11/14/1998

Data Evaluation Report

Compound Thiocarbamates; EPTC, cycloate, butylate, pebulate and vernolate

Study Type Dermal Absorption (85-3)

Citation

Thiocarbamates: comparative in vivo percutaneous absorption study in the rat. Lythgoe, R.E. & Platt, J.A. Zeneca. CTL/P/4594, URG445. Jan 12, 1995. MRID 437125-02

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Core Classification Acceptable (guideline 85-3)

Conclusions

Five thiocarbamates , EPTC, cycloate, butylate, pebulate and vernolate, were dosed at a 1/100 water dilution of their respective emulsifiable concentrate formulations for 10 hours. The largest portion of the dose was lost by volatilization, 63 to 80 %. Up to 20% of the volatile dose of EPTC was lost by failure to promptly affix the activated carbon filter on the application site chamber. Percent absorbed at 10 hours was 5.83, 16.06, 4.11, 9.99 and 7.52 respectively. At 10 hours blood concentration was 0.028, 0.045, 0.010, 0.039 and 0.028 ug/g and plasma concentration 0.004, 0.013, 0.007, 0.028 and 0.011 ug/g respectively.

Materials

Test substance chemical nomenclature

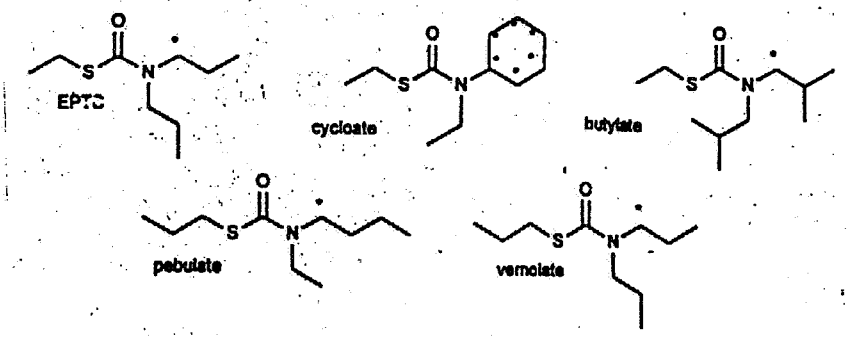
EPTC	S-ethyl dipropylthiocarbamate
Cycloate	S-ethyl cyclohexyl(ethyl)thiocarbamate
Butylate	S-ethyl di-isobutylthiocarbamate
Pebulate	S-propyl butyl(ethyl)thiocarbamate
Vernolat	S-propyl dipropylthiocarbamate

Unlabeled from Jealott's Hill Research Station, UK

	CTL Reference	Purity(w/)	Mole Wt	TORR	Physical Appearance
EPTC	YO6368/014	98.4%	189	1.6×10^{-2}	Yellow liquid
Cycloate	YO6375/012	98.4%	215	6.2×10^{-3}	pale yellow liquid
Butylate	YO6370/007	95.7%	217	1.3×10^{-2}	amber liquid
Pebulate	YO6381/008	96.1%	203	8.9×10^{-3}	brown/orange liquid
Vernolat	YO6369/014	97.4%	203	1.0×10^{-2}	yellow liquid

Labeled from Zeneca Inc. Richmond CA

	CTL Reference	Specfic activity	Radiochemical Purity
EPTC	YO6368/019	2.0720GBq/mmol	98.6%
Cycloate	YO6375/015	1.2247GBq/mmol	96.6%
Butylate	YO6370/011	0.8806GBq/mmol	98.4%
Pebulate	YO6381/011	1.1211GBq/mmol	97.2%
Vernolat	YO6369/013	2.0720GBq/mmol	97.4%



* Postion of ratiolabel

Dose vehicle

Blank formulation concentrates prepared and supplied by Zeneca Richmond CA

CTL reference numnbers

EPTC	Y06368/018
Cycloate	Y06375/014
Butylate	Y06370/010
Pebulate	Y06381/010
Vernolat	Y06369/020

Dilutant

deionozed sterile water CLT/Y04517/015

Experimental animals

Male rats (CD(Crl:CD(SD)BR0 5-8 weeks of age from Charles River UK

Doses and duration of exposure

Each test substance was dosed at a 1/100 aqueous dilution of its emulsifiable concentrate for 10 hours. Four rats were dosed for each test substance.

Formulation

EPTC	WF1119	840g/l
Cycloate	WF1164	720g/l
Butylate	WF1189	804g/l
Pebulate	WF1197	(cannot be read in copy of study on hand)
Vernolat	WF2007	840g/l

Preparation and analysis of dosing solutions

"For each preparation, the required amounts of radiolabeled and unlabeled test substance were dissolved in acetone and the solvent evaporated under a stream of nitrogen. The required blank formulation was then added and allowed to mix with the test substance to give a [^{14}C]-labeled concentrate. Finnaly, the required amount of dionized water was added and the resulting preparation mixed by stirring and ultra-sonication." Samples were assessed prior to dosing, and concentration of test substance and radiolabeled test substance calculated. Dose preparations were found to be stable for longer then the period of use in the study.

Animal preparation

"Approximately 24 hours before dosing the fur from the dorso-lumber region of each rat was shaved." "Two 26mm internal diameter, 34 mm external diameter, 10 mm deep glass rings were gluded to the skin surface, one behind each shoulder, using cyano-acrylate glue" "The internal surface area encompussed by each ring was approximately 5 cm^2.

Dosing

Each animal was weighed imediately prior to dosing. The required volume of dosing solution was applied to the 5 cm^2 area with a 25ul capacity positive displacement pipette, with a disposable tip, and spread with the tip. Then a circle of active carbon filter pad was glued to the upper surface of the glass ring to trap any volatilizing test material. The rat was then placed in a glass metabolism cage to collect urine, feces, and volatile material in the expired air.

Termination

After 10 hours of exposure the rat was removed from the matabolism cage, the cage was washed and the wash retained for analysis.

The rat was anestatised with flurothane. The carbon filter pads were removed and retained for analysis. The skin surface was washed with 3% aqueous Teepol L and rinsed with water. The wash, rinse and swabs were retained for analysis.

The animals was exsangunated by cardiac puncture and the blood sample retianed as whole blood and plasma. The glass rings were removed and retained for analysis. The application site skin and the surrounding skin were collected and retained, separately, for analysis. Residual urine from the bladder was collected and added to the voided urine. The remaining carcass was retained for analysis. The following samples from each rat were analysed;

Dosing solution
Expired air traps
Cage wash
non-occlusive cover
ring wash
Pipette tip wash
Plasma
Blood
Urine
feces
carcass

Results

Dose distribution is summarized in Table 1 and whole blood and plasma concentrations in Table 2.

Discussion

Recovery was low for EPTC due to the method used to apply the test material and affix the active carbon filter pad. For EPTC only, the dose material was applied and then allowed to dry before affixing the filter pad. For all other thiocarbamates the filter pad was affixed imediately after dosing. This short delay was found to be sufficient to allow a measureable portion of dose to evaporate without capture. This was tested with a special group of four rats. The rats were dosed with EPTC exactly as the first group, the dose allowed to dry and covered with the filter pad and the animals were immediately processed (two to five minutes after dosing). This approach essentially limited the possible mechanisms of loss to the delay in covering the application site. For these animals the mean dose distribution is shown in Table 3. Total recovery was 71.184%, 5% lower than the 76.10% in the main study. Thus it is reasonable to conclude that the loss of EPTC was due to the delay of covering the application site. This is a simple failure to capture volatilized material and will not effect the absorption of EPTC. The absorption and dose distribution data are usable with the caviat that an additional approximately 20% of the dose was lost by evaporation.

Table 1. Percent dose distribution of five thiocarbamates applied to male rats as a 1/100 dilution of the respective emulsifiable concentrates for ten hours. Mean of four rats. Data from table two of the report. MRID 437125-02

	EPTC	Cycloate	Butylate	Pebulate	Vernolate
Dose (ug/cm^2)	29	29	28	36	31
Skin wash	3.01	10.19	3.21	4.26	3.76
Non-occlusive cover[1]	65.83	63.24	86.76	79.37	79.92
Unabsorbed[2]	68.84	73.43	98.97	83.63	83.68
Application site	1.43	4.22	0.79	1.72	1.67
Untreated skin	0.07	0.16	0.07	0.09	0.17
Urine	1.94	6.14	1.31	3.11	2.10
Feces	0.56	0.37	0.12	0.14	0.11
Cage wash	0.34	0.49	0.06	0.40	0.26
Carbon dioxide	0.41	0.10	0.17	1.32	1.26
Expired Volatiles	0.11	<0.03	0.44	0.14	0.18
Carcass	2.40	8.78	2.34	4.81	3.44
Total absorbed[3]	5.83	16.06	4.11	9.99	7.52
Total recovered	76.10	93.70	94.86	95.35	92.86

1. material evaporated from application site.
2. sum of skin wash and non-occlusive cover
3. sum of untreated skin, urine, feces, cage wash, carbon dioxide, expired volatiles and carcass.

Table 2 Mean whole blood and plasma concentrations as ug equivalents/gram. Exposure conditions as in Table 1 above. Data from Table 3 of the report MRID 437125-02

Thiocarbamate	Whole Blood	Plasma
EPTC	0.028	0.004
Cycloate	0.045	0.013
Butylate	0.010	0.007
Pebulate	0.039	0.028
Vernolat	0.028	0.011

Table 3. Mean percent dose distribution of EPTC aplied to four males rats that were immediately processed. Data from Appendex K of the report. MRID 437125-02

Dose (mg/cm^2)	0.0273
Skin wash	38.290
Non-occlusive cover$_1$	24.997
Unabsorbed$_2$	63.287
Application site	6.611
Untreated skin	0.147
Urine	NA
Feces	NA
Cage wash	NA
Carbon dioxide	NA
Expired Volatiles	NA
Carcass	1.138
Total absorbed$_3$	1.285
Total recovered	71.184

1. material evaporated from application site.
2. sum of skin wash and non-occlusive cover
3. sum of untreated skin, urine, feces, cage wash, carbon dioxide, expired volatiles and carcass.