CA Site 6-5-85

7595 / Linuron SC

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Linuron, Calculation of Risk Assesment for use on Crops

TO: Ingrid Sunzenauer
Special Review Branch
Registration Division (TS-767C)

6/5/85

FROM: Robert P. Zendzian PhD, Acting head
Review Section IV
Toxicology Branch
HED (TS-769)

and

William Burnam, Deputy Chief
Toxicology Branch

6-5-85

THROUGH: Theodore M. Farber PhD, Chief
Toxicology Branch

Compound Linuran Tox Chem #528

Action Requested

A. Determine the systemic dose of linuron for the 36 field exposure scenarios presented in the documents listed below.

B. Calculate an oncogneic risk assesment for the 36 field exposure scenarios.

1. Memo, Lunchick to Sunzenauer, Linuron Turf Exposure with protective clothing 5/20/85

2. Document, by Lunchick untitled and undated re exposure during application to soybeans

3. Draft Memo, Lunchick, Commercial Ground Application of Linuron to Corps, undated

4. Draft Memo, Private Ground Application of Linuron to Vegetables, undated

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5. Memo, Lunchick to Sunzenauer, Exposure Estimates for the Application of Linuron to Rights-of-Way, 3/26/85.

Discussion

The calculated lifetime risk assesments range from 1 X $10^{-4}$ to 1 X $10^{-6}$ and are detailed in Table 2 .

Discussion

The exposure of field workers to linuron during application to crops is essentially all by the dermal route. Mr Lunchick of Exposure Assesment Branch has prepared a set of 36 exposure scenarios which cover the major patterns of pesticide exposure for these workers. Table 1 presents the dermal dose in mg/kg/day, the daily duration of exposure in hours and the yearly dermal dose in mg/kg/year for each scenario from the referenced documents. From this data a systemic dose is calculated utilizing data developed in a dermal absorption study of linuron in the rat.

The appropriate rate of absorption will be taken from the results of the rat dermal absorption study submitted by the Registrant, du Pont. The values utilized are taken from Table D from the DER by Zendzian on this study.

Table D. Percentage of applied radioactivity absorbed as a function of time corrected for outlying values. Total of blood, urine and feces. (mean of 4 animals)

| Time (hours) | 0.5 | 1.0 | 2.0 | 4.0 | 10 |
|---|---|---|---|---|---|
| Dose mg/rat (Female,Male) | | | | | |
| 0.12 F | 0.8 | 2.1[a] | 3.4 | 6.2 | 13.9 |
| 0.12 M | 0.7 | 2.7 | 5.3 | 9.0 | 18.1 |
| 1.00 M | 0.2 | 0.3[b] | 2.1 | 2.8 | 14.5 |
| 7.4 M | <0.1 | 0.1 | 0.7 | 1.5 | 2.5 |

a.mean of 3 urine and 3 fecal values
b.mean of 2 urine and 3 fecal values

Only the values for male animals will be used. The doses listed in the table are each applied to the same area of skin on the individual rats (4 $in^2$) and it is necessary to determine the dose per 4 $cm^2$ of skin for each field worker scenario. This transformation is made by assuming that the area of human skin exposed is 260 $in^2$ and dividing each individual daily dose by 65. These values are presented in table 1 as 'mg/unit skin area'.

The dose per unit area and the duration of exposure are used to determine the percent of absorption from the rat data. Most of the values of dose per unit area fall well below the lowest dermal dose given in the rat study (0.12mg/unit area). Since the percent of the dose absorbed increases with decreasing dose it is necessary to estimate a percent of absorption for the lower doses from the data of the rat study. For this purpose the data from Table D are plotted as log of dose against log of percent absorbed for each duration of dosing (figure 1). Experience with data generated by the rat dermal absorption study had shown that such a plot usually produces a family of curves that approximate straight lines and are parallel. The data from the linuron rat study reasonably approximate this pattern.

In determining which curve to use for a particular exposure duration, percent absorption is read directly from the respective curve for 0.5, 1.0 and 10 hours. Absorption rates for 10.5 hours are read from the 10 hour curve. Absorption rates for 4.8 and 6 hours are read from the 4 hour curve and multiplied by 1.25 and 1.5 respectively. The absorption rate for 8 hours is read from the 10 hour curve and multiplied by 0.8. Note that the figure included in this document has been reduced (75& reduction) but all absorption values were read from the origional unreduced graph.

The rates determined in this manner assume that the full dose of linuron is placed on the skin at the beginning of the exposure period to be absorbed for the whole duration of exposure. This is patently not true particularly in the case of the extended exposure of the applicator. This makes a significant difference only in the case of the applicator and a correction factor will be applied. When one assumes that the linuron falls randomly onto the skin over the full period of exposure an integral function can be derived that defines the limit of absorption under these conditions (Lacayo, pers comm). This function can be reasonably approximated by determining the absorption under the single dose conditions and dividing it by two (the correction factor). This correction is shown in Table 1 where the % Abs is given as X/2.

The systemic dose for those scenarios which involve one person in mixing, loading and application is determined by simply adding the systemic doses for the applicable parts of the work.

Although it has not been entered into these calculations, the rat skin is usually considered to be five times more premeable to foreign compounds than the human skin. Thus the human dose, and the oncogenic risk, can be considered as one/fifth that calculated in this document.

The $Q_1^*$ ($0.33 mg/kg/^{-1}$) for oncogenic risk was obtained from the results of a lifetime feeding study in rats. A dose-related increase in testicular tumors was observed in this study.

Determination of "Lifetime oncogenic risk" is shown on Table 2. The systemic dose (mg/kg/yr) from Table 2 is divided by 365 to provide the 'Annulized Dose' (mg/kg/day). This dose is multiplied by 30/70 (years working/years of life) to provide the 'Lifetime Daily Dose' (mg/kg). This dose is multiplied by the $Q_1^*$ ($0.33 mg/kg/^{-1}$) to provide the 'Lifetime Risk'.

cc Anne Barton
Amy Rispin
Robert Taylor

Reference

DER by Zendzian on,
Dermal absorption of [$^{14}C$] linuron in the Lorox® L formulation by the Rat, J.J. Anderson, du Pont, Document No. AMR-259-84, undated, accession #255148.

Table 1. Determination of systemic dose from exposure estimates and dermal absorption.

| Source of Exposure Data[a] | | Exposure | | | | Dose | |
|---|---|---|---|---|---|---|---|
| | Type | mg/kg/day | hr/day | mg/kg/ year | mg/unit skin area | % Abs | systemic dose mg/kg/yr |
| Memo Turf 5/20/85 | M, L & apply | 4.5 | 8 | 37.00 | 5.25 | 2.0/2 | 0.370 |
| Document 1 Private Soybeans | M/L pre emergence | 0.063 | 0.5 | 0.380 | 0.074 | 0.9 | 0.003 |
| 2 | M/L post emergence | 0.083 | 0.5 | 0.500 | 0.097 | 0.8 | 0.004 |
| 3 | App pre emergence | 0.011 | 4.8 | 0.068 | 0.013 | 15/2 | 0.005 |
| 4 | App post emergence | 0.004 | 4.8 | 0.023 | 0.004 | 24/2 | 0.003 |
| 5 | pre-emergence M/L and applicator add 1 & 3 | | | 0.450 | N/A | N/A | 0.007 |
| 6 | Pre & post emergence M/L and applicator add 2[b], 3 & 4 | | | 0.590 | N/A | N/A | 0.015 |
| 7 | Pre & post emergence M/L equals 2[b] | | | 0.500 | N/A | N/A | 0.007 |
| 8 | Pre & post emergence Applicator add 3 & 4 | | | 0.091 | N/A | N/A | 0.008 |
| Draft Memo To crops | Commercial Soybeans | | | | | | |
| 1 | Average M/L | 0.022 | 1 | 0.330 | 0.027 | 8.5 | 0.028 |
| 2 | High M/L | 0.220 | 1 | 3.300 | 0.257 | 1.3 | 0.142 |
| 3 | Average applicator | 0.007 | 10.5 | 0.110 | 0.008 | 67/2 | 0.037 |
| 4 | High applicator | 0.032 | 10.5 | 0.470 | 0.037 | 31/2 | 0.073 |
| 5 | Average M/L & Applicator add 1 & 3 | | | 0.440 | N/A | N/A | 0.065 |
| 6 | High M/L & Applicator add 2 & 4 | | | 3.800 | N/A | N/A | 0.215 |
| | Commercial Use | | | | | | |
| 7 | Carrots CA M/L | 0.032 | 0.5 | 1.100 | 0.037 | 1.4 | 0.015 |
| 8 | Carrots CA Applicator | 0.015 | 10 | 0.510 | 0.018 | 44/2 | 0.112 |
| 9 | Carrots FA M/L | 0.021 | 0.5 | 1.300 | 0.025 | 1.8 | 0.023 |
| 10 | Carrots FA App Low | 0.005 | 10 | 0.300 | 0.006 | 75/2 | 0.110 |
| 11 | Carrots FA App High | 0.005 | 10 | 0.600 | 0.006 | 75/2 | 0.225 |

[a] All referenced documents prepared by Curt Lunchick EAB

[b] Includes #1

Table 1. (continued)

| Source of Exposure Data | | Exposure Type | mg/kg/day | hr/day | mg/kg/ year | mg/unit skin area | Dose % Abs | systemic dose mg/kg/yr |
|---|---|---|---|---|---|---|---|---|
| Draft Memo Vegetables Private Use | | Carrots TX | | | | | | |
| | 1 | M/L | 0.021 | 0.5 | 0.360 | 0.025 | 1.8 | 0.006 |
| | 2 | Applicator | 0.010 | 10 | 0.170 | 0.011 | 60/2 | 0.051 |
| | 3 | M/L & Applicator add 1 & 2 | | | 0.530 | N/A | N/A | 0.057 |
| | | Carrots FA | | | | | | |
| | 4 | M/L | 0.100 | 0.5 | 0.630 | 0.117 | 0.7 | 0.004 |
| | 5 | Applicator | 0.005 | 10 | 0.330 | 0.006 | 80/2 | 0.132 |
| | 6 | M/L & Applicator add 4 & 5 | | | 0.930 | N/A | N/A | 0.136 |
| | | Hand Spray | | | | | | |
| Memo Rights of Way 3/26/85 | 1 | M/L WP | 0.002 | 0.5 | 0.240 | 0.002 | 7.5 | 0.018 |
| | 2 | M/L Lorox L | 0.004 | 0.5 | 0.660 | 0.005 | 4.5 | 0.030 |
| | 3 | Applicator | 0.060 | 6 | 9.000 | 0.070 | 13.5/2 | 0.607 |
| | 4 | WP M/L & applicator add 1 & 3 | | | 9.200 | N/A | N/A | 0.625 |
| | 5 | Lorox L M/L & applicator add 2 & 3 | | | 9.700 | N/A | N/A | 0.637 |
| | | Ground Boom | | | | | | |
| | 6 | M/L WP | 0.005 | 0.5 | 0.740 | 0.005 | 4.52 | 0.033 |
| | 7 | M/l Lorox L | 0.013 | 0.5 | 2.000 | 0.015 | 2.8 | 0.056 |
| | 8 | Applicator | 0.066 | 6 | 9.900 | 0.077 | 13.5/2 | 0.668 |
| | 9 | WP M/L & applicator add 6 & 8 | | | 11.000 | N/A | N/A | 0.701 |
| | 10 | Lorox L M/L & applicator add 7 & 8 | | | 12.000 | N/A | N/A | 0.724 |

Table 2. Determination of lifetime oncogenic risk from systemic dose. $Q_1^* = 0.33$ mg/kg/$^{-1}$.

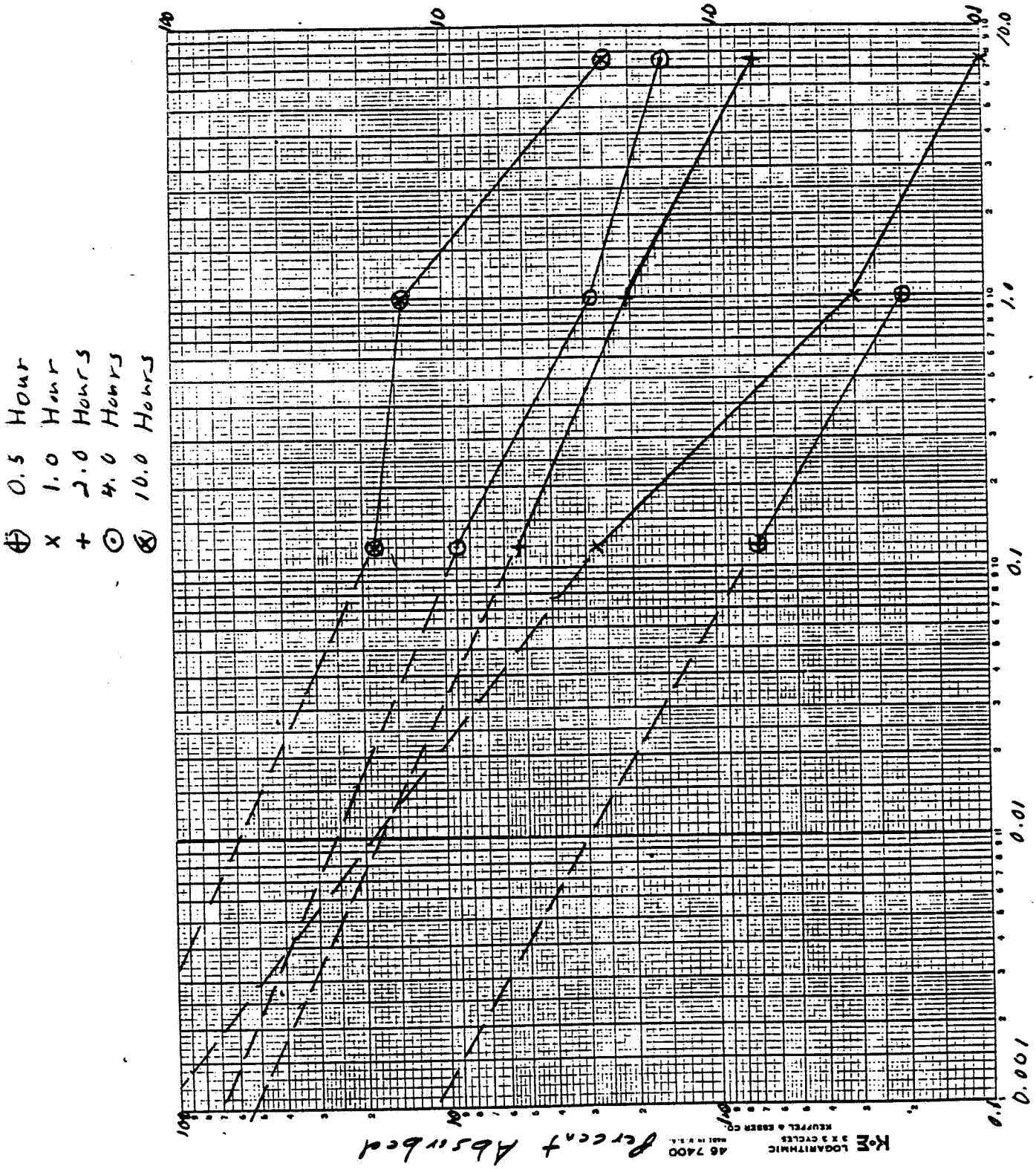
| Source of Exposure Data[a] | Exposure Type | Systemic Dose mg/kg/yr | Annulized Dose mg/kg/day | Lifetime Daily Dose mg/kg | Lifetime Oncogenic Risk |
|---|---|---|---|---|---|
| Memo Turf 5/20/85 | M, L & apply | 0.370 | 0.001 | 0.4 X 10 -3 | 1 X 10 -4 |
| Document 1 Private Soybeans | M/L pre emergence | 0.003 | 0.008 X 10- 3 | 0.004 X 10 -3 | 1 X 10 -6 |
| 2 | M/L post emergence | 0.004 | 0.011 X 10 -3 | 0.005 X 10 -3 | 2 X 10 -6 |
| 3 | App pre emergence | 0.005 | 0.014 X 10 -3 | 0.006 X 10 -3 | 2 X 10 -6 |
| 4 | App post emergence | 0.003 | 0.008 X 10 -3 | 0.004 X 10 -3 | 1 X 10 -6 |
| 5 | pre-emergence M/L and applicator add 1 & 3 | 0.007 | 0.019 X 10 -3 | 0.008 X 10 -3 | 3 X 10 -6 |
| 6 | Pre & post emergence M/L & Applicator add $2_b$, 3 & 4 | 0.015 | 0.041 X 10 -3 | 0.018 X 10 -3 | 6 X 10 -6 |
| 7 | Pre & post emergence M/L equals $2_b$ | 0.007 | 0.019 X 10 -3 | 0.008 X 10 -3 | 3 X 10 -6 |
| 8 | Pre & post emergence Applicator add 3 & 4 | 0.008 | 0.022 X 10 -3 | 0.009 X 10 -3 | 3 X 10 -6 |
| Draft Memo To crops | Commercial Soybeans | | | | |
| 1 | Average M/L | 0.028 | 0.077 X 10 -3 | 0.033 X 10 -3 | 1 X 10 -5 |
| 2 | High M/L | 0.142 | 0.389 X 10 -3 | 0.167 X 10 -3 | 6 X 10 -5 |
| 3 | Average applicator | 0.037 | 0.101 X 10 -3 | 0.043 X 10 -3 | 1 X 10 -5 |
| 4 | High applicator | 0.073 | 0.200 X 10 -3 | 0.086 X 10 -3 | 3 X 10 -5 |
| 5 | Average M/L & applicator add 1 & 3 | 0.065 | 0.178 X 10 -3 | 0.076 X 10 -3 | 3 X 10 -5 |
| 6 | High M/L & Applicator add 2 & 4 | 0.215 | 0.589 X 10 -3 | 0.252 X 10 -3 | 8 X 10 -5 |
| | Commercial Use | | | | |
| 7 | Carrots CA M/L | 0.015 | 0.041 X 10 -3 | 0.018 X 10 -3 | 6 X 10 -6 |
| 8 | Carrots CA Applicator | 0.112 | 0.307 X 10 -3 | 0.131 X 10 -3 | 4 X 10 -5 |
| 9 | Carrots FA M/L | 0.023 | 0.063 X 10 -3 | 0.017 X 10 -3 | 9 X 10 -6 |
| 10 | Carrots FA App Low | 0.110 | 0.301 X 10 -3 | 0.129 X 10 -3 | 4 X 10 -5 |
| 11 | Carrots FA App High | 0.225 | 0.616 X 10 -3 | 0.264 X 10 -3 | 8 X 10 -5 |

[a] All referenced documents prepared by Curt Lundhick EAB

Table 2 (continued)

| Source of Exposure Data [a] | | Exposure Type | Systemic Dose mg/kg/yr | Annulized Dose mg/kg/dsy | Lifetime Daily Dose mg/kg | Lifetime Oncogenic Risk |
|---|---|---|---|---|---|---|
| Draft Memo Vegetables Private Use | | Carrots TX | | | | |
| | 1 | M/L | 0.006 | 0.016 X 10 -3 | 0.007 X 10 -3 | 2 X 10 -6 |
| | 2 | Applicator | 0.051 | 0.139 X 10 -3 | 0.060 X 10 -3 | 2 X 10 -5 |
| | 3 | M/L & Applicator add 1 & 2 | 0.057 | 0.156 X 10 -3 | 0.067 X 10 -3 | 2 X 10 -5 |
| | | Carrots FA | | | | |
| | 4 | M/L | 0.004 | 0.011 X 10 -3 | 0.005 X 10 -3 | 2 X 10 -6 |
| | 5 | Applicator | 0.132 | 0.362 X 10 -3 | 0.155 X 10 -3 | 5 X 10 -5 |
| | 6 | M/L & Applicator add 4 & 5 | 0.136 | 0.372 X 10 -3 | 0.160 X 10 -3 | 5 X 10 -5 |
| | | Hand Spray | | | | |
| Memo Rights of Way 3/26/85 | 1 | M/L WP | 0.018 | 0.049 X 10 -3 | 0.021 X 10 -3 | 7 X 10 -6 |
| | 2 | M/L Lorox L | 0.030 | 0.082 X 10 -3 | 0.035 X 10 -3 | 1 X 10 -5 |
| | 3 | Applicator | 0.607 | 1.663 X 10 -3 | 0.713 X 10 -3 | 2 X 10 -4 |
| | 4 | WP M/L & applicator add 1 & 3 | 0.625 | 1.712 X 10 -3 | 0.734 X 10 -3 | 2 X 10 -4 |
| | 5 | Lorox L M/L & applicator add 2 & 3 | 0.637 | 1.745 X 10 -3 | 0.748 X 10 -3 | 2 X 10 -4 |
| | | Ground boom | | | | |
| | 6 | M/L WP | 0.033 | 0.090 X 10 -3 | 0.039 X 10 -3 | 1 X 10 -5 |
| | 7 | M/L Lorox L | 0.056 | 0.153 X 10 -3 | 0.066 X 10 -3 | 2 X 10 -5 |
| | 8 | Applicator | 0.668 | 1.830 X 10 -3 | 0.784 X 10 -3 | 3 X 10 -4 |
| | 9 | WP M/L & applicator add 6 & 8 | 0.701 | 1.920 X 10 -3 | 0.823 X 10 -3 | 3 X 10 -4 |
| | 10 | Lorox L M/L & applicator add 7 & 8 | 0.724 | 1.984 X 10 -3 | 0.850 X 10 -3 | 3 X 10 -4 |

[a] All referenced documents prepared by Curt Lundhick EAB




mg / sq in of rat skin

Figure I Plot of Dermal Absorption