Mobil Oil Corporation

ENVIRONMENTAL HEALTH
AND SAFETY DEPARTMENT
P.O. BOX 1031
PRINCETON, NEW JERSEY 08543

April 8, 1993

Mary Paxton
American Petroleum Institute
1220 L Street, Northwest
Washington, DC 20005

Dear Mary,

As agreed at the last Benzene Task Group meeting, I have reworked the table of risk calculations in which I attempted to recapitulate Kenny's numbers for a variety of models. The enclosed two-page Table gives Kenny's results for a full set of models, with restricted assumptions such as L = 5 in cumulative risk situations, all leukemia and AMMLs.

All of the output is based upon the Paustenbach exposure assumptions. In addition, the Table shows my calculations for a representative sub-set of the output. With no exceptions the Crump calculations and the Craig calculations coincide, within a few percentage points of difference. The Table permits a clear appreciation of the influence of model choice and effect of interest, leukemias or AMML.

It is clear from the Table that the choice of target tumor does not greatly influence the imputed risk, in the any of the models or any of the exposure scenarios explored here. Choice of exposure metric also has minimal influence, except in the case of its combination with multiplicative models. In that circumstance the attributed risks are greater in comparison to analogous model-metric combinations. Perhaps the most striking disparities are between the inside non-linear models and all the other outputs.

There are, I think, a number of questions which deserve exploration. Kenny has briefly looked at the relative merit of models and metrics using maximum likelihood estimates as criteria. There surely is a great deal more to say about that. To begin that discussion, I enclose four (4) graphs of the hazard functions from selected models. In Crump's parlance, these are $H(0)_i$ (unexposed) and $H(1)_i$ (exposed). The hazard function is of interest because it illustrates the direct play of the exposure metric and risk model upon the background rate

of the target disease. Two exposure scenarios are represented in the graphs; one is the typical industrial exposure as in Kenny's paper, and the other is an approximately equivalent exposure (in terms of time times concentration), 10 ppm for five years of life. It is obvious in the graphs, I think, why the combination of cumulative exposure metric and multiplicative risk model yields high estimates of attributed risk.

I hope we can get Kenny to reconsider the decision he made to rework his API report a little bit and submit it for publication as an "update of 1984 work". Thousands of man hours and millions of dollars have been devoted to assembling the most accurate possible cancer incidence and exposure data for this Cohort. There will be no better basis for evaluating benzene risks in exposed workers for a long time to come, if ever. The paper needs to provide sufficient information and context that those who would use the risk calculations will not feel compelled to do what the EPA did in 1985: take the geometric mean of a series of model outputs and multiply by a fudge factor.

In a paper which attempts to portray a modern and effective picture of benzene risks, it is important to explain the exposure metrics, the risk models and the combinations among them from the standpoint of how they work and how that relates to reality. Does choice of model influence choice of metric, or vice versa? How well do model/metric characteristics reflect biological phenomena, or perhaps just plain biological common sense? Alternatively, are there some model/metric characteristics which do not make biological sense? Kenny describes the inside and outside variations on non-linear models as being different ways of describing the data mathematically, yet there are very large differences between the two. We most certainly need a better explanation and understanding of that. There is an almost irresistible temptation for anyone reading the paper to look at the risk numbers at the end and then choose model and metric which yield the numbers that suit his purposes best, or are most politically acceptable. The paper should give enough information about metrics and models so there is a rational alternative to that.

Perhaps you would be kind enough to send a copy of this to the Benzene Task Group. I have already sent a copy to Kenny in Louisiana.

Best Regards,

P. H. Craig

040793.phc
Attachment

cc: C. J. DiPerna
K. Crump

Crump's Estimated Additional Lifetime Risks Due to Benzene*

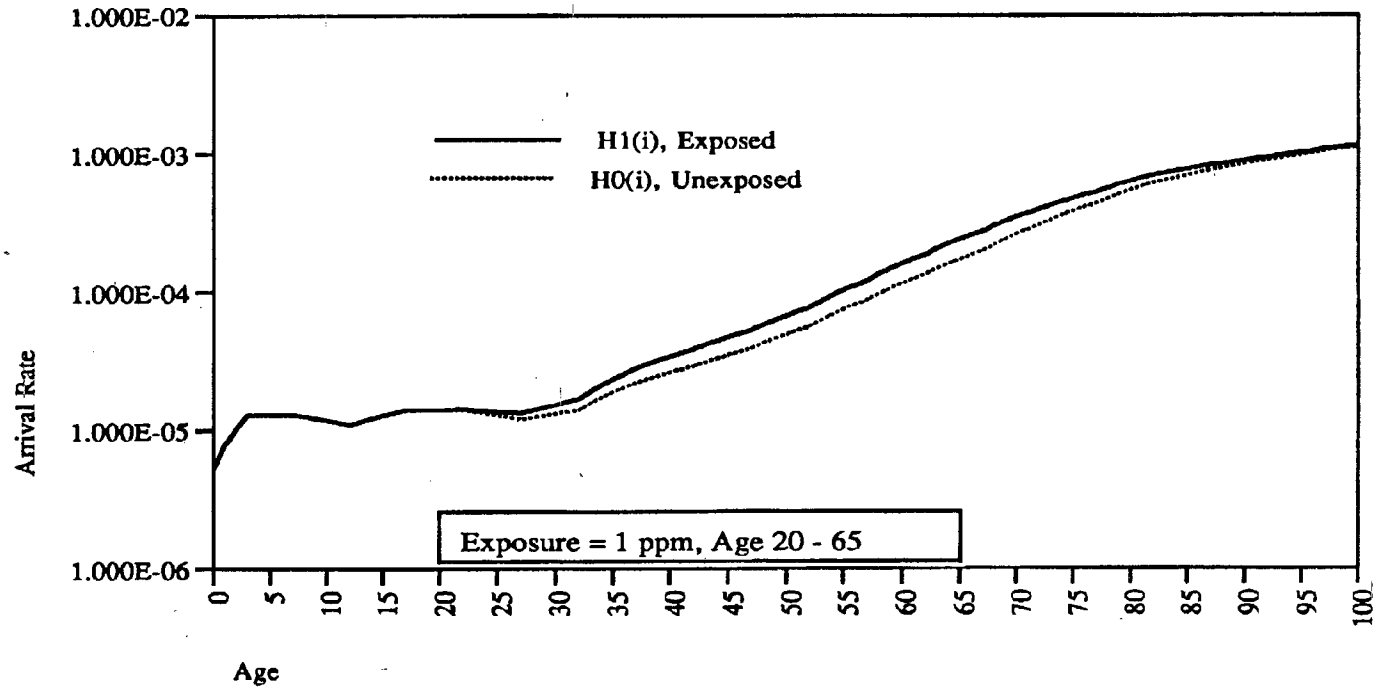
Model		AMMLs			Leukemias		
		1 ppb Contin x 10E-4	1 ppm Contin x 10E-4	1 ppm Occup x 10E-4	1 ppb Contin x 10E-4	1 ppm Contin x 10E-4	1 ppm Occup x 10E-4
Linear Models							
Weighted	kc	**0.072**	**71**	**15**	**0.10**	**99**	**19**
Additive	pc		73	15		101	20
Linear	kc/pc		0.97	1.00		0.98	0.97
Weighted	kc	**0.078**	**77**	**17**	**0.10**	**83**	**17**
Multiplicative	pc						18
Linear	kc/pc						0.97
Cumulative	kc	**0.100**	**99**	**18**	**0.10**	**99**	**18**
Additive	pc						18
Linear	kc/pc						1.02
Cumulative	kc	**0.130**	**120**	**26**	**0.15**	**150**	**31**
Multiplicative	pc						33
Linear	kc/pc						0.94
Non-Linear Models							
Weighted	kc	**0.005**	**16**	**1.7**	**0.04**	**35**	**7.2**
Additive	pc	0.005	17	1.8	0.04	36	7.6
Outside	kc/pc	0.98	0.95	0.97	0.97	0.96	0.95
Weighted	kc	**0.036**	**36**	**7.5**	**0.03**	**32**	**5.6**
Multiplicative	pc			7.60			5.8
Outside	kc/pc			0.99			0.97
Cumulative	kc	**0.014**	**36**	**3.4**	**0.02**	**36**	**3.5**
Additive	pc	0.015	38	3.5	0.02	37	3.6
Outside	kc/pc	0.95	0.94	0.96	0.99	0.97	0.97

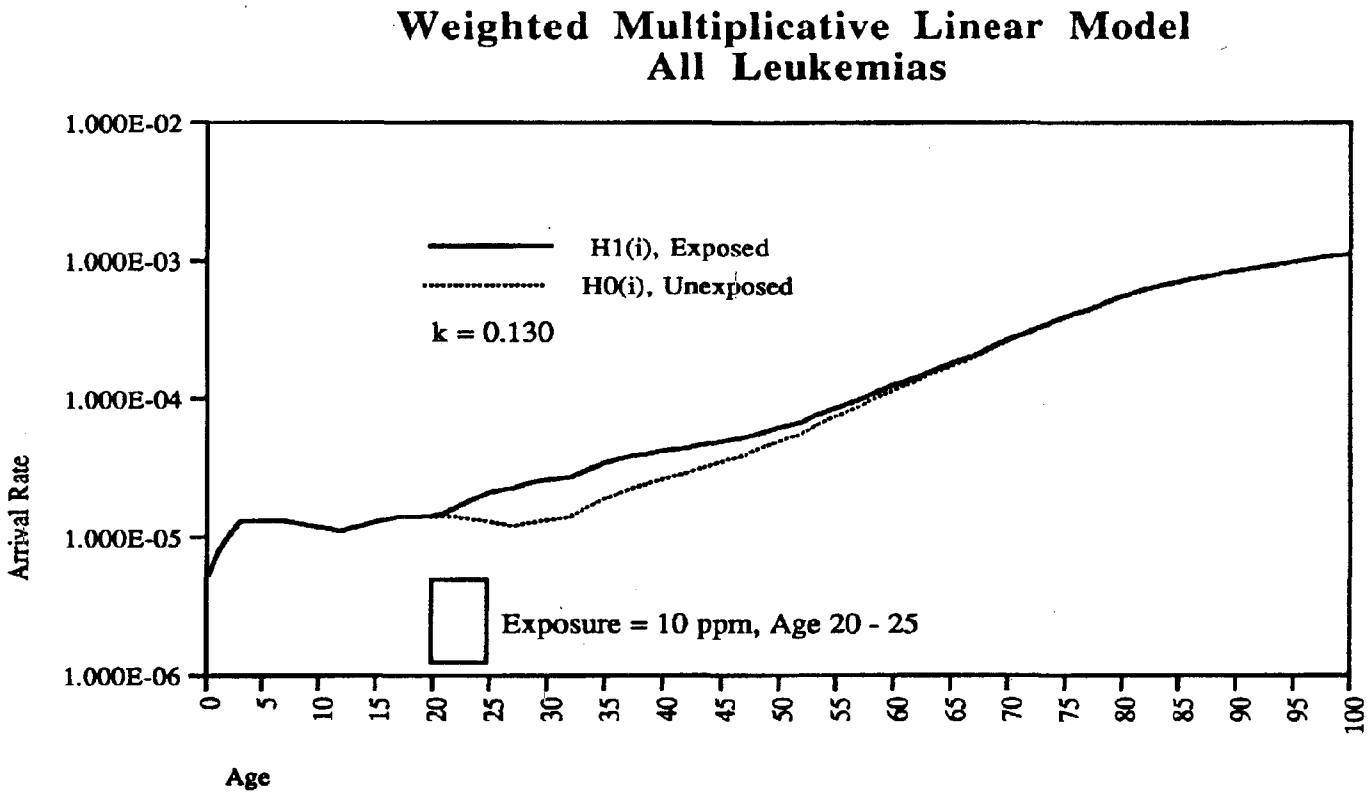
Non-Linear Models (con't)							
Cumulative	kc	**0.044**	**65**	**10.0**	**0.14**	**140**	**29**
Multiplicative	pc	0.044	65	10.0	0.14	139	28
Outside	kc/pc	1.01	1.00	1.00	1.01	1.00	1.02
Weighted	kc	**0.00000086**	**0.86**	**0.18**	**0.00000120**	**1.2**	**0.23**
Additive	pc						0.24
Inside	kc/pc						0.96
Weighted	kc	**0.00000097**	**0.97**	**0.20**	**0.00000100**	**1.0**	**0.22**
Multiplicative	pc						0.22
Inside	kc/pc						1.00
Cumulative	kc	**0.00000120**	**1.2**	**0.21**	**0.00000120**	**1.2**	**0.22**
Additive	pc						0.22
Inside	kc/pc						1.01
Cumulative	kc	**0.00000140**	**1.4**	**0.30**	**0.00000170**	**1.7**	**0.36**
Multiplicative	pc						0.35
Inside	kc/pc						1.03

Mobil EHSD
04-06-93

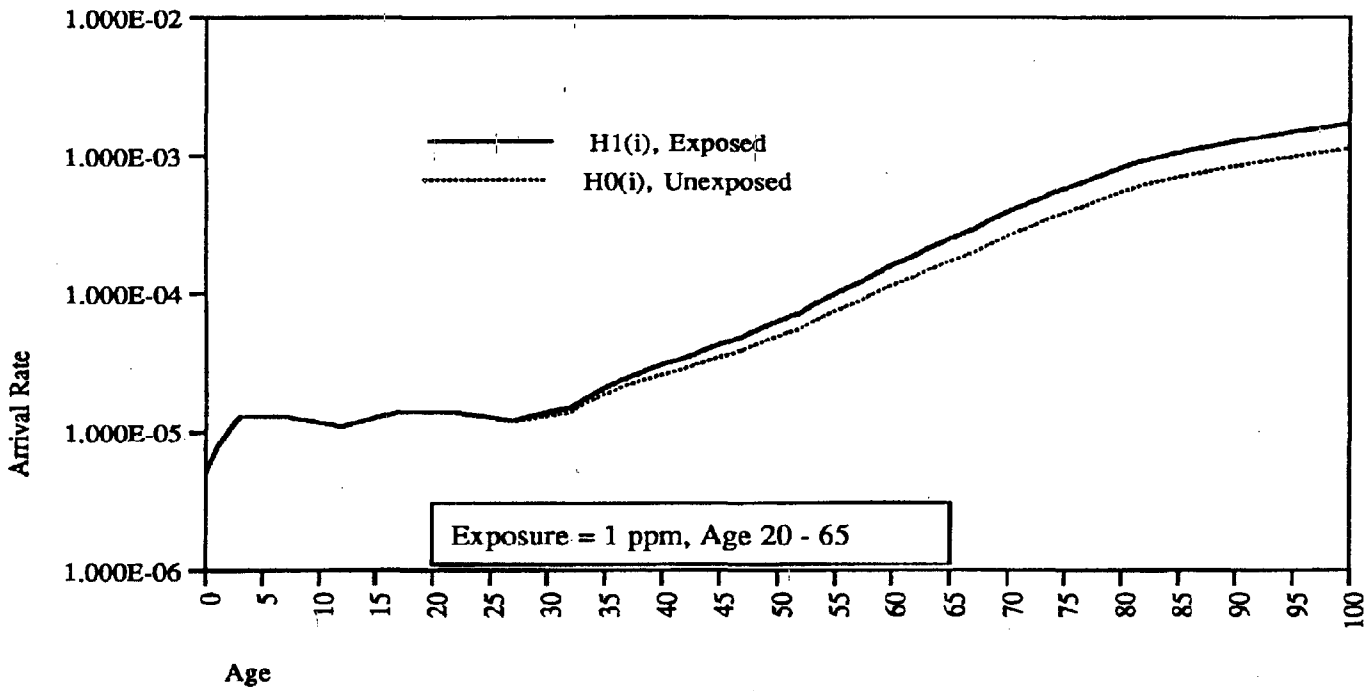
* Paustenbach exposure estimates, risk models by K. Crump (kc)
For all models with cumulative exposure, Lag = 5 years
For models with weighted exposure, k varies from 0.05 to 0.175
Recapitulated calculations of selected models by P. Craig (pc)

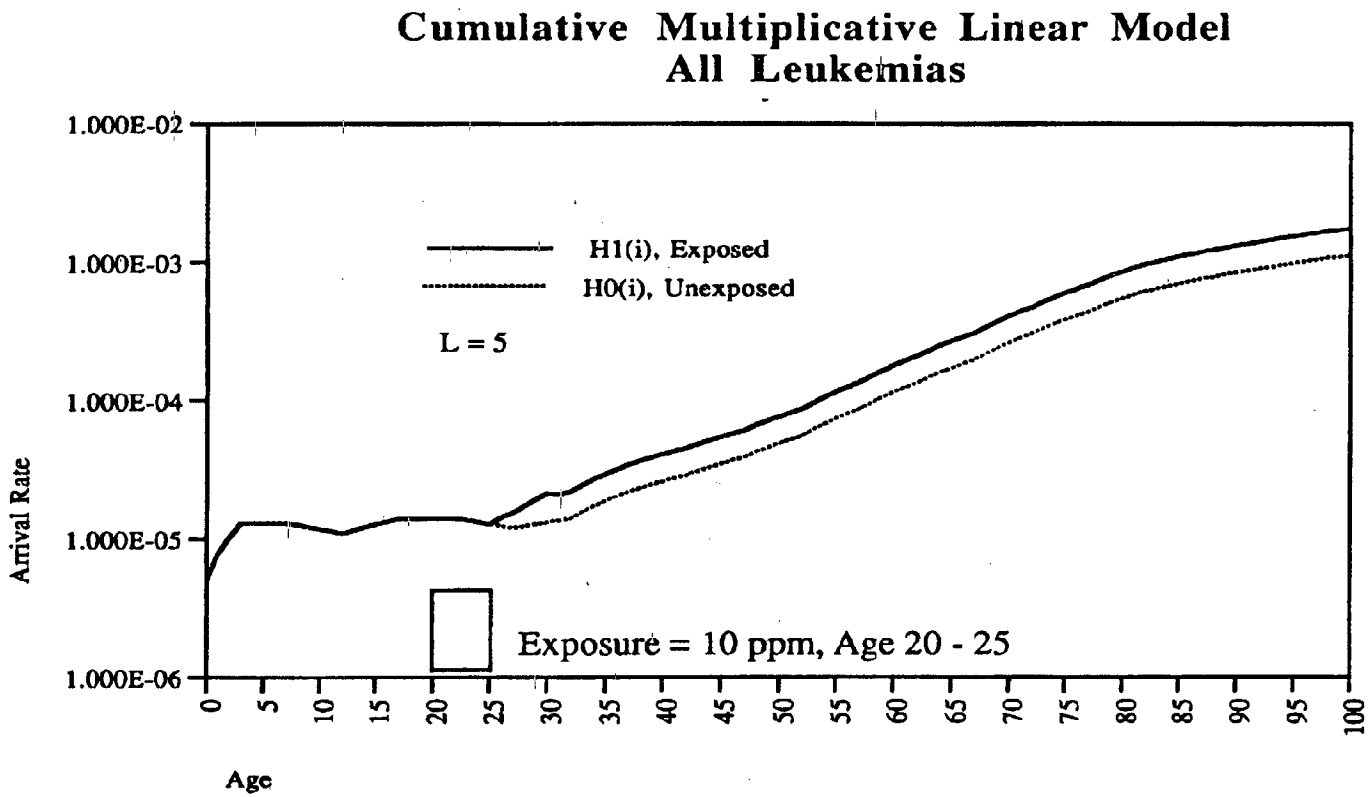
Weighted Multiplicative Linear Model




Weighted Multiplicative Linear Model
All Leukemias
1.000E-02
1.000E-03
1.000E-04
1.000E-05
1.000E-06
Arrival Rate
H1(i), Exposed
H0(i), Unexposed
k = 0.130
Exposure = 10 ppm, Age 20 - 25
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
Age

Cumulative Multiplicative Linear Model




Cumulative Multiplicative Linear Model
All Leukemias
1.000E-02
1.000E-03
1.000E-04
1.000E-05
1.000E-06
Arrival Rate
H1(i), Exposed
H0(i), Unexposed
L = 5
Exposure = 10 ppm, Age 20 - 25
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
Age