)}$$

Where:
UF_A = interspecies variation. A factor used to account for uncertainty when extrapolating from valid results of long-term studies on experimental animals to humans.
UF_H = intraspecies variation. A factor used to account for variation in sensitivity among members of the human population.

The BMDL for male rat eosinophilic focus in the liver was used for the numerator in the above equation:

$$RfD\left(\,{}^{mg}/_{\frac{kg}{day}}\right) = \frac{0.27939\,{}^{mg}/_{kg}}{10\times 10} = 0.0027939\,{}^{mg}/_{kg/day}$$

The equation for Rule 232(1)(b) is:

$$ITSL = Oral\ RfD \times \frac{70\ kg}{20\ m^3} = 0.0027939\,{}^{mg}/_{kg/day} \times \frac{70\ kg}{20\ m^3} = 0.00977865\,{}^{mg}/_{m^3}$$
$$= 9.77865\,{}^{\mu g}/_{m^3}$$

After rounding to two significant figures, the ITSL is 9.8 µg/m^3. According to Rule 232(2)(b) a 24-hour averaging time period should be used, but as this ITSL is based on a 21 month drinking water rat study, it is appropriate to utilize a longer averaging time, which would be an annual averaging time. Therefore, the ITSL for 3,3'-dimethoxybenzidine is 9.8 µg/m^3 based on an annual averaging time.

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Appendix 1

The models were run using the Benchmark Dose Software version 2.6.0.1 (build 88) and was run using dichotomous data utilizing the default settings with a Benchmark response (BMR) of 10% extra risk for the benchmark dose (BMD) and 0.95 lower confidence limit for the benchmark dose lower bound (BMDL), which gives a $BMDL_{10}$. After running statistical analysis of the data in table 2 above, the results should be evaluated using the EPA (2012) technical guidance for BMDS. The results were visually inspected to see if there are any problems with the plots (the model plot line should visually fit the data). To select the $BMDL_{10}$ generated from different BMD models, first evaluate the scaled residuals. All scaled residuals should be within 2 (2 to -2) for the model to be considered for a BMDL. Then evaluate the goodness-of-fit p-values to make sure that they are greater than 0.1; the higher the p-value the better the model fits the data. Also, look at the chi^2 value – the lower the chi^2 the better the model fits the data. If the $BMDL_{10}$ values are within a 3-fold range then look at the AIC to pick lowest AIC. The AIC allows the comparison of models by parameters when the results are similar. In the data below, the $BMDL_{10}$ results ranged from 0.27939 to 7.27467, which is greater than a 3-fold difference in range. When the $BMDL_{10}$ range is this great, the recommendation is to use the lowest $BMDL_{10}$.

In Table 3, the $BMDL_{10}$ curve calculation plotline for male rat liver hematopoietic cell proliferation for the loglogistic and logprobit models did not work correctly (graphs not presented). Similarly, the $BMDL_{10}$ curve calculation plotline for female rat liver hematopoietic cell proliferation for the loglogistic and logprobit models did not work correctly (graphs not presented). It was prudent to remove these models from further consideration. When reviewing the scaled residuals, the values for female liver hematopoietic cell proliferation for the logistic and probit models were above two and were also removed from consideration. When evaluating the p-values; the p-values for male liver hematopoietic cell proliferation for the logistic and probit models were below 0.1 and were removed from consideration. After removing the above models from consideration, the lowest remaining $BMDL_{10}$ is selected. The $BMDL_{10}$ for male rat liver lesions: eosinophilic focus using the loglogistic model had the lowest $BMDL_{10}$ of 0.27939 mg/kg. This value was used in the ITSL derivation calculations above to give an ITSL of 9.8 $\mu g/m^3$.

Table 3. Summary of BMDS Runs for Non-neoplastic Liver Lesions in F344 Rats Exposed to 3,3'-Dimethoxybenzidine for 21 Months.

Liver Lesion in Male Rats	Model	Chi-Square	p-Value	Scaled Residual	AIC	$BMDL_{10}$
Eosinophilic focus	Gamma	0.14	0.9328	-0.102	281.662	1.9078
Eosinophilic focus	Logistic	3.54	0.1705	0.93	285.191	3.94744
Eosinophilic focus	**LogLogistic**	**0.05**	**0.8148**	**-0.011**	**283.579**	**0.27939**
Eosinophilic focus	LogProbit	0.07	0.7949	-0.009	283.592	0.362748
Eosinophilic focus	Multistage	0.03	0.8608	-0.019	283.555	1.32026
Eosinophilic focus	Probit	3.18	0.2034	0.924	284.794	3.78435
Eosinophilic focus	Weibull	0.14	0.9328	-0.102	281.662	1.9078
Eosinophilic focus	Quantal-Linear	0.14	0.9328	-0.102	281.662	1.9078
Hematopoietic cell proliferation	Gamma	0.32	0.8525	-0.072	256.429	1.54211
Hematopoietic cell proliferation	Logistic	9.53	0.0085	1.298	266.922	3.75096
Hematopoietic cell proliferation	LogLogistic	0	0.9958	0	258.113	0.355344
Hematopoietic cell proliferation	LogProbit	0	0.9967	0	258.113	0.444617
Hematopoietic cell proliferation	Multistage	0.01	0.9393	0.004	258.119	1.07877
Hematopoietic cell proliferation	Probit	8.9	0.0117	1.334	265.978	3.60261
Hematopoietic cell proliferation	Weibull	0.32	0.8525	-0.072	256.429	1.54211
Hematopoietic cell proliferation	Quantal-linear	0.32	0.8525	-0.072	256.429	1.54211

Liver Lesion in Female Rats	Model	Chi-Square	p-Value	Scaled Residual	AIC	$BMDL_{10}$
Eosinophilic focus	Gamma	0.1	0.7477	0.218	248.979	4.28026
Eosinophilic focus	Logistic	0.01	0.9966	0.067	246.883	7.27467
Eosinophilic focus	LogLogistic	0.13	0.721	0.252	249.003	3.93083
Eosinophilic focus	LogProbit	0.24	0.6207	0.326	249.119	4.13296
Eosinophilic focus	Multistage	0.03	0.8654	0.114	248.905	4.13743
Eosinophilic focus	Probit	0.02	0.9887	0.012	246.899	6.814
Eosinophilic focus	Weibull	0.06	0.8024	0.181	248.939	4.29308
Eosinophilic focus	Quantal-linear	1.49	0.4754	-0.587	248.379	3.94568
Hematopoietic cell proliferation	Gamma	1.81	0.4046	-0.127	252.736	1.5644
Hematopoietic cell proliferation	Logistic	15.13	0.0005	2.041	268.856	3.93052
Hematopoietic cell proliferation	LogLogistic	0	0.9924	0	252.979	0.0280404
Hematopoietic cell proliferation	LogProbit	0	0.9838	0	252.979	0.0402285
Hematopoietic cell proliferation	Multistage	0.04	0.8428	-0.007	253.018	0.950507
Hematopoietic Cell proliferation	Probit	14.61	0.0007	2.099	267.805	3.79731
Hematopoietic cell proliferation	Weibull	1.81	0.4046	-0.127	252.736	1.5644
Hematopoietic cell proliferation	Quantal-linear	1.81	0.4046	-0.127	252.736	1.5644