

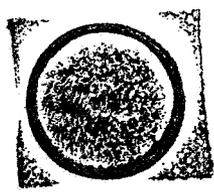
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460



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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

NOV 9 1984

MEMORANDUM

SUBJECT: Linuron, Calculation of Mixer/Loader and Applicator
Body Dose from Dermal Exposure and Dermal Absorption

TO: Robert Taylor PM-25
Registration Division (TS-767)

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

11/7/84

*WJP
11/8/84*

THROUGH: William Burnam, Chief
Toxicology Branch

Compound Linuron

Tox. Chem #528

Registration #352-326

Registrant duPont

Accession #255148

Action Requested

1) Review dermal absorption study.

2) Determine body dose of applicators and mixer-loaders
exposed to linuron from exposure data provided by Curt Lunchick
Chemist EAB, HED.

Conclusion

1) The dermal absorption study is scientifically acceptable
and is reviewed in the attached DER.

2) The maximum annualized dose has been calculated for
the following conditions as;

a) Mixer-Loader, high exposure 83.3×10^{-3} mg/kg/day.
i) 1/2 hour exposure for 6 days each year.

Dose = 9.5×10^{-6} mg/kg/day

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ii) 1 hour exposure for 6 days each year

Dose = 36.9×10^{-6} mg/kg/day

b) Mixer-loader, low exposure, 63.3×10^{-3} mg/kg/day.

i) 1/2 hour exposure for 6 days each year

Dose = 7.3×10^{-6} mg/kg/day

ii) 1 hour exposure for 6 days each year

Dose = 28.1×10^{-6} mg/kg/day

c) Applicator, high exposure, 11×10^{-3} mg/kg/day, 5 hours exposure for 6 days each year

Dose = 9.9×10^{-6} mg/kg/day

d) Applicator, low exposure, 3.8×10^{-3} mg/kg/day, 5 hours exposure for 6 days each year

Dose = 3.6×10^{-6} mg/kg/day

Discussion

Data on the dermal exposure to linuron during field use has been provided by Curt Lunchick of EAB as follows.

a) Mixer-Loader, high exposure, 83.3×10^{-3} mg/kg/day.

i) 1/2 hour exposure for 6 days each year.

ii) 1 hour exposure for 6 days each year

b) Mixer-loader, low exposure, 63.3×10^{-3} mg/kg/day.

i) 1/2 hour exposure for 6 days each year

ii) 1 hour exposure for 6 days each year

c) Applicator, high exposure, 11×10^{-3} mg/kg/day, 5 hours exposure for 6 days each year

d) Applicator, low exposure, 3.8×10^{-3} mg/kg/day, 5 hours exposure for 6 days each year

The appropriate rate of absorption will be taken from the results of the dermal absorption submitted by the Registrant, du Pont. The values utilized are taken from Table E from the DER.

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 (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	16.4
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 in²). It will be noted that for each time interval the percentage of the dose absorbed decreases (the quantity absorbed increases up to the limit imposed by the nature of the compound and the permeability of the skin). thus it is necessary to select, to percent absorption from the dose to the rat which most closely approximates the dose, per 2 in², that is received by to workers. The exposed skin on the workers is considered to be 260 in².

- a) Mixer-Loader, high exposure, 83.3×10^{-3} mg/kg/day. is equilivlant to 1.28×10^{-3} mg/4in².
- b) Mixer-loader, low exposure, 63.3×10^{-3} mg/kg/day. is equilivlant to 0.97×10^{-3} mg/4in².
- c) Applicator, high exposure, 11×10^{-3} mg/kg/day is equilivlant to 0.17×10^{-3} mg/4in².
- d) Applicator, low exposure, 3.8×10^{-3} mg/kg/day is equilivlant to 0.06×10^{-3} mg/4in².

The nearest dose in the rat study to the human exposure is 0.12mg/4in² and the absorption values for this dose will be used.

Time (hours)	0.5	1.0	2.0	4.0	10
Dose mg					
0.12 M	0.7	2.7	5.3	9.0	18.1

For the mixer-loaders the absorption rates for 1/2 hour (0.7%) and one hour (2.7%) will be used. For the applicators an absorption rate for five hours is determined by taking 5/4 of the four hour rate (11.3%). These rates 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 1/2 hour, 1 hour or 5 hours. This is patently not true particularly in the case of the 5 hour applicator exposure. 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 5 hour period an intragrual 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).

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

Appendix

Attachment DER

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

Appendix

Linuron dermal dose from dermal exposure via dermal absorption

1) Mixer-Loader, high exposure

a) 83.3×10^{-3} mg/kg/day, 1/2 hour exposure for 6 days each year

0.7% absorbed per 1/2 hour

0.58×10^{-3} mg/kg/day

6 days/year

3.49×10^{-3} mg/kg/year

/365 days

$.0095 \times 10^{-3}$ mg/kg/day

or

9.5×10^{-6} mg/kg/day

b) 83.3×10^{-3} mg/kg/day, 1 hour exposure for 6 days each year

2.7% absorbed per one hour

2.25×10^{-3} mg/k/day

6 days/year

13.49×10^{-3} mg/kg/year

/365 days

$.0369 \times 10^{-3}$ mg/kg/day

or

36.9×10^{-6} mg/kg/day

2) Mixer-loader, low exposure

a) 63.3×10^{-3} mg/kg/day, 1/2 hour exposure for 6 days each year

0.7% absorbed per 1/2 hour

0.44×10^{-3} mg/kg/day

6 days/year

2.65 mg/kg/year

/365 days

$.0073 \times 10^{-3}$ mg/kg/day

or

7.3×10^{-6} mg/kg/day

b) 63.3×10^{-3} mg/kg/day, 1 hour exposure for 6 days each year

2.7% absorbed per one hour

1.70×10^{-3} mg/kg/day

6 days/year

10.20×10^{-3} mg/kg/year

/365 days

$.0281 \times 10^{-3}$ mg/kg/day

or

28.1×10^{-6} mg/kg/day

3) Applicator high exposure

11×10^{-3} mg/kg/day, 5 hours exposure for 6 days each year

11.3% absorbed 5 hours single dose

1.2×10^{-3} mg/kg/day

/2 correction for accumulation over 5 hours

0.6×10^{-3} mg/kg/day

6 days/year

3.7×10^{-3} mg/kg/year

/365 days

$.0102 \times 10^{-3}$ mg/kg/day

or

10.2×10^{-6} mg/kg/day

4) Applicator low exposure

3.8×10^{-3} mg/kg/day, 5 hours exposure for 6 days each year

11.3% absorbed 5 hours single dose

0.43×10^{-3} mg/kg/day

/2 correction for accumulation over 5 hours

$.21 \times 10^{-3}$ mg/kg/day

6 days/year

1.3×10^{-3} mg/kg/year

/365 days

$.0035 \times 10^{-3}$ mg/kg/day

or

3.5×10^{-6} mg/kg/day

Data Evaluation Report

Compound Linuron

Citation 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.

Reviewed by Robert P. Zendzian PhD 11/7/84
Pharmacologist

Core Classification Acceptable

Conclusion

Linuron dermal absorption is demonstrated as dose and time dependent. Values useful for estimating human absorption during field conditions are found in tables C and D.

Materials

Linuron [^{14}C -phenyl], specific activity 23.5uCi/mg synthesized by the Agricultural Chemicals Department of Du Pont

Charles River CD rats five to 12 weeks old from Charles River.

Methods

"Radiolabeled linuron was formulated in the proper ratio with the appropriate inert ingredients to prepare the Lorox® L test material. Unlabeled linuron was added to the radiolabeled linuron in the Lorox® L applied to the high dose animals to reduce the specific activity to 2.35uCi/mg. Linuron accounted for 41% of the total weight of Lorox® L.

The resulting Lorox® L with radiolabeled linuron was diluted with water to produce suspensions that could be conveniently applied."

Rats were assigned to four groups of 20 each, one group of females and three groups of males. Females received the low dose and males the low, medium and high dose. Doses were 0.12, 1.00 and 7.4 mg linuron applied for two square inches of the rats back. The amount of radioactivity applied was 2.82, 23.5 and 17.4 uCi respectively.

Twenty-four hours before treatment "the backs, shoulders and an area just under the rib cage were clipped free of hair". Fifteen minutes before treatment the area was wiped clean with acetone and allowed to dry. Compound was applied in two aliquotes of 100uL Lorox® suspension with a micropipette and spread with a glass rod. The rod was rinsed with acetone and the quantity remaining thereon was determined.

The treated area was covered with a non-occlusive gauze pad and the animals placed individually in metabolism cages which collected urine and feces separately. Four animals from each dose group were terminated at 0.5, 1, 2, 4 and 10 hours after dosing. Each animal was sacrificed with chloroform and blood withdrawn for analysis by cardiac puncture. The gauze pad and the treated skin were removed for analysis. Residual urine in the bladder was added to the collected urine. The following organs and tissues were removed from two of the high dose 10 hour animals for analysis; spleen, brain, lung, kidney, heart, gastrointestinal tract, testes, muscle, fat and liver. The remaining carcasses of all animals were stored frozen.

Results

The levels of radioactive material in the blood and the quantity excreted for each experimental group are given in Tables 1 and 4 from the report.

Table 1. Levels of radiolabeled materials in the blood of rats as a function of time. Parts per million of radioactivity* in the blood. (% of applied, mean of 4 animals)

Time (hours)	0.5	1.0	2.0	4.0	10
Dose mg (Female, Male)					
0.12 F	0.079(0.4)	0.044(0.6)	0.032(0.2)	0.037(0.2)	0.021(0.2)
0.12 M	0.078(0.6)	0.056(0.4)	0.029(0.2)	0.024(0.2)	0.015(0.1)
1.00 M	0.22 (0.2)	0.092(0.1)	0.16 (0.2)	0.094(0.1)	0.10 (0.1)
7.4 M	0.27(<0.1)	0.30(<0.1)	0.32(<0.1)	0.32(<0.1)	0.32(<0.1)

*Calculated as Linuron

Table 4. Percentage of applied radioactivity excreted in the urine and feces as a function of time. (mean of 4 animals)

Time (hours)	0.5	1.0	2.0	4.0	10
Dose mg (Female, Male)					
0.12 F	0.4	2.6	3.2	6.0	13.7
0.12 M	0.1	2.3	5.1	8.8	18.0
1.00 M	<0.1	0.1	1.9	2.7	16.3
7.4 M	<0.1	0.1	0.7	1.4	2.5

Discussion

The data collected can be transposed in several ways in order to reveal internal relationships. Table A presents the hourly absorption rate for each collection interval.

Table A. Hourly percentage of applied radioactivity excreted in the urine and feces. (mean of 4 animals).

Time (hours)	0.5	1.0	2.0	4.0	10
Dose mg (Female, Male)					
0.12 F	0.8	2.6	1.6	1.5	1.4
0.12 M	0.2	2.3	2.6	2.2	1.8
1.00 M	<0.1	0.1	1.0	0.7	1.6
7.4 M	<0.1	0.1	0.4	0.4	0.3

For each dose the hourly rate for the first half hour is considerably less than the rate for the remaining periods indicating a delay or lag period. This lag period is also present for the one hour interval at 1.00 and 7.4mg males. The calculated hourly values are relative consistent for the remaining intervals for each dose but there are two values which appear "out of line". The one hour value for the females appears too high and the one hour value for the 1.00mg males appears too low. Examination of the individual animal values shows that one female has a relative high urine value and a very high fecal value compared to the other three females in the group. This is probably due to sample contamination and is corrected for in Tables D and E. The individual values for the 1.00mg males show that two males did not excrete any urine during the collection period and another male had a relatively low fecal excretion. This is also corrected for in Tables D and E.

Tables B presents the total percent of applied compound that was absorbed as a function of time by adding the percent of dose found in the blood to that excreted. Table C converts this to hourly percentage which again shows the "out of line values". Tables D, total percent absorbed, and E, hourly percent absorbed, include the corrected values and can be used for calculation of quantity absorbed in field exposure situations.

Table B. Percentage of applied radioactivity absorbed as a function of time. Total of blood, urine and feces. (mean of 4 animals).

Time (hours)	0.5	1.0	2.0	4.0	10
Dose mg (Female, Male)					
0.12 F	0.8	3.2	3.4	6.2	13.9
0.12 M	0.7	2.7	5.3	9.0	18.1
1.00 M	0.2	0.2	2.1	2.8	16.4
7.4 M	<0.1	0.1	0.7	1.5	2.5

Table C. Hourly percentage of applied radioactivity absorbed. Total of blood, urine and feces. (mean of 4 animals)

Time (hours)	0.5	1.0	2.0	4.0	10
Dose mg (Female, Male)					
0.12 F	1.6	3.2	1.7	1.4	1.4
0.12 M	1.4	2.7	2.7	2.3	1.8
1.00 M	0.4	0.2	1.1	0.7	1.6
7.4 M	<0.1	0.1	0.4	0.4	0.3

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 (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	16.4
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

Table E. Percentage of applied radioactivity absorbed hourly 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 (Female, Male)					
0.12 F	1.6	2.1 ^a	1.7	1.6	1.4
0.12 M	1.4	2.7	2.7	2.3	1.8
1.00 M	0.4	0.3 ^b	1.1	1.4	1.6
7.4 M	<0.1	0.1	0.4	0.4	0.3

a. mean of 3 urine and 3 fecal values

b. mean of 2 urine and 3 fecal values