



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Amitrole - Quantitative Risk Assessment based on FDRL
Lifetime Pulse Feeding Study in F 344 Rats

CAS Number 61-82-5

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Summary

"The Health Effects Division Peer Review Committee met on August 1 and November 21, 1990, to discuss and evaluate the weight-of-the-evidence on Amitrole with particular reference to its carcinogenic potential. The Committee concluded that Amitrole should be classified as a Group B₂, Probable Human Carcinogen, and recommended that the low dose extrapolation multi-stage model, based on the thyroid tumors in the rat (Johnson '81 study) be used for the quantification of human risk (Q₁*)." (Draft Memorandum from E. Rinde to J. Yowell, 3rd and 4th Peer Review of Amitrole, 1/16/91.)

The unit risk, Q₁*, of Amitrole in human equivalents is:

$$Q_1^* = 1.13 \text{ (mg/kg/day)}^{-1}$$

This estimate is the geometric mean of estimates computed separately for male and female rats.

Dose-Response Analysis

The calculations of the unit risk, Q_1^* , were performed using a computer program provided by K. Crump (TOX_RISK Version 3). The Global multi-stage model was fit to the combined thyroid follicular cell tumor data (adenomas and/or carcinomas) in male and female F 344 rats in Johnson Study (Johnson, W.D., Becci, P.J., Parent, R.A. (1981), Lifetime Feeding Study of Amitrole in Fischer 344 Rats. Laboratory No.5651. Unpublished study prepared by Food and Drug Research Laboratories, Inc.; submitted by Union Carbide Agricultural Products Co., Ambler, PA.)

The multi-stage model was fit separately to the males and females, i.e., two Q_1^* 's were calculated. The input data were the proportions of animals in the Lifetime Study developing thyroid follicular cell adenomas and/or carcinomas. The experimental groups included were the control group and the low-, mid-, and high-dose pulsed groups. The dosing regimen and the computation of the "effective" doses, i.e., the equivalent continuous doses in ppm which would yield the same total intakes of compound over the course of the study, are given in Tables 1 and 2 below..

The resulting estimates of risk were

Females: $Q_{1F}^* = 8.78 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$

Males: $Q_{1M}^* = 1.46 \text{ (mg/kg/day)}^{-1}$

These were combined by taking the geometric mean to obtain

$$Q_1^* = 1.13 \text{ (mg/kg/day)}^{-1}$$

Table 1

Dosing Schedule (ppm) [- indicates standard lab chow]

Weeks	Control	Low Dose	Mid Dose	High Dose	Continuous Dose
0-3	-	1	3	10	5
4-7	-	-	-	-	5
8-11	-	1	3	10	5
12-15	-	-	-	-	5
16-19	-	1	3	10	5
20-23	-	-	-	-	5
24-27	-	1	3	10	5
28-31	-	-	-	-	5
32-35	-	1	3	10	5
36-39	-	-	-	-	5
40-43	-	20	60	200	100
44-47	-	-	-	-	100
48-51	-	20	60	200	100
52-55	-	-	-	-	100
56-59	-	20	60	200	100
60-63	-	-	-	-	100
64-67	-	20	60	200	100
68-71	-	-	-	-	100
72-75	-	20	60	200	100
76-79	-	-	-	-	100
80-83	-	20	60	200	100
84-87	-	-	-	-	100
88-91	-	20	60	200	100
92-95	-	-	-	-	100
96-99	-	20	60	200	100
100-103	-	-	-	-	100
104-107	-	20	60	200	100
108-111	-	-	-	-	100
112-115	-	20	60	200	100
116-119	-	-	-	-	100

Table 2

Average Dose Computations to Terminal Sacrifice

	Dose x Time (ppm) (weeks)		Total Dose (ppm-weeks)		Average* Males	Dose (ppm) Females
Low Dose	1	x 20	=	20	7.07	6.83
	20	x 40	= +	<u>800</u> 820		
Mid Dose	3	x 20	=	60	21.2	20.5
	60	x 40	= +	<u>2400</u> 2460		
High Dose	10	x 20	=	200	70.7	68.3
	200	x 40	= +	<u>8000</u> 8200		

* Average = Total Dose/116 weeks (males)
 = Total Dose/120 weeks (females)

Amitrole Male Rat Thyroid 116 Weeks

Model: Multistage Dataset: C:\TOXVER3\AMITROLE.TXS\MRTHY2
 Functional form: $1 - \text{EXP}(-Q_0 - Q_1 * D - Q_2 * D^2 \dots - Q_k * D^k)$
 Chi-square: 3.33 P-value: 0.07
 Parameter Estimates : k = 3

Q 0 = 1.204483E-002
 Q 1 = 4.060730E-003
 Q 2 = 3.424983E-004
 Q 3 = 0.000000E+000

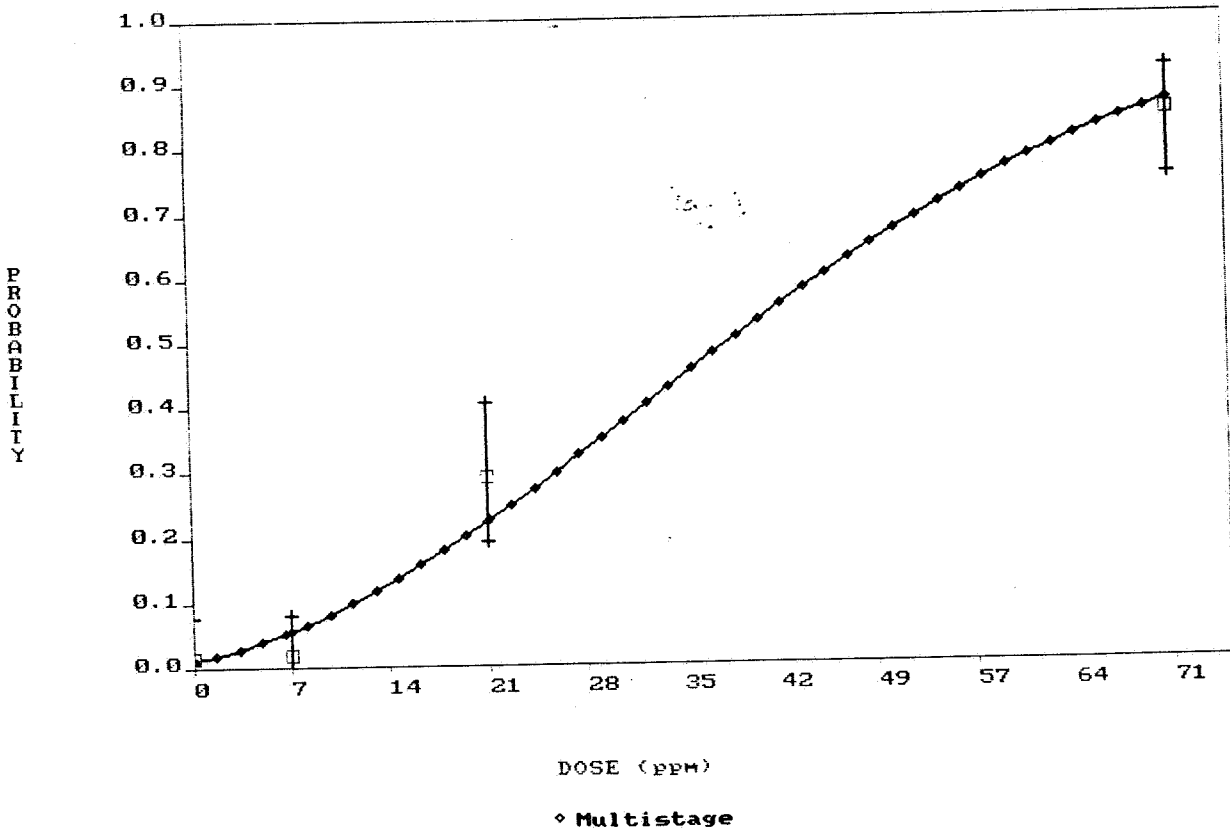
Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits	
			Lower	Upper
0	1 / 60	0.72	0.070	4.592
7.07	1 / 57	3.21	0.067	4.584
21.20	16 / 55	12.25	10.581	22.403
70.70	51 / 60	51.97	45.172	55.207

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/M² SURFACE AREA/DAY

Unit Potency [per mg/kg/day] (computed for Risk of 1.0E-6)
 MLE = 4.5428E-001 Upper Bound(ql*) = 1.4563E+000

Amitrole Male Rat Thyroid 116 Weeks
 (Bars indicate conf. limit for data)



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Amitrole Female Rat Thyroid 120 Weeks

Model: Multistage

Dataset: C:\TOXVER3\AMITROLE.TXS\FRTHY2

Functional form: $1 - \text{EXP}(-Q_0 - Q_1 * D - Q_2 * D^2 \dots - Q_k * D^k)$

Chi-square: 0.00

P-value: 1

Parameter Estimates : k = 3
 Q 0 = 0.000000E+000
 Q 1 = 1.183126E-003
 Q 2 = 2.179817E-004
 Q 3 = 1.389706E-006

Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits	
			Lower	Upper
0	0 / 52	0.00	0.000	2.911
6.83	1 / 54	1.00	0.063	4.576
20.50	6 / 50	6.00	2.575	11.133
68.30	44 / 56	44.00	37.870	48.796

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/M² SURFACE AREA/DAY

Unit Potency [per mg/kg/day] (computed for Risk of 1.0E-6)
 MLE = 1.3238E-001 Upper Bound(q1*) = 8.7801E-001

Amitrole Female Rat Thyroid 120 Weeks
 (Bars indicate conf. limit for data)

