



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

004058

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Linuron, Review of Dermal Absorption and Metabolism
Studies in the Rat

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

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

10/14/84

10/19/84

THROUGH: William Burnam, Chief
Toxicology Branch

Compound Linuron

Tox Chem #528

Registration #352-326

Registrant Du Pont

Accession #254943

Action Requested

Review the following studies.

Dermal absorption of [^{14}C] linuron in the Lurox® L formulation
by the Rat, J.J. Anderson, du Pont, Document No. AMR-259-84,
undated, accession #254943,

Metabolism of Linuron [phenyl- ^{14}C (U)] in male rats.
(Pilot study), J.P. Dulka, Du Pont, Document No. AMR-270-84
undated, Accession #254943

Conclusions

1) Dermal Absorption

The report as submitted lacks individual animal data and
cannot be properly evaluated. For information purposes only
one can say that dermal absorption of linuron in the rat
proceeds at a slow rate. The data for absorption in the
medium dose males (0.87mg) at one hour appears to be about
one-tenth of that expected.

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2) Metabolism Study

In the male rat, maintained for three weeks on a diet containing 625ppm linuron, a single oral dose of 20mg/kg is essentially completely excreted in the urine and feces in 72 hours. Linuron, nine metabolites and conjugated metabolites of linuron were detected.

Attachments
DERs

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Data Evaluation Report

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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 #254943.

Reviewed by Robert P., Zendzian PhD
Pharmacologist

Core Classification Unacceptable, report incomplete

Conclusion

The report as submitted lacks individual animal data and cannot be properly evaluated. For information purposes only one can say that dermal absorption of linuron in the rat proceeds at a slow rate. The data for absorption in the medium dose males (0.87mg) at one hour appears to be about one-tenth of that expected.

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Data Evaluation Report

DD 4858

Compound Linuron

Citation Metabolism of Linuron [phenyl-¹⁴C(U)] in male rats. (Pilot study), J.P. Dulka, Du Pont, Document No. AMR-270-84 undated, Accession #254943

Reviewed by Robert P. Zendzian PhD
Pharmacologist

Core Classification Supplementary

Conclusion

In the male rat, maintained for three weeks on a diet containing 625ppm linuron, a single oral dose of 20mg/kg is essentially completely excreted in the urine and feces in 72 hours. Linuron, nine metabolites and conjugated metabolites of linuron were detected.

Materials

Linuron [¹⁴C-phenyl] specific activity 6.1 uCi/mr, 97% pure

Male Charles River CD® rats.

Methods

Two male rats were fed a diet containing 625ppm of nonradiolabeled linuron for three weeks. The rats then received a single oral dose of 6.14mg (37.5 uCi) radiolabeled linuron. The rats were maintained individually in metabolism cages for 72 hours. Urine and feces were collected separately at 6, 30, 48 and 72 hours. Expired air was collected for OC₂ and volatiles at the same intervals. Rats were anesthetized by chloroform and sacrificed. Blood, liver, heart, lungs, kidneys, spleen, testes, skin, muscle, fat, carcass and hide were collected.

Samples collected were analysed for radioactivity and the urine and feces extracted and analysed to characterize the metabolites.

Results

Due to contamination of the feces with urine in rat number two only the excretion data from rat number one can be used. This data is extracted from table 1 of the report and presented below.

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<u>Fraction</u>	<u>Conc. as Equivalent Linuron ppm</u>	<u>% of Dose</u>
Urine, 30 hrs	122	35.1
48 hrs	181	31.3
72 hrs	29	4.4
Total in urine		70.8
Feces, 6 hrs	0.02	0.0009
30 hrs	133	1.1
48 hrs	204	7.4
72 hrs	383	4.2
Total in feces		12.7
Gastrointes- tinal tract	2.3	0.2
Cage Washings		5.8
Total Excreted		89.5
Total in organs and tissue samples		1.3
Respired 6 hrs		0.01
air 30 hrs		0.03
48 hrs		0.02
72 hrs		0.02
Total in respired air		0.08
Total recovery		91.6

Oral dose 20mg/kg, preconditioned and maintained on diet containing 624ppm linuron

Concentrations of linuron in the tissues were less than 0.1 percent of the dose in all tissues except liver (0.49 & 0.42%) and carcass (0.28 and 1.01%). The high carcass concentration of attributed to urine contamination of the skin of the second rat.

Linuron, eight metabolites and unidentified polar conjugates were identified in the urine. Linuron, six metabolites and unidentified polar conjugates were identified in the feces. The metabolites and quantities thereof found in rat number one are presented below. Contamination of feces with urine in rat number two makes metabolite identification worthless.

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<u>Compound</u>	<u>% of total radioactivity in each urine sample</u>		
	<u>30 hrs</u>	<u>48 hrs</u>	<u>72 hrs</u>
Linuron	3.4	1.3	0.9
Metabolite A	0.7	0.4	0.7
Desmethyl linuron	0.4	0.5	0.7
Metabolite B	0.5	2.8	3.1
Desmethoxy linuron	0.4	0.4	1.6
Metabolite C	0.4	0.7	0.9
Nor Linuron	2.1	1.3	2.5
Metabolite D	7.4	13.0	14.9
Metabolite E	6.8	8.4	6.4
Polar Conjugates	77.9	71.3	68.3

<u>Compound</u>	<u>% of total radioactivity in each fecal sample</u>		
	<u>30 hrs</u>	<u>48 hrs</u>	<u>72hrs</u>
Unidentified Metabolite 1	8.1	2.8	14.7
Linuron	2.7	2.7	2.0
Desmethyl linuron	28.3	6.9	7.9
Metabolite B	3.1	4.7	3.6
Metabolite C1	<0.01	1.3	<0.01
Nor Linuron	6.7	18.6	6.6
Metabolite D1	17.8	28.0	9.7
Polar Conjugates	33.4	35.6	55.5

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Metabolite A (N'-(4,5-dichloro-2-hydroxyphenyl) methox-
N-methylurea
Metabolite B (N'-(3,4-dichlorophenyl) N-methoxyurea
Metabolite C (N'-(3,4-dichloro-2-hydroxyphenyl) N-methylurea
Metabolite D (N-(4,5-dichloro-2-hydroxyphenyl) urea)
Metabolite E (N-(4,5-dichloro-2-hydroxyphenyl) urea

or

(N-3,4-dichloro-2-hydroxyphenyl) urea

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END