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

005914

MAY 27 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Lindane, Dermal Absorption Studies in Rat and Rabbit

TO: George La Rocca PM-15
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD
Pharmacologist
Mission Support Staff
Toxicology Branch
HED (TS-769)

THROUGH: Reto Engler PhD, Head
Mission Support Staff

Theodore M. Farber PhD, Chief
Toxicology Branch

Compound; Lindane

Tox Chem #527

Registration #52904-C

Registrant; Centre International D"Etude Du Lindane

MRID #400561-07 & -08

Tox Project #7-0552
7-0563

Action requested

Review the following studies;

Dermal absorption of ^{14}C-Lindane in male rats; A.L. Bosch, Hazleton Laboratories America, HLA Study No. 6188-103; Jan 13, 1987; Accession number 400561-07

Dermal absorption of ^{14}C-Lindane in male rabbits; A.L. Bosch, Hazleton Laboratories America, HLA Study No. 6188-104; Jan 7, 1987; Accession number 400561-08

Conclusions

Lindane is significantly absorbed by the rat, percents absorbed for 0.5 to 24 hours exposure are 0.66 - 5.05 (10mg dose), 0.96 - 20.86 (1.0mg dose) and 0.60 - 27.72 (0.1mg dose). The process appears to be approaching saturation at the high dose. The study is acceptable.

Lindane is significantly absorbed by the rabbit, percents absorbed for 0.5 to 24 hours exposure are 1.99 - 16.56 (50mg dose), 6.68 - 39.99 (5.0mg dose) and 5.96 - 55.68 (0.5mg dose). No evidence of saturation of absorption was observed in this study. Due to high relative permeability of the rabbit compared to man, the data cannot be used to estimate human absorption of lindane. The study is scientifically acceptable.

Recommendation

The data produced in the rat dermal absorption study must be used in calculating margins of safety or of risk due to human dermal exposure to lindane. The rabbit data is not usable.

Discussion

The two studies reviewed here follow the Agency's protocol for dermal absorption in their experimantal design. However, that protocol specifies that the male rat be used as the experimental animal. The rat is specified because of its convenient size, background of toxicological data (particularly metabolism) on the test compound, the growing body of data on dermal absorption of pesticides in the rat and the proven utility of the data generated from the rat studies. The rat does overestimate dermal absorption when compared to man. The usually accepted factor is five. Considering the veriability of of human dermal permeability, depending upon the area of the body, this overestimation is acknowledged and considered acceptable. The rabbit skin is even more permeable than the rat and grossly overestimates dermal absorption for application to man.

In order to compare dermal absorption date between two species, the dose(s) must be the same per unit area of skin. In these two studies the doses are not the same but they are sufficiently close to allow comparison as shown below;

	Dose mg/cm^2	
Group	Rat	Rabbit
1	2.00	1.7700
2	0.20	0.1770
3	0.02	0.0177

Comparison of dermal absorption in the rat and the rabbit studies, by group and duration of exposure, are show in the table below. The data generated in these two studies clearly show the relative high permeability of rabbit skin.

Group	Duration exposure (hours)	Total Absorbed % Rat	Total Absorbed % Rabbit	Relative absorption rabbit/rat
1	0.5	0.66	1.99	3.00
	1	1.00	2.84	2.84
	2	1.50	5.53	3.69
	4	2.03	7.32	3.60
	10	2.81	10.96	3.90
	24	5.05	16.56	3.28
2	0.5	0.96	6.68	6.96
	1	2.42	8.22	3.40
	2	2.61	12.05	4.62
	4	5.27	18.31	3.47
	10	8.31	23.76	2.86
	24	20.86	39.99	1.92
3	0.5	0.60	5.97	9.93
	1	3.34	13.56	4.06
	2	4.55	16.41	3.61
	4	10.08	29.63	2.94
	10	18.07	51.17	2.83
	24	27.72	55.68	2.01

Data Evaluation Report

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Compound Lindane

Citation Dermal absorption of ^{14}C-Lindane in male rats; A.L. Bosch, Hazleton Laboratories America, HLA Study No. 6188-103; Jan 13, 1987; Accession number 400561-07

Reviewed by Robert P. Zendzian PhD 11/23/87
Pharmacologist

Core Classification Accepotable

Conclusion

Lindane is significantly absorbed by the rat, percents absorbed for 0.5 to 24 hours exposure are 0.66 - 5.05 (10mg dose), 0.96 - 20.86 (1.0mg dose) and 0.60 - 27.72 (0.1mg dose). The process appears to be approaching saturation at the high dose.

Materials

Prentiss lindane 20% EC (emulsifiable concentrate), Lot No. 11276
UL-^{14}C-lindane 27,5% EC, Reference number RP2051-116-1

Albine male rats, Crl:CD®(SD)BR, Charles River Laboratories.

Experimantal Design

Male rats were assigned randomly to the following experimental groups.

Group Number	Number of rats	Dose Level	Dose mg/rat	Volume of Test Compound/ Animal (uL)
1	24	Concentrate (20% emulsion)	10	50
2	24	1:9 Dilution with distilled water	1.0	50
3	24	1:99 Dilution with distilled water	0.1	50

"Because the predose and the postdose analysis of the test material did not agree within 10% of their mean for the 1.0 and the 0.1-mg dose levels (groups 2 and 3) these dose levels were repeated (with new animals) and analysis of samples from these two groups was terminated."

"Approximately 24-hours before dosing, the back and shoulders of each animal were clipped free of hair and the clipped area washed with acetone." "The test site, a circular area approximately 2.5 cm in diameter (4.9-sq cm area) was prepared as follows: A ring made of 1/4-in rubber tubing was prepared by gluing the ends of an approximately 4.25-in. piece

of tubing together with cyanoacrylic adhesive (Pronto® CA8). The ring was affixed to the prepared area on the rat's back with a cyanoacrylate adhesive (Pronto CA8)." "The test material was spread evenly with a blunt-end glass rod within the circumscribed area (4.9 sq cm)." "-a circle of filter paper --- was glued to the top surface of the ring" Animals were caged individually in metabolism cages and total urine and feces collected. "Four rats/test group were bled and sacrificed at intervals of 0.5, 1, 2, 4, 10 or 24 hours after appliction of the test material." The following samples were collected for analysis from each animal:

1 Applicator rinse.
2. Total urine
3. Total feces
4. Blood
5. Skin wash (soap and water and water rinse)
6. Filter paper
7. Skin at the application site
8. Carcass

Results

Results are summarized in Table 1. Quantities absorbed increased with dose and duration of exposure while percent absorbed increased with time and decreased with dose.

Discussion

The data indicate that the doses utilized are approaching a maximum for skin absorption and that a significant portion of the dose is lost at the 24 hour exposure most likely by sublimation.

The ratio between quantities (mg) absorbed at doses of 10 and 1.0 mg and 1.0 and 0.1 mg at equal durations of exposures are presented below;

EXPOSURE (hours)	DOSE 10mg / 1.0mg		ratio	DOSE 1.0mg / 0.1mg		ratio
0.5	0.07	0.01	7	0.01	0.001	10
1.0	0.10	0.02	5	0.02	0.003	6.7
2.0	0.15	0.03	5	0.03	0.005	6
4.0	0.20	0.05	4	0.05	0.010	5
10.0	0.28	0.08	3.5	0.08	0.018	4.4
24.0	0.51	0.21	2.4	0.21	0.028	7.5

The decrease in the ratio of absorption with increasing dose and duration of exposure clearly shows that the absorption process is approaching saturation for lindane.

Table 1. Mean distribution of Lindane (percent of applied dose). Data from Tables 3 through 11 of the report.

Group & Dose (mg/rat)	Duration exposure (hours)	Mean percent of dose in urine	feces	Carcass	Total Absorbed[a] %	mg	In Skin	Skin Rinse	Total[b]
1 (10.0)	0.5	ND	ND	0.66	0.66	0.07	6.85	73.16	82.13
	1	<0.01	ND	1.00	1.00	0.10	7.37	74.79	85.29
	2	0.01	ND	1.49	1.50	0.15	4.01	76.57	84.15
	4	0.02	ND	2.01	2.03	0.20	5.04	73.58	83.26
	10	0.17	ND	2.64	2.81	0.28	4.33	66.04	76.20
	24	0.61	0.08	4.01	5.05	0.51	2.85	64.80	74.19
2 (1.0)	0.5	ND	ND	0.96	0.96	0.01	8.48	89.84	101.08
	1	0.01	ND	2.41	2.42	0.02	15.99	72.36	92.73
	2	0.01	ND	2.60	2.61	0.03	22.99	55.56	83.66
	4	0.08	ND	5.19	5.27	0.05	26.91	55.78	90.24
	10	0.53	ND	7.78	8.31	0.08	13.25	66.32	90.40
	24	3.20	0.25	16.37	20.86	0.21	5.50	39.35	70.19
3 (0.1)	0.5	ND	ND	0.60	0.60	0.001	11.39	78.92	93.11
	1	ND	ND	3.34	3.34	0.003	24.46	55.98	86.94
	2	0.01	ND	4.54	4.55	0.005	31.61	41.24	80.27
	4	0.28	ND	9.81	10.08	0.010	30.68	38.53	82.84
	10	1.24	ND	16.69	18.07	0.018	17.55	43.34	82.59
	24	4.38	0.37	21.66	27.72	0.028	7.15	21.00	58.35

ND None detected, (counts less than twice background)
a. sum of urine, feces and carcass
b. also includes filter paper and spreader rinse.

Data Evaluation Report

Compound Lindane

Citation Dermal absorption of ^{14}C-Lindane in male rabbits; A.L. Bosch, Hazleton Laboratories America, HLA Study No. 6188-104; Jan 7, 1987; Accession number 400561-08

Reviewed by Robert P. Zendzian PhD 11/2/87
Pharmacologist

Core Classification Acceptable

Conclusion

Lindane is significantly absorbed by the rabbit, percents absorbed for 0.5 to 24 hours exposure are 1.99 - 16.56 (50mg dose), 6.68 - 39.99 (5.0mg dose) and 5.96 - 55.68 (0.5mg dose). Due to high relative permeability, data cannot be used to estimate human absorption of lindane.

Materials

Prentiss lindane 20% EC (emulsifiable concentrate), Lot No. 11276
UL-^{14}C-lindane 27,5% EC, Reference number RP2051-116-1

Albino male rabbits, Hra:(NZW)SPF, Hazleton Research Products

Experimantal Design

Male rabbits were assigned randomly to the following experimental groups.

Group Number	Number of rabbits	Dose Level	Dose mg /rabbit	Volume of Test Compound/ Animal (uL)
1	24	Concentrate (20% emulsion)	50	250
2	24	1:9 Dilution with distilled water	5.0	250
3	24	1:99 Dilution with distilled water	0.5	250

"Approximately 24-hours before dosing, the back and shoulders of each animal were clipped free of hair and the clipped area washed with acetone." "The test site, a circular area approximately 6.0 cm in diameter (28.3-sq cm area) was prepared as follows: A double ring made of 1/4-in rubber tubing was prepared by gluing the ends of an approximately 21-cm piece of tubing together with cyanoacrylic adhesive (Pronto® CA8). The double ring was affixed to the prepared area on the rat's back with a cyanoacrylate adhesive (Pronto CA8)." "The test solution was spread evenly with a blunt-end

glass rod within the circumscribed area (23.8 sq cm)[typo error should read 28.3 sq cm]." "-a circle of filter paper --- was glued to the top surface of the ring" Animals were caged individually and total urine and feces collected. "Four rabbits/test group were bled and sacrificed at intervals of 0.5, 1, 2, 4, 10 or 24 hours after appliction of the test material." The following samples were collected for analysis from each animal:

1. Applicator rinse.
2. Total urine
3. Total feces
4. Blood
5. Skin wash (soap and water and water rinse)
6. Filter paper
7. Skin at the application site
8. Carcass

Results

Results are summarized in Table 1. Quantities absorbed increased with dose and duration of exposure while percent absorbed increased with time and decreased with dose.

Discussion

The rabbit is not the prefered species for dermal absorption studies as it grossly overestimates absorption compared to man. In addition the relatively large size of the individual animals requires excessive quantities of radioactive material and creates problems with recovary. Total recovery in this study is relatively low compared with total recovery in rat dermal absorption studies performed by this laboratory and is mainly a function of the animal size. The falloff in recovery with time in the low dose group may be further indicative of this problem or it may be a 'real' effect. The possibilities cannot be clearly differentiated.

The ratio between quantities (mg) absorbed at doses of 10 and 1.0 mg and 1.0 and 0.1 mg at equal durations of exposures are presented below. There is no evidence of saturation of the absorption process.

EXPOSURE	DOSE			DOSE		
(hours)	50mg	/ 5.0mg	ratio	5.0mg	/ 0.5mg	ratio
0.5	1.01	0.33	3.1	0.33	0.03	11
1.0	1.45	0.41	3.5	0.41	0.07	5.9
2.0	2.83	0.60	4.7	0.60	0.08	7.5
4.0	3.74	0.92	4.1	0.92	0.15	6.1
10.0	5.60	1.19	4.7	1.19	0.26	4.6
24.0	8.46	2.00	4.2	2.00	0.28	7.1

Table 1. Mean distribution of Lindane (percent of applied dose). Data from Tables 3 through 11 of the report.

Group & Dose (mg/rat)	Duration exposure (hours)	Mean percent of dose in urine	feces	Carcass	Total Absorbed[a] %	mg	In Skin	Skin Rinse	Total[b]
1	0.5	0.03	ND	1.96	1.99	1.01	6.34	65.43	74.50
(50.0)	1	0.15	ND	2.69	2.84	1.45	7.86	70.93	82.69
	2	0.50	ND	5.03	5.53	2.83	8.74	63.52	78.30
	4	1.25	0.02	6.00	7.32	3.74	8.30	63.64	79.88
	10	2.22	0.18	8.44	10.96	5.60	9.12	59.97	81.32
	24	6.82	0.47	8.94	16.56	8.46	7.37	57.48	82.01
2	0.5	0.07	ND	6.61	6.68	0.33	6.33	75.17	89.32
(5.0)	1	0.44	ND	7.78	8.22	0.41	4.11	67.65	81.34
	2	0.98	ND	11.07	12.05	0.60	3.35	69.14	86.39
	4	2.62	0.02	15.67	18.31	0.92	2.32	65.01	87.80
	10	4.37	0.41	18.43	23.76	1.19	2.26	57.42	86.15
	24	11.59	2.82	24.61	39.99	2.00	2.81	33.55	78.27
3	0.5	0.06	<0.01	5.89	5.97	0.03	14.56	63.36	86.11
(0.5)	1	0.25	ND	13.31	13.56	0.07	11.26	53.00	81.92
	2	1.06	ND	15.35	16.41	0.08	10.36	40.05	71.74
	4	3.77	ND	26.77	29.63	0.15	7.96	24.73	68.30
	10	8.12	0.27	42.54	51.17	0.26	4.76	6.55	66.44
	24	25.51	3.49	26.16	55.68	0.28	4.38	4.65	66.34

ND None detected, (counts less than twice background)
a. sum of urine, feces and carcass
b. also includes filter paper and spreader rinse.