Table I-1. Summary of BMD Analyses for JISA (1993) and NTP (1986) Data Sets Using Selected Dose Metrics

Figure #	Data Set	Source of Incidence Values	Dose Metric	Multistage Cancer Slope Factor from BMD	SF (units)$^{-1}$	CSF Based on Human Equivalent Metabolized Dose BW$^{3/4}$ (mg/kg-day)	% Metabolism Human Assumed	CSF based on Human Applied Dose	Unit Risk (ug/m^3)$^{-1}$
	Hepatocellular Carcinoma and Adenoma								
	Male Mouse								
I-1	JISA HAC Mouse Male HEC	WHO	HEC	0.0352992	ppm	---	---	---	5.12E-06
I-2	JISA HAC Ms male Hum metab	WHO	Human Metab BW3/4	0.0990969	mg/kg-day	9.910E-02	0.61	6.04E-02	6.91E-06
I-3	NTP HAC Mouse Male 10 HEC who	WHO	HEC	0.0468416	ppm	---	---	---	6.80E-06
I-4	NTP HAC Ms Male WHO Hattis 92	WHO	Hattis Met dose 1992 (animal)	0.020944	mg/kg-day	1.381E-01	0.61	8.43E-02	9.63E-06
I-5	NTP HAC ms Male WHO MM anim met	WHO	MM Met dose (animal) CAEPA 1992	0.0228453	mg/kg-day	1.507E-01	0.61	9.19E-02	1.05E-05
I-6	JISA NTP Combined HAC Mouse Male	WHO	HEC	0.0384769	ppm	---	---	---	5.58E-06
I-7	NTP HAC Mouse Male HEC calc	CAEPA	HEC	0.0458026	ppm	---	---	---	6.65E-06
I-8	NTP HAC ms male tz Met dose Hat	CAEPA 1992	Hattis Met dose 1992 (animal)	0.0205795	mg/kg-day	1.357E-01	0.61	8.28E-02	9.46E-06
I-9	NTP HAC ms male tz Met dose MM	CAEPA 1992	MM Met dose (animal) CA1992	0.0228646	mg/kg-day	1.508E-01	0.61	9.20E-02	1.05E-05
	Female Mouse								
I-10	JISA HAC Mouse Female 10 HEC	WHO	HEC	0.023136	ppm	---	---	---	3.36E-06
I-11	JISA HAC Ms female Hum Metab	WHO	Human Metab BW3/4	0.0415079	mg/kg-day	4.151E-02	0.61	2.53E-02	2.89E-06
I-12	NTP HAC Mouse Female WHO HEC	WHO	HEC	0.0341676	ppm	---	---	---	4.96E-06
I-13	NTP HAC Mouse Female HECcalc	CAEPA 1992	HEC	0.0324985	ppm	---	---	---	4.72E-06
	Mononuclear Cellular Leukemia								
	Male Rat								
I-14	JISA MCL Rat Male HEC	WHO	HEC	0.00770446	ppm	---	---	---	1.12E-06
I-15	JISA MCL Rat Male Hum Metab	WHO	Human Metab BW3/4	0.133665	mg/kg-day	1.337E-01	0.61	8.15E-02	9.32E-06
I-16	NTP mcl rat male HEC	WHO/CAEPA 1992	HEC	0.0150749	ppm	---	---	---	2.19E-06
I-17	NTP MCL Rat Male Hattis Anima M	WHO/CAEPA 1992	Hattis Met dose 1992 (animal)	0.0484028	mg/kg-day	1.719E-01	0.61	1.05E-01	1.20E-05
I-18	NTP MCL Rat Male MM Anima Metab	WHO/CAEPA 1992	MM Met dose (animal) CA1992	0.0611654	mg/kg-day	2.172E-01	0.61	1.33E-01	1.51E-05
	Female Rat								
I-19	JISA mcl rat female HEC	WHO	HEC	0.00380114	ppm	---	---	---	5.52E-07
I-20	JISA MCL Rat Female Hum Metab	WHO	Human Metab BW3/4	0.0693484	mg/kg-day	6.935E-02	0.61	4.23E-02	4.83E-06
I-21	NTP mcl rat female HEC WHO	WHO	HEC	0.0112196	ppm	---	---	---	1.63E-06
I-22	NTP MCL Rat Female MM Metab WH	WHO	MM Met dose (animal) CA1992	0.0384331	mg/kg-day	1.478E-01	0.61	9.02E-02	1.03E-05
I-23	NTP mcl rat female HEC CAEPA	CAEPA 1992	HEC	0.011036	ppm	---	---	---	1.60E-06
I-24	NTP mcl rat female MM metaCAEPA	CAEPA 1992	MM Met dose (animal) CA1992	0.0378936	mg/kg-day	1.457E-01	0.61	8.89E-02	1.02E-05

Table I-1. Summary of BMD Analyses for JISA (1993) and NTP (1986) Data Sets Using Selected Dose Metrics

Figure #	Data Set	Source of Incidence Values	Dose Metric	BMC	BMCL	BMC/L units	BMR (%)	AIC	Summary Statistics		
	Hepatocellular Carcinoma and Adenoma										
	Male Mouse										
I-1	JISA HAC Mouse Male HEC	WHO	HEC	8.22773	2.83292	ppm	10	240.8	Chi^2 = 1.90	d.f. = 1	P-value = 0.1679
I-2	JISA HAC Ms male Hum metab	WHO	Human Metab BW3/4	3.45181	1.00911	mg/kg-day	10	241.0	Chi^2 = 2.12	d.f. = 1	P-value = 0.1457
I-3	NTP HAC Mouse Male 10 HEC who	WHO	HEC	2.93343	2.13485	ppm	10	174.7	Chi^2 = 0.00	d.f. = 1	P-value = 0.9780
I-4	NTP HAC Ms Male WHO Hattis 92	WHO	Hattis Met dose 1992 (animal)	9.12751	4.77463	mg/kg-day	10	176.7	Chi^2 = 0.00	d.f. = 0	P-value = NA
I-5	NTP HAC ms Male WHO MM anim met	WHO	MM Met dose (animal) CAEPA 1992	16.6967	4.37727	mg/kg-day	10	176.7	Chi^2 = 0.00	d.f. = 0	P-value = NA
I-6	JISA NTP Combined HAC Mouse Male	WHO	HEC	3.45971	2.59896	ppm	10	413.7	Chi^2 = 3.63	d.f. = 3	P-value = 0.3043
I-7	NTP HAC Mouse Male HEC calc	CAEPA	HEC	2.99287	2.18328	ppm	10	176.3	Chi^2 = 0.09	d.f. = 1	P-value = 0.7692
I-8	NTP HAC ms male tz Met dose Hat	CAEPA 1992	Hattis Met dose 1992 (animal)	7.43586	4.85922	mg/kg-day	10	176.3	Chi^2 = 0.00	d.f. = 0	P-value = NA
I-9	NTP HAC ms male tz Met dose MM	CAEPA 1992	MM Met dose (animal) CA1992	11.9703	4.37358	mg/kg-day	10	178.2	Chi^2 = 0.00	d.f. = 0	P-value = NA
	Female Mouse										
I-10	JISA HAC Mouse Female 10 HEC	WHO	HEC	9.65407	4.32227	ppm	10	152.8	Chi^2 = 0.04	d.f. = 1	P-value = 0.8347
I-11	JISA HAC Ms female Hum Metab	WHO	Human Metab BW3/4	4.39549	2.40918	mg/kg-day	10	154.8	Chi^2 = 0.00	d.f. = 0	P-value = NA
I-12	NTP HAC Mouse Female WHO HEC	WHO	HEC	7.68302	2.92675	ppm	10	138.8	Chi^2 = 0.00	d.f. = 0	P-value = NA
I-13	NTP HAC Mouse Female HECcalc	CAEPA 1992	HEC	8.22294	3.07707	ppm	10	135.4	Chi^2 = 0.00	d.f. = 0	P-value = NA
	Mononuclear Cellular Leukemia										
	Male Rat										
I-14	JISA MCL Rat Male HEC	WHO	HEC	20.1208	12.9795	ppm	10	254.8	Chi^2 = 1.27	d.f. = 2	P-value = 0.5295
I-15	JISA MCL Rat Male Hum Metab	WHO	Human Metab BW3/4	1.13861	0.748142	mg/kg-day	10	255.7	Chi^2 = 0.10	d.f. = 1	P-value = 0.7464
I-16	NTP mcl rat male HEC	WHO/CAEPA 1992	HEC	12.2677	6.63356	ppm	10	183.4	Chi^2 = 1.80	d.f. = 1	P-value = 0.1793
I-17	NTP MCL Rat Male Hattis Anima M	WHO/CAEPA 1992	Hattis Met dose 1992 (animal)	3.62987	2.066	mg/kg-day	10	182.7	Chi^2 = 1.08	d.f. = 1	P-value = 0.2994
I-18	NTP MCL Rat Male MM Anima Metab	WHO/CAEPA 1992	MM Met dose (animal) CA1992	2.84064	1.63491	mg/kg-day	10	182.5	Chi^2 = 0.89	d.f. = 1	P-value = 0.3458
	Female Rat										
I-19	JISA mcl rat female HEC	WHO	HEC	59.0663	26.3079	ppm	10	249.4	Chi^2 = 2.15	d.f. = 2	P-value = 0.3411
I-20	JISA MCL Rat Female Hum Metab	WHO	Human Metab BW3/4	2.91439	1.442	mg/kg-day	10	248.8	Chi^2 = 1.56	d.f. = 2	P-value = 0.4580
I-21	NTP mcl rat female HEC WHO	WHO	HEC	15.401	8.91297	ppm	10	206.5	Chi^2 = 1.85	d.f. = 1	P-value = 0.1739
I-22	NTP MCL Rat Female MM Metab WH	WHO	MM Met dose (animal) CA1992	4.25171	2.60193	mg/kg-day	10	205.4	Chi^2 = 0.71	d.f. = 1	P-value = 0.3982
I-23	NTP mcl rat female HEC CAEPA	CAEPA 1992	HEC	15.9366	9.06125	ppm	10	205.5	Chi^2 = 1.76	d.f. = 1	P-value = 0.1852
I-24	NTP mcl rat female MM metaCAEPA	CAEPA 1992	MM Met dose (animal) CA1992	4.37658	2.63897	mg/kg-day	10	204.5	Chi^2 = 0.68	d.f. = 1	P-value = 0.4080

Figure I-1
Study, Species, Sex: JISA (1993), Mouse, Male
Data Source: HAC Tumor Incidence as Reported in WHO (2006)
Dose Metric: HEC calculated by WHO (2006)

```
====================================================================
            Multistage Cancer Model. (Version: 1.5;  Date: 02/20/2007)
            Input Data File: C:\BMDS\TETRA\JISA_HAC_MOUSE_MALE.(d)
            Gnuplot Plotting File:  C:\BMDS\TETRA\JISA_HAC_MOUSE_MALE.plt
           Thu Sep 13 15:13:02 2007
====================================================================
```

BMDS MODEL RUN
~~~~~~

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(
        -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

The parameter betas are restricted to be positive

Dependent variable = COLUMN2
Independent variable = COLUMN1

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

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

```
              Default Initial Parameter Values
                Background =    0.345657
                  Beta(1) =   0.0108483
                  Beta(2) =          0
                  Beta(3) = 8.58286e-006
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(2)
     have been estimated at a boundary point, or have been specified by the user,
     and do not appear in the correlation matrix)

	Background	Beta(1)	Beta(3)
Background	1	-0.68	0.6
Beta(1)	-0.68	1	-0.96
Beta(3)	0.6	-0.96	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0.341525	*	*	*
Beta(1)	0.0122683	*	*	*
Beta(2)	0	*	*	*
Beta(3)	7.93686e-006	*	*	*

* - Indicates that this value is not calculated.

Study, Species, Sex: JISA (1993), Mouse, Male
Data Source: HAC Tumor Incidence as Reported in WHO (2006)
Dose Metric: HEC calculated by WHO (2006)

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-116.442	4			
Fitted model	-117.389	3	1.89526	1	0.1686
Reduced model	-132.99	1	33.0977	3	<.0001

AIC: 240.779

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.3415	15.710	13	46	-0.843
1.8000	0.3559	17.441	21	49	1.062
9.0000	0.4138	19.861	19	48	-0.252
45.0000	0.8161	39.987	40	49	0.005

Chi^2 = 1.90   d.f. = 1   P-value = 0.1679

Benchmark Dose Computation

Specified effect =   0.1

Risk Type   =   Extra risk

Confidence level =   0.95
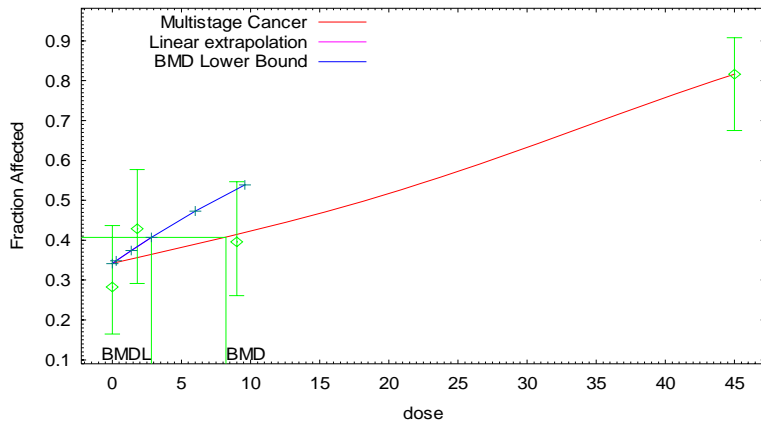
BMD =   8.22773

BMDL =   2.83292

BMDU =   22.7346

Taken together, (2.83292, 22.7346) is a 90   % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor =   0.0352992 ppm

Multistage Cancer Model with 0.95 Confidence Level

15:16 09/13 2007

Figure I-2
Study, Species, Sex: JISA (1993), Mouse, Male
Data Source: HAC Tumor Incidence as Reported in WHO (2006)
Dose Metric: Human Equivalent Metabolized Dose (MassDEP, 2007)

```
====================================================================
          Multistage Cancer Model. (Version: 1.5;  Date: 02/20/2007)
          Input Data File: C:\BMDS\TETRA\JISA_HAC_MOUSE_MALE_H_METAB.(d)
          Gnuplot Plotting File:  C:\BMDS\TETRA\JISA_HAC_MOUSE_MALE_H_METAB.plt
          Mon Oct 29 12:48:32 2007
====================================================================
```

BMDS MODEL RUN
~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
           -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive

   Dependent variable = COLUMN2
   Independent variable = COLUMN1

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

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

              Default Initial Parameter Values
                  Background =   0.344792
                    Beta(1) =   0.010984
                    Beta(2) =   0
                    Beta(3) =   0.00125023

       Asymptotic Correlation Matrix of Parameter Estimates

       (*** The model parameter(s) -Beta(2)
             have been estimated at a boundary point, or have been specified by the user,
             and do not appear in the correlation matrix)

           Background   Beta(1)   Beta(3)

Background   1   -0.71   0.52

   Beta(1)   -0.71   1   -0.89

   Beta(3)   0.52   -0.89   1

                    Parameter Estimates

                              95.0% Wald Confidence Interval
      Variable   Estimate   Std. Err.   Lower Conf. Limit   Upper Conf. Limit
      Background   0.340315   *   *   *
       Beta(1)   0.0164098   *   *   *
       Beta(2)   0   *   *   *
       Beta(3)   0.00118452   *   *   *

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-116.442	4			
Fitted model	-117.493	3	2.10288	1	0.147
Reduced model	-132.99	1	33.0977	3	<.0001

AIC: 240.986

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3403	15.654	13	46	-0.826
0.9700	0.3514	17.220	21	49	1.131
3.9100	0.4236	20.333	19	48	-0.389
9.7600	0.8131	39.844	40	49	0.057

Chi^2 = 2.12   d.f. = 1   P-value = 0.1457

Benchmark Dose Computation

Specified effect =   0.1

Risk Type   =   Extra risk

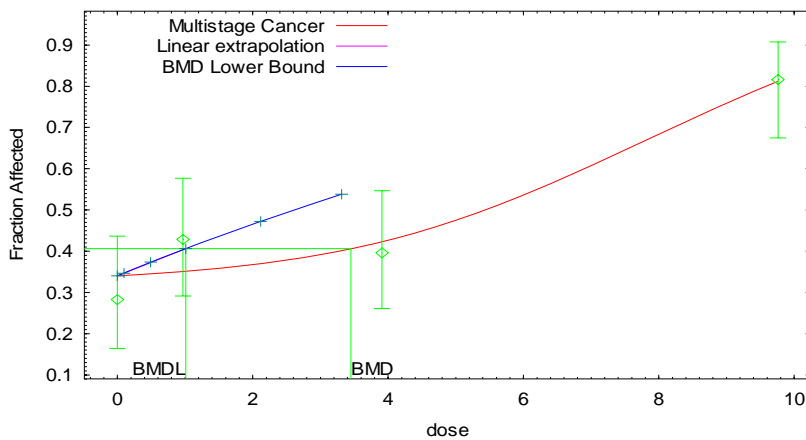Confidence level =   0.95

BMD =   3.45181

BMDL =   1.00911

BMDU =   4.96111

Taken together, (1.00911, 4.96111) is a 90   % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor =   0.0990969

Multistage Cancer Model with 0.95 Confidence Level

12:48 10/29 2007