11-19-91

COPY

MEMORANDUM:

Subject: Ethylenethiourea Cancer Potency Factor (Q_1^*) Calculations Based on Female Mouse Liver Tumors Using Both Pooled Data and the Diagonal Data Set from the National Toxicology Program Study (NTP -TR-No.388).

From: Albin B. Kocialski Ph.D., Head
Registration Standards Section
Health Effects Division (H7509c) ABK 11/19/91

To: Kathleen Martin, Review Manager
Special Review Branch
Special Review and Reregistration Division (H7508W)

The Science Advisory Panel (SAP) at an open meeting on September 18, 1991, endorsed the position of the Health Effects Division Peer Review Committee (HED/PRC) and that of the Ethylene thiourea Task Force (ETU/TF) that the female mouse liver tumor data can be pooled in determining a Q_1^* for ETU. (Attachments 1 and 2.)

The SAP also indicated that "Whole life exposure (the diagonal in the factorial experimental design) is probably most appropriate for utilization for public health purposes." The application of the model to the data resulted in statistically acceptable fits with respective Q_1^* values of 0.11 and 0.16 $mg/kg/day^{-1}$. (Attachments 3 and 4.)

Recommendation: It is recommended that since both cancer potency (Q_1^*) values are statistically acceptable the cancer potency value (Q_1^*) of 0.11 $mg/kg/day^{-1}$ as previously used in all preliminary risk calculations be formally adopted by OPTS as the cancer potency value for ethylenethiourea (ETU).

Attachment 1. Issues Related to the Dose Response Assessment of Ethylene thiourea Tumor Data in Rats and Mice. Revised 09/11/91. Presentation to the FIFRA Scientific Advisory Panel September 18, 1991.

Attachment 2. Report of the Science Advisory Panel dated October 2, 1991. Robert B. Jaeger Designated Federal Official. A Set of Scientific Issues Being Considered by the Agency in Connection with a Dose-Response Analysis for Ethylenethiourea (ETU).

Attachment 3. Memorandum by Dr. Hugh Pettigrew dated November 13, 1991. Ethylenethiourea (ETU) Q_1^* Calculation Based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study.

Attachment 4. Memorandum by Dr. Hugh Pettigrew dated November 13, 1991. Ethylenethiourea (ETU) Q_1^* Calculation Based on Female Mouse Liver Tumors (Diagonal Data Set) from the NTP Study]

ISSUES RELATED TO THE DOSE RESPONSE ASSESSMENT OF ETHYLENETHIOUREA TUMOR DATA IN RATS AND MICE

FIFRA SCIENTIFIC ADVISORY PANEL
SEPTEMBER 18, 1991

Revised 09/11/91

BACKGROUND

The data on Ethylenethiourea (ETU) have been discussed previously before the Scientific Advisory Panel (SAP), May 15, 1990. The SAP agreed with the Agency concerning the classification of ETU as a Group B2 Carcinogen, according to the EPA guidelines for Carcinogen Risk Assessment. The SAP concluded that the liver tumor data in the mouse study was most appropriate for a dose response assessment, but also suggested that the tumor data for the rat be analyzed in evaluating the dose response assessment, for the purpose of human risk characterization.

It should be recalled that the NTP cancer bioassays in both the rat and the mouse were complex and different from the standard assay where the dosing of animals is started only after weaning. In the ETU bioassay, some groups of animals were exposed to ETU in utero and fed ETU after weaning for their lifetime. In the mouse study for example, the doses for the parent animals were 0, 33, 110, and 330 ppm, and the lifetime doses for the test animals after weaning were 0, 100, 330, and 1000 ppm. The rat study had a similar protocol but with different doses, predicated on the differences between the two species in tolerating ETU. Not all combinations of this 4 by 4 matrix of exposures were, however, tested. In fact only 8 of the possible 16 exposure/dosing scenarios were included in the long term feeding tests. (See attached table).

The actual exposure of the fetus and nursing animals as a result of the in utero dosing regimen was not possible to assess. Therefore, the Agency, in its preliminary dose response assessment limited its analysis to those animal groups which were exposed in the standard fashion, i.e. were naive with respect to in utero exposure or exposure through milk and were put on the ETU containing diets after weaning; the SAP agreed with this approach.

The industry sponsored ETU task force contended, however, that all the female mouse liver tumor data should be considered for the purpose of dose response assessment. This contention, which was presented at the 1990 SAP meeting was based primarily on the fact that, qualitatively or quantitaviley, the liver tumor response in female mice appeared not to be significantly influenced by the in utero exposure and therefore all animals with the same post weaning dose could be considered as a single test group (i.e. the data can be pooled); the SAP, however, questioned this approach. Some months after the 1990 SAP meeting, the ETU task force formally presented their evaluation of the data in writing to the Agency for consideration.

RE-EVALUATION OF TUMOR DATA

The Office has, in the past several months, analyzed in greater depth the tumor data in both the rat and the mouse and has presented the evaluation for discussion to the Health Effects Division Peer Review Committee on Cancer Risk Assessment. The Peer Review Committee (PRC) was asked specifically to address the following issues:

(1) The re-assessment of thyroid tumors in the rat and the liver tumors in the mouse and to provide an opinion on the most appropriate data set for a dose response assessment.

(2) Whether to continue to use the default value for converting ppm in the diet to mg/kg/day rather than to use actual food consumption values.

(3) To determine the most appropriate scaling fctor for a comparative dose response assessment between animals and humans, and;

(4) To determine the most relevant use of the data for the purpose of a dose response assessment, i.e. the inclusion or exclusion of certain data points.

The PRC came to the following conclusions and recommendations (the details of the discussion are contained in the attached third peer review of ETU):

(1) The PRC reaffirmed its earlier decision to use the liver tumor data in female mice to perform the dose response assessment This data set was the most convincing one, and dose response assessments performed on other tumor data (including the rat) were consistent with the analysis of the female mouse data. This decision had been reached at previous PRC meetings and, when presented to the SAP in 1990, was supported by the SAP.

(2) The PRC also concluded that use of actual food consumption data and body weights for calculating the animal doses, rather than the standard default conversion factors, was appropriate. (At the time the ETU data were analyzed for the 1990 SAP presentation the actual food consumption data and body weights were not available; thus the use of the default value of 1 ppm = 0.15 mg/kg body weight in the mouse.)

(3) The PRC further decided to adhere to the traditional EPA default interspecies scaling factor which is based on body surface area. The PRC acknowledged that a proposal existed to change the interspecies scaling factor, but decided not to use it because a final decision on that position has not been reached.

(4) The most significant deliberation focused on the inclusion of the 33/100 ppm low dose group and the exclusion of the 1000 ppm dose group for the purpose of dose response assessment.

A bare plurality of the PRC recommended inclusion of the low dose female mouse dose group. By doing this, and applying the linearized multistage (model) procedure, the highest dose (1000 ppm) group needed to be dropped in order to obtain a statistically acceptable fit for doses of 0, 100, 330 and 1000 ppm. Others recommended against the addition of the low dose group for the dose response assessment. Basically the arguments for not including this data point were based primarily on statistical incongruities of the experimental design (sample size and the absence of any corresponding control group) as well as no explanation for the lack of a sufficient number of litters or pups per litter from which one could randomly select animals for this dose group in a manner compared to other experimental groups. However, poor breeding performance on a random basis was concluded in the ETU Peer Review Document. The arguments for including the data point were based primarily on biological considerations, thereby allowing the lowest dose treatment group to provide a better estimate and extrapolation to the events occuring at low dose exposures. There was no indication that <u>in utero</u> exposure affected the liver tumor formation in any group, and conceding the small sample size of the 33/100 ppm female dose group survival was excellent and offspring were basically from the same homogeneous gene pool as all other groups. The resulting Q_1* was also the same as that calculated from an earlier mouse study (Innes 1969) which used neonate (7-28 day gavage) followed by an 18-month dietary exposure (the Agency had used that data in its previous calculations of the ETU cancer potency).

In a general sense the tumor-dose response assessment from the ETU data turns out to be consistent; we have calculated Q_1* values on a number of data sets and they are all very similar. However, as might be expected for such a large data set, there are minor variations in the outcome of the dose response assessment. Nevertheless, using various potentially appropriate data sets in the dose response assessment process, the calculated Q_1* cover a range of only 0.1 to 0.6.

In the main, inclusion or exclusion of the low dose (100 ppm) data point is the primary reason for this six-fold quantitative difference of the dose response assessment of the present data set on the carcinogenicity of ETU. The deliberations of the PRC did not provide a clear cut scientific conclusion perferring one approach over the other. Thus, one can argue in a scientific arena, that either dose response assessment has some merit as well as some shortcomings, and therefore either assessment can be considered as useful in expressing the human risk scenario for ETU.

QUESTION/ISSUE
(TRANSPARENCY)

Is it appropriate to use the 100 ppm dose group for the risk characterization of ETU, considering that (1) this dose group represents several design flaws; and (2) necessitates the exclusion

of the highest dose group because of lack of model fit; but (3) provides some valid and significant biological data at a lower exposure level and thus may be more relevant for low dose extrapolation than data points with high exposure and nearly saturated tumor response? We specifically ask that the SAP provide, to the extent possible, all the scientific arguments for either inclusion or exclusion of the low dose data point in the dose response assessment.

Liver Tumor Dose Response of Ethylenethiourea (ETU)

In Female B6C3F1 Mice (NTP-TR-No. 388).

Doses (ppm)

F_0/F_1	0	100	330	1000
0	4/49		44/50	48/49
33		4/27		
110			46/50	
330	5/49		46/50	49/49
Pooled	9/98	4/27	136/150	97/98

Issue

Is it appropriate to use the (33)100 ppm dose group for risk characterization considering that:

- this group represents several design flaws,
- necessitates the exclusion of the highest dose group (1000 ppm) because of the lack of (linearized multistage) model fit,
- but provides some valid and significant biological data at a lower exposure level and thus may be more relevant for low dose extrapolation than data points with high exposure and nearly saturated tumor response?

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with a Dose-Response Analysis for Ethylene Thiourea (ETU)

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues regarding the Environmental Protection Agency Peer Review Committee's review of a dose-response risk assessment for the carcinogenic effects of Ethylene Thiourea (ETU) in rats and mice. The review was conducted in an open meeting held in Arlington, Virginia, on September 18, 1991. Panel members present for the review were Dr. Edward Bresnick (Chairman), Dr. Mont Juchau and Dr. Peter Magee (Dr. Curtis Travis was recused from the proceedings). In addition, Dr. Edmund Crouch of Cambridge Environmental, Inc., Dr. Richard Griesemer and Dr. Christopher Portier of the National Institute of Environmental Health Sciences, served as Agency representatives; and Dr. Dale Hattis of Clark University, and Dr. Ernest McConnell of Raleigh, NC served as Special Government Employees on the Panel.

Public notice of the meeting was published in two Federal Registers on Friday, August 23, and Friday, September 13, 1991.

Oral presentations were made by the EBDC/ETU Task Force: Mr. Edward Ruckert, Dr. Gary Flamm, Dr. Thomas Starr, Dr. Robert Sielken, Jr., and Dr. Kenny Crump.

Written comments were received from the EBDC/ETU Task Force members: Atochem North America, Inc., BASF Corporation, E.I. du Pont de Nemours and Company, and Rohm and Haas Company.

NOTE: Prior to the Panel's discussion and deliberations on ETU, an announcement was made that the ETU Task Force had expressed concern over a possible conflict of interest regarding Dr. Travis. Although discussions between the Designated Federal Official (DFO, FIFRA SAP) and the EPA Office of General Counsel (OGC Ethics Office), prior to the afternoon discussion of ETU, failed to substantiate the alleged conflict of interest, Dr. Travis informed both the DFO and the Chairman of the FIFRA SAP that he recused himself from all proceedings on ETU before the Panel, both public and private discussions of the issues. This does not reflect any real conflict of interest regarding the matter before the Panel, but rather the belief by Dr. Travis that (1) there were several other experts on the Panel who were equally capable of discussing the issues on ETU, (2) at such late notice, it gave the "appearance" of a problem, (3) when there is

no benefit to be gained there should be no risks taken, and (4) the matter deserved more detailed written response by OGC to verify there is no conflict of interest, and to prevent unnecessarily impugning the reputation and scientific integrity of the FIFRA SAP.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

The Agency requested comments from the Panel relative to the Peer Review Committee's recommendations for appropriate use of the (33)100 ppm dose group for risk characterization considering that:

- o this group represents several design flaws,
- o necessitates the exclusion of the highest dose group (1000 ppm) because of the lack of (linearized multistage) model fit,
- o but provides some valid and significant biological data at a lower exposure level and thus may be more relevant for low dose extrapolation than data points with high exposure and nearly saturated tumor response?

Specifically:

The Panel was asked to provide, to the extent possible, the scientific arguments for either inclusion or exclusion of the low dose data point in the dose response assessment.

Panel Response:

The Panel is of the opinion that adequate data should always be included unless there is strong reason to exclude them. In this case, there is a strong reason for the Agency's standard approach which results in the exclusion of the highest dose group since its inclusion was associated with gross distortion of estimates of the probable effects at lower doses when used in the Agency's standard dose-response formula (e.g., linearized multi-stage model).

The Panel felt strongly that the data from the 33/100 ppm group should be included in the analyses. The arguments for inclusion are:

1. The usual form of the linearized multistage model is probably not statistically appropriate for use in calculating Q_1^* if all data except the control show over 90% rates of cancer.

2. Whole life exposure (the diagonal in the factorial experimental design) is probably most appropriate for utilization for public health purposes.

The principal argument against using the low dose point is potential litter bias, and this appears to have been relatively well addressed in the analyses presented to the Panel.

The Panel noted that the available data would not likely enable the robust detection of an interactive effect between the effects of pre-weaning and post-weaning exposure for the liver cancer endpoint if such an effect were to have been present. Despite the fact that not enough information exists to statistically evaluate the potential for a protective effect of the prenatal exposure, such an effect is not seen in the high dose groups. There is also supporting evidence for this view since no consistent patterns of interaction were observed in other tissues.

The Panel was informed during the meeting that some pharmacokinetic data exist for ETU. The Panel suggested that the analysis could be improved by using (and if necessary gathering) pharmacokinetic data which would allow expression of the results in terms of the internal dose of ETU [e.g. area under a curve (AUC) of concentration vs. time following comparable oral exposures, if possible based on experiments in subchronically dosed animals]. Pharmacodynamic data (e.g., the dynamics of thyroid hormone changes and cell proliferation responses in the thyroid and liver) may also aid in producing an improved estimation of low dose risks.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Robert B Jaeger — 10/2/91

Robert B. Jaeger (date)
Designated Federal Official
FIFRA Scientific Advisory Panel

Attachment No. 3.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study.

Caswell No. 443AA

From: Hugh M. Pettigrew, Ph.D. 11/13/91
Science Support and Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

To: Albin Kocialski, Ph.D., Head
Registration Standards Section
Health Effects Division (H7509C)

Thru: Kerry Dearfield, Ph.D., Acting Head 11.13.91
Science Support and Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Summary

The unit risk, Q_1^*, of Ethylene thiourea derived by applying the linearized multistage procedure to the pooled incidences of combined hepatocellular adenoma/carcinoma in female $B_6C_3F_1$ mice is

$$Q_1^* = 1.1x10^{-1}(mg/kg/day)^{-1}$$

in human equivalents. This estimate was derived using actual food consumption and body weight data from the NTP study. The interspecies scaling factor was based upon the ratio of human to laboratory animal body weights raised to the one-third power.

Background

The Q_1^* for Ethylene thiourea is based on the NTP $B_6C_3F_1$ mouse study. The following table summarizes the design of the study and the results. [For full details, see HED Memorandum "Third Peer Review of ETHYLENE THIOUREA. Selecting the Q_1^* for Ethylenethiourea [ETU]", dated 9/26/91.] The numerators are the numbers of animals having either hepatocellular adenoma or carcinoma and the denominators are the numbers of animals surviving 52 weeks or longer.

F_0 Dose (ppm)	F_1 Dose (ppm)			
	0	100	330	1000
0	4/49		44/50	48/49
33		4/27		
100			46/50	
330	5/49		46/50	49/49
Pooled	9/98	4/27	136/150	97/98

Following the recommendation of the HED Peer Review Committee, the linearized multistage model was fit to the pooled data (the bottom row of the above table). This resulted in a statistically unacceptable fit (Chi-square =16.51, P-value =0.0003.) The multistage procedure in such a case then drops the highest dose from the computation, and fits the multistage model to the remaining data. This resulted in a statistically acceptable fit (Chi-square = 1.71, P=0.19.), and yielded the Q_1^* of 0.11.

These results were obtained by applying the multistage model using the TOX_RISK (**Tox**icology **Risk** Assessment Program) Version 3 developed by Kenny S. Crump et al. The details are provided on the attached copy of printout from the program.

FILE NAME : C:\TOXVER3\FINAL.TXS\PAD4D.TXD

TITLE : Mouse Liver Tumors Pooled 52 week adjustment
CHEMICAL
MOLECULAR WT. : 102
SPECIES : MOUSE
ROUTE/DOSE UNITS: FOOD (ppm)

DOSE	RESPONDERS / NUMBER	DOSE	RESPONDERS / NUMBER	DOSE	RESPONDERS / NUMBER
0	9 /98		/		/
100	4 /27		/		/
330	136 /150		/		/
1000	97 /98		/		/
	/		/		/
	/		/		/

WEEKS OF STUDY: 104

ADJUSTMENT FACTOR FOR EXPER. LENGTH : 1.0

EXPERIMENTAL SPECIES :			DOSING :	
BODY WEIGHT	: .0343	kg	WEEKS	: 104
LIFE-SPAN	: 104	weeks	DAYS/WEEK	: 7
BREATHING RATE	: .0347	1/min	HOURS/DAY	: 24
FOOD CONSUMPTION	: 5.7	g/day	AVERAGING FACTOR	: 1.0
DRINKING RATE	: 6	ml/day		

********** NOTES **********

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study. Memorandum of ~~11~~/13/~~91~~ from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Mouse Liver Tumors Pooled 52 week adjus

Model: Multistage Dataset: C:\TOXVER3\FINAL.TXS\PAD4D
Functional form: 1 - EXP(-Q0 - Q1 * D - Q2 * D^2 ... - Qk * D^k)
Chi-square: 16.51 P-value: 0.0003
Parameter Estimates : k = 3
Q 0 = 8.568642E-002
Q 1 = 5.735323E-003
Q 2 = 0.000000E+000
Q 3 = 0.000000E+000

Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits Lower	Upper
0	9 / 98	8.05	4.718	15.211
100	4 / 27	13.03	1.413	8.316
330	136 / 150	129.26	128.611	141.407
1000	97 / 98	97.71	93.363	97.949

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Mouse Liver Tumors Pooled 52 week adjus

Dataset: C:\TOXVER3\FINAL.TXS\PAD4D

		Exposure Pattern			
Model:	Multistage	Age Begins:	0	Age Ends:	70
Target Species:	Human	Weeks/Year:	52	Days/Week:	7
Route:	Food			Hours/Day :	24

Animal to human conversion method: MG/M^2 SURFACE AREA/DAY

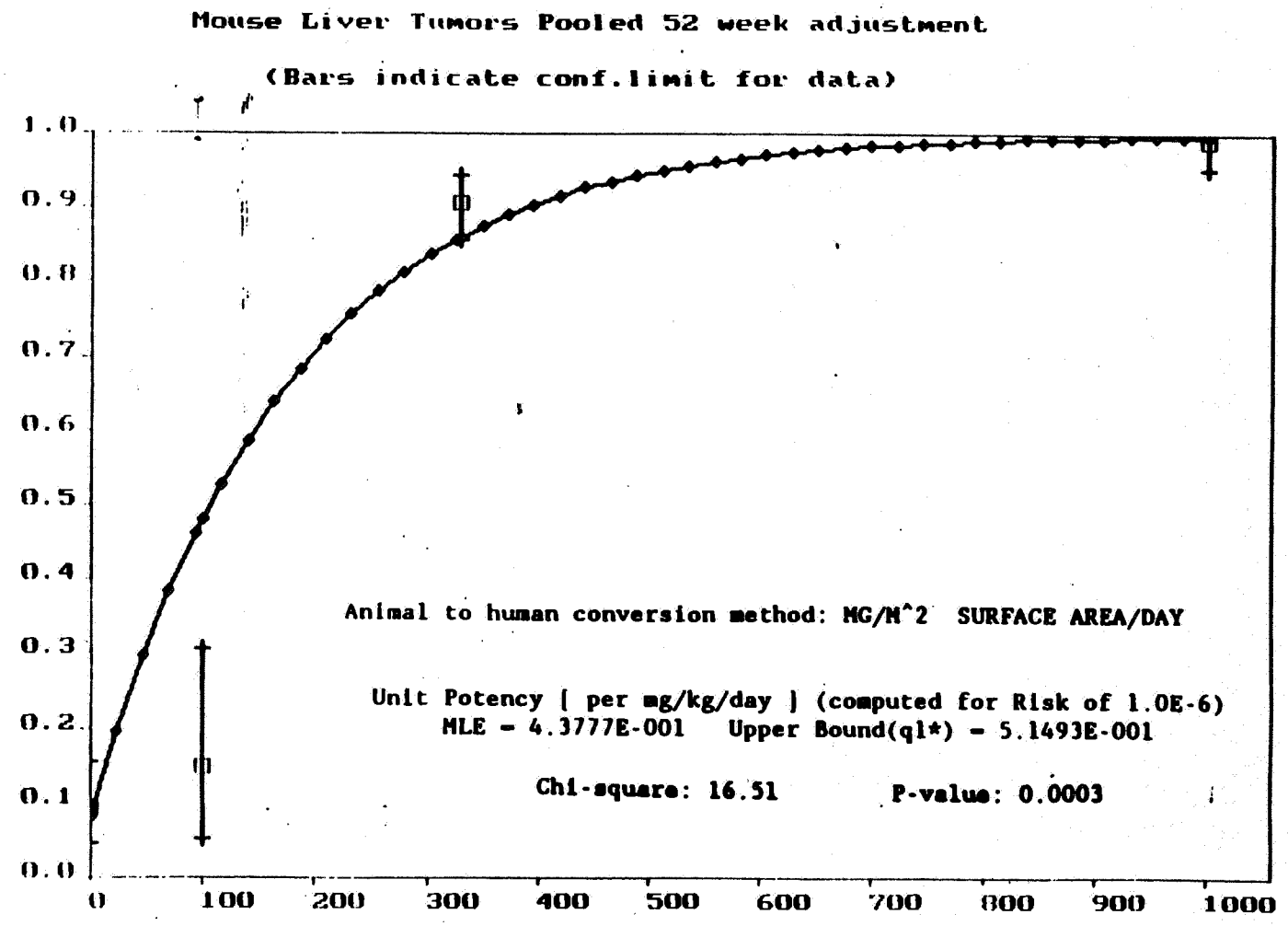
Unit Potency [per mg/kg/day] (computed for Risk of 1.0E-6)
MLE = 4.3777E-001 Upper Bound(q1*) = 5.1493E-001

Dose Estimates (ppb)

Extra Risk	95.0% Lower Bound	MLE
1.0000E-006	9.7101E-002	1.1422E-001
1.0000E-005	9.7101E-001	1.1422E+000

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study.
Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.



FILE NAME : C:\TOXVER3\FINAL.TXS\PA123.TXD

TITLE : Mouse Liver Tumors 52 week adjustment
CHEMICAL
MOLECULAR WT. : 102
SPECIES : MOUSE
ROUTE/DOSE UNITS: FOOD (ppm)

DOSE	RESPONDERS / NUMBER	DOSE	RESPONDERS / NUMBER	DOSE	RESPONDERS / NUMBER
0	9 /98		/		/
100	4 /27		/		/
330	136 /150		/		/
	/		/		/
	/		/		/
	/		/		/

WEEKS OF STUDY: 104

ADJUSTMENT FACTOR FOR EXPER. LENGTH : 1.0

EXPERIMENTAL SPECIES :			DOSING :	
BODY WEIGHT	: .0343	kg	WEEKS	: 104
LIFE-SPAN	: 104	weeks	DAYS/WEEK	: 7
BREATHING RATE	: .0347	l/min	HOURS/DAY	: 24
FOOD CONSUMPTION	: 5.7	g/day	AVERAGING FACTOR	: 1.0
DRINKING RATE	: 6	ml/day		

********** NOTES **********

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Mouse Liver Tumors 52 week adjustment

Model: Multistage Dataset: C:\TOXVER3\FINAL.TXS\PA123
Functional form: 1 - EXP(-Q0 - Q1 * D - Q2 * D^2 ... - Qk * D^k)
Chi-square: 1.71 P-value: 0.19
Parameter Estimates : k = 2
Q 0 = 8.690526E-002
Q 1 = 0.000000E+000
Q 2 = 2.039386E-005

Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits Lower	Upper
0	9 / 98	8.16	4.718	15.211
100	4 / 27	6.81	1.413	8.316
330	136 / 150	135.08	128.611	141.407

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Mouse Liver Tumors 52 week adjustment

Dataset: C:\TOXVER3\FINAL.TXS\PA123

		Exposure Pattern			
Model:	Multistage	Age Begins:	0	Age Ends:	70
Target Species:	Human	Weeks/Year:	52	Days/Week:	7
Route:	Food			Hours/Day :	24

Animal to human conversion method: MG/M^2 SURFACE AREA/DAY

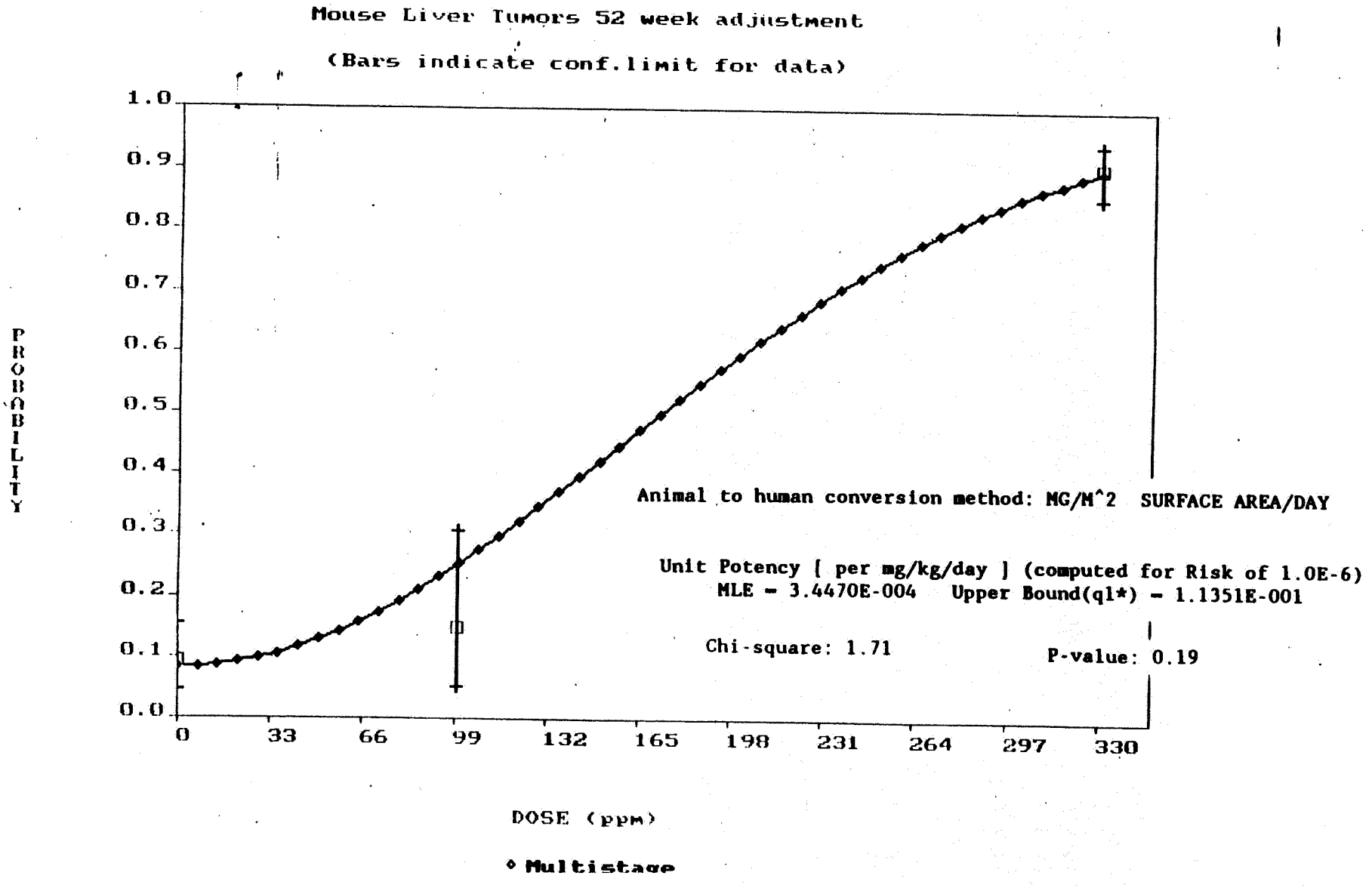
Unit Potency [per mg/kg/day] (computed for Risk of 1.0E-6)
MLE = 3.4470E-004 Upper Bound(q1*) = 1.1351E-001

Dose Estimates (ppb)

Extra Risk	95.0% Lower Bound	MLE
1.0000E-006	4.4050E-001	1.4506E+002
1.0000E-005	4.4047E+000	4.5871E+002

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Pooled Data) from the NTP Study.
Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.



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Attachment No. 4.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Diagonal Data) from the NTP Study.

Caswell No. 443AA

From: Hugh M. Pettigrew, Ph.D. H.M. Pettigrew 11/13/91
Science Support and Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

To: Albin Kocialski, Ph.D., Head
Registration Standards Section
Health Effects Division (H7509C)

Thru: Kerry Dearfield, Ph.D., Acting Head Kerry L Dearfield 11.13.91
Science Support and Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Summary

The unit risk, Q_1^*, of Ethylene thiourea derived by applying the linearized multistage procedure to the incidences of combined hepatocellular adenoma/carcinoma in groups of female $B_6C_3F_1$ mice along the diagonal in the NTP study is

$$Q_1^* = 1.6 \times 10^{-1} (mg/kg/day)^{-1}$$

in human equivalents. This estimate was derived using actual food consumption and body weight data from the NTP study. The interspecies scaling factor was based upon the ratio of human to laboratory animal body weights raised to the one-third power.

Background

The Q_1^* for Ethylene thiourea is based on the NTP $B_6C_3F_1$ mouse study. The following table summarizes the design of the study and the results. [For full details, see HED Memorandum "Third Peer Review of ETHYLENE THIOUREA. Selecting the Q_1^* for Ethylenethiourea [ETU]", dated 9/26/91.] The numerators are the numbers of animals having either hepatocellular adenoma or carcinoma and the denominators are the numbers of animals surviving 52 weeks or longer.

F_0 Dose (ppm)	F_1 Dose (ppm)			
	0	100	330	1000
0	4/49		44/50	48/49
33		4/27		
100			46/50	
330	5/49		46/50	49/49
Pooled	9/98	4/27	136/150	97/98

Following the suggestion of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) meeting on September 18, 1991, the linearized multistage model was fit to the groups along the diagonal of the design matrix, (i.e., those groups receiving 0-0, 33-100, 100-330 and 330-1000 ppm.) This resulted in a statistically acceptable fit : Chi-square =0.00, P-value =1.00.) and resulted in a Q_1^* of 0.16.

These results were obtained by applying the multistage model using the TOX_RISK (**Tox**icology **Risk** Assessment Program) Version 3 developed by Kenny S. Crump et al. The details are provided on the attached copy of printout from the program.

FILE NAME : C:\TOXVER3\FINAL.TXS\DIAG.TXD

TITLE : Female Mouse Liver 52 week adj. diagonal
CHEMICAL
MOLECULAR WT. : 102
SPECIES : MOUSE
ROUTE/DOSE UNITS: FOOD (ppm)

DOSE	RESPONDERS / NUMBER	DOSE	RESPONDERS / NUMBER	DOSE	RESPONDERS / NUMBER
0	4 /49		/		/
100	4 /27		/		/
330	46 /50		/		/
1000	49 /49		/		/
	/		/		/
	/		/		/

WEEKS OF STUDY: 104

ADJUSTMENT FACTOR FOR EXPER. LENGTH : 1.0

EXPERIMENTAL SPECIES :			DOSING :	
BODY WEIGHT	: .0343	kg	WEEKS	: 104
LIFE-SPAN	: 104	weeks	DAYS/WEEK	: 7
BREATHING RATE	: .0347	l/min	HOURS/DAY	: 24
FOOD CONSUMPTION	: 5.7	g/day	AVERAGING FACTOR	: 1.0
DRINKING RATE	: 6	ml/day		

********** NOTES **********

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Diagonal Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Female Mouse Liver 52 week adj. diagona

Model: Multistage Dataset: C:\TOXVER3\FINAL.TXS\DIAG
Functional form: 1 - EXP(-Q0 - Q1 * D - Q2 * D^2 ... - Qk * D^k)
Chi-square: 0.00 P-value: 1
Parameter Estimates : k = 3
Q 0 = 8.515781E-002
Q 1 = 8.256468E-007
Q 2 = 1.032667E-006
Q 3 = 6.477560E-008

Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits Lower	Upper
0	4 / 49	4.00	1.397	8.683
100	4 / 27	4.00	1.413	8.316
330	46 / 50	46.00	41.326	48.616
1000	49 / 49	49.00	46.091	49.000

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Diagonal Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Female Mouse Liver 52 week adj. diagona

Dataset: C:\TOXVER3\FINAL.TXS\DIAG

Exposure Pattern

Model:	Multistage	Age Begins: 0	Age Ends: 70
Target Species:	Human	Weeks/Year: 52	Days/Week: 7
Route:	Food		Hours/Day : 24

Animal to human conversion method: MG/M^2 SURFACE AREA/DAY

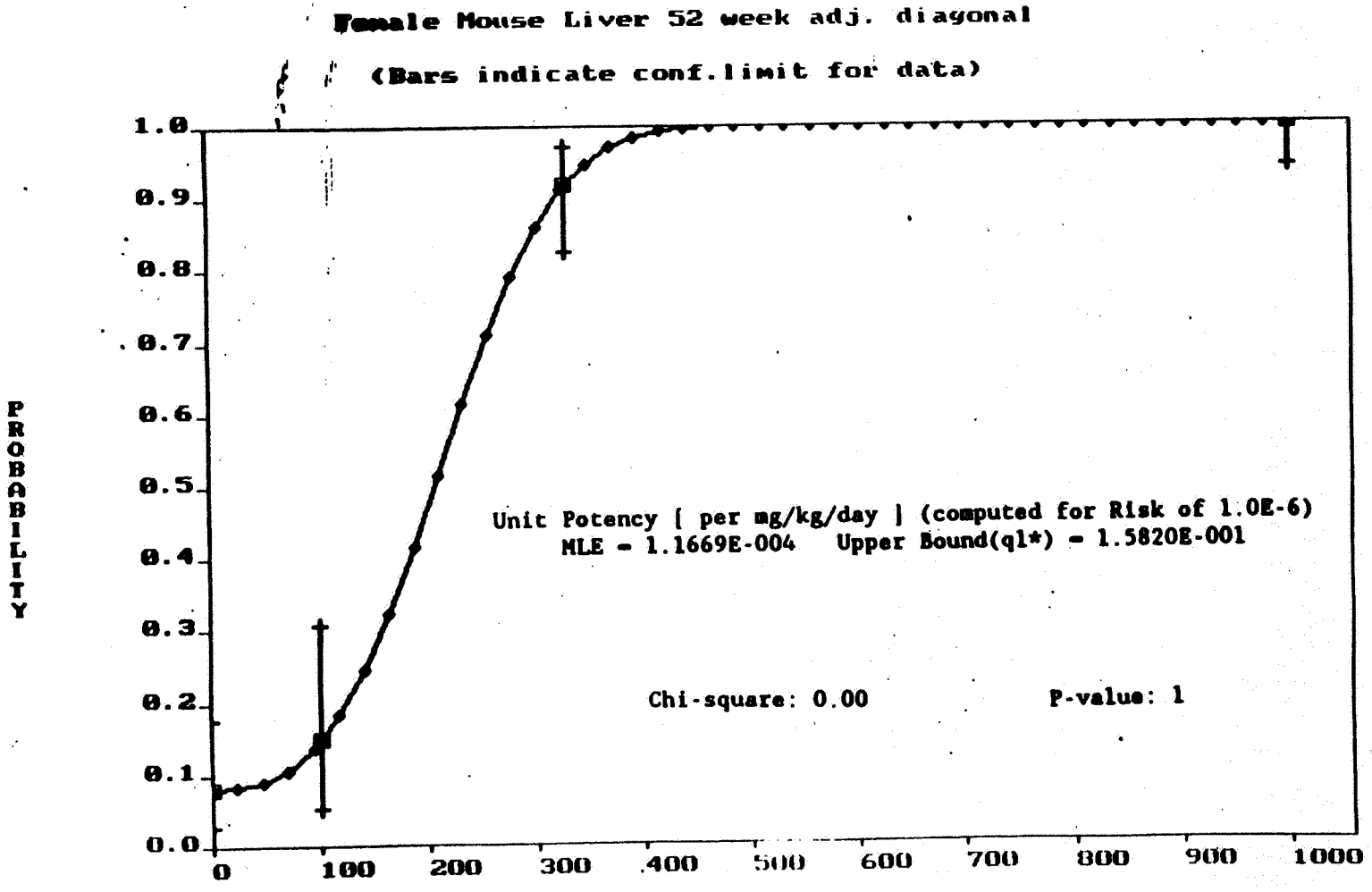
Unit Potency [per mg/kg/day] (computed for Risk of 1.0E-6)
MLE = 1.1669E-004 Upper Bound(q1*) = 1.5820E-001

Dose Estimates (ppb)

Extra Risk	95.0% Lower Bound	MLE
1.0000E-006	3.1605E-001	4.2848E+002
1.0000E-005	3.1605E+000	1.6798E+003

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Diagonal Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.

Ethylene thiourea [ETU] - Q_1^* Calculation based on Female Mouse Liver Tumors (Diagonal Data) from the NTP Study. Memorandum of 11/13/91 from Hugh M. Pettigrew, PhD, to Albin Kocialski, PhD.



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