

US EPA ARCHIVE DOCUMENT



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

FILE COPY

MAR 22 1991

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

From: Hugh Pettigrew, Ph.D., Statistician *Hugh Pettigrew 3/22/91*
Science Support Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

To: Larry Dorsey
Science Support Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Thru: Esther Rinde, Ph.D., Acting Head *E. Rinde 3/22/91*
Science Support Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

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 (Q_1)." (Draft Memorandum from E. Rinde to J. Yowell, 3rd and 4th Peer Review of Amitrole, 1/16/91.)

The unit risk, Q_1^* , 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 Unpublished study prepared by Food and Drug Research Laboratories, Inc.; submitted by Union Carbide Agricultural Products Co., Ambler, PA.)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 |

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

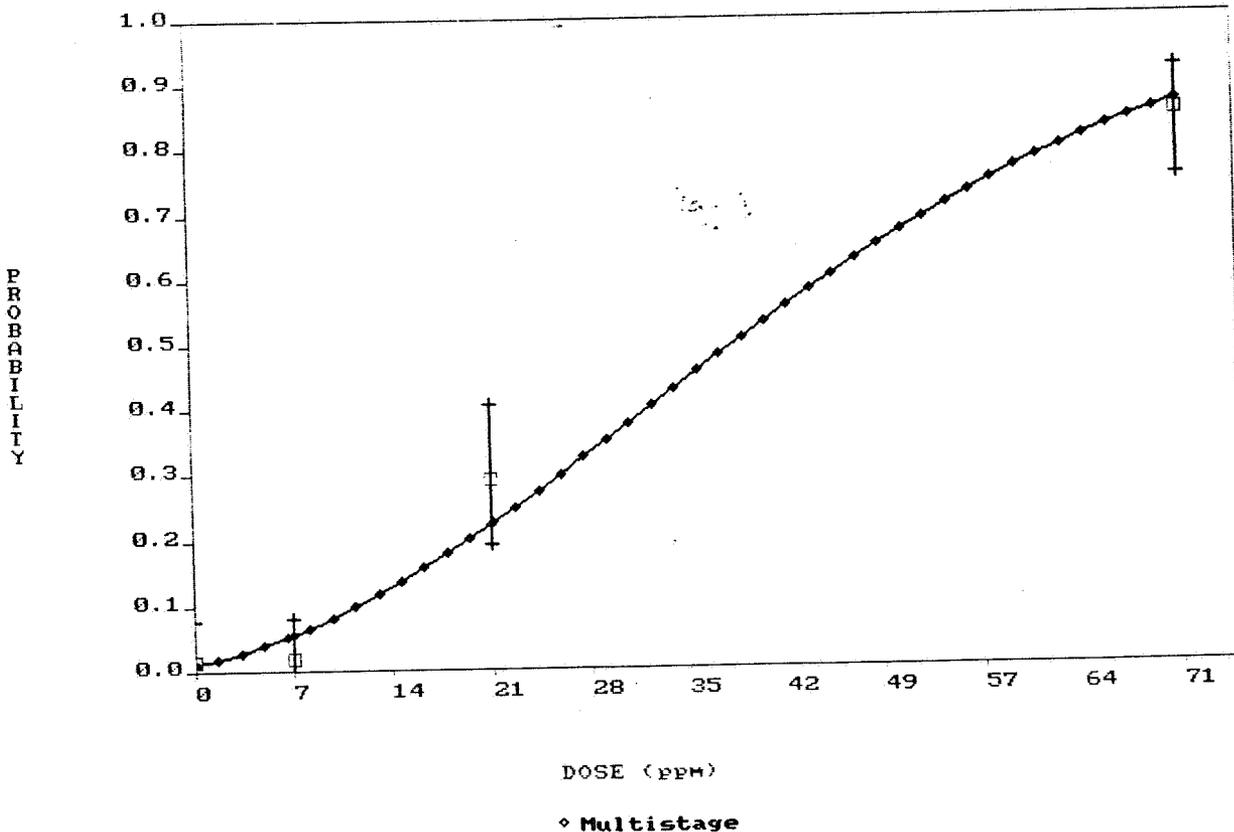
| Experimental Doses (ppm) | #responses/ #subjects | Expected number of responders | 90.0% Binomial Limits | |
|--------------------------|--------------------------|-------------------------------|-----------------------|--------|
| | | | Lower | Upper |
| 0 | 1 / 60 | 0.72 | 0.070 | 4.592 |
| 7.07 | 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)



5

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/M^2 SURFACE AREA/DAY

Unit Potency [per mg/kg/day] (computed for Risk of $1.0E-6$)
 MLE = $1.3238E-001$ Upper Bound(q_1^*) = $8.7801E-001$

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

