12-30-93

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

DEC 30 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DEC 10 1993

MEMORANDUM

SUBJECT: Hydramethylon in MAXIFORCE® Formulation, dermal Absorption

TO: William Dykstra PhD
Toxicologist
Review Sec 1,TB I

FROM: Robert P. Zendzian Ph.D. 12/30/93
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (H7509C)

Action Requested

Review the following study;

Hydramethynon: Pharmacokinetics and material balance study following cutaneous administration to male Sprague Dawley® Rats, S.W. Frantz and J.L. Beskitt, Bushy Run Research Center, Laboratory Project ID # 92N1073, Oct 15, 1993, MRID 429891-01

Core Classification Acceptable

Conclusions

MAXIFORCE® Gel formulation (2% hydromethynon) at a 2 gm nominal dose was applied to 10 cm^2 on the shaved back of the male rat (4/group). The application site was washed at 10 hours and groups terminated at 10, 24 hr and 7 and 14 days. Hydramethylnon was absorbed 0.414, 0.861, 0.413 and 0.587 % respectively, skin residue 0.902, 0.926, 0.215 and 0.039 % respectively.

Attachments
DER
1-liner

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Data Evaluation Report

Compound Hydramethynon

Citation

Hydramethynon: Pharmacokinetics and material balance study following cutaneous administration to male Sprague Dawley® Rats, S.W. Frantz and J.L. Beskitt, Bushy Run Research Center, Laboratory Project ID # 92N1073, Oct 15, 1993, MRID 429891-01

Reviewed by Robert P. Zendzian PhD 12/30/93
Senior Pharmacologist

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MAXIFORCE® Gel formulation (2% hydromethynon) at a 2 gm nominal dose was applied to 10 cm^2 on the shaved back of the male rat (4/group). The application site was washed at 10 hours and groups terminated at 10, 24 hr and 7 and 14 days. Hydramethylnon was absorbed 0.414, 0.861, 0.413 and 0.587 % respectively, skin residue 0.902, 0.926, 0.215 and 0.039 % respectively.

Materials

^{14}C-Hydramethylnon	Lot No 930297 CASA No 67485-29-4 Specific Activity 5.1 mCi/mmol Radio Purity 98.3% yellow powder From Wizard Laboratories Davis Ca
^{14}C-Hydramethylnon	Gel formulation Formulated from above material By Clorox Co Lot No 5309-55 specific activity 14.1 mCi/g of gel Hydramethylnon content 1.8-2.05 % (w/w)
Hydramethylnon	Lot No 343 CASA No 67485-29-4 Purity 97.4% From Clorox Technical Center
Hydramethylnon	gel formulation Hydramethylnon content 2.15 % (w/w) From Clorox Technical Center

Blank Gel MAXIFORCE Gel (without hydramethylnon
Lot No 5442-8-1
From Clorox Technical Center

Young adult male Sprague Dawley® Rats
Approximately 8 weeks old
From Harlen Sprague Dawley Inc

Experimental Design

Group	# Rats	Dose Removed	Termination
1*	4	10 hr	10 hr
2*	4	10 hr	24 hr
3**	4	10 hr	1 week
4**	4	10 hr	2 week

Animals were dosed with a nominal dose of 2 gm of 2 % hydramethylnon gel containing 20 uCi per 10 cm^2 application site. The syringe used to apply the dose was weighed prior to and after dosing to determine the actual dose applied.

Site Preparation

"Approximately 24 hours prior to dose administration, the animals were lightly anesthetized using Metofane® and the fur cliped from the dorsal trunk of the animal in the thoracic region. The clipped area was wipped with acetone to produce a uniform dosing area across animals in the study. The dose site was contained using a "nonoclusive" covering consisting of a "frame" created from wafers made of Stomahesive® skin barrier (E.R. Squibb and Sons, Princeton NJ) that was applied to the animal under Metofane® anesthesia. This containment device allowed air circulation over the application site. These "frames" were cemented to the skin surface using Skin-Bond Cement which was spread evenly around a 0.5 cm border surrounding the dose site. A nylon mesh screen was affixed to the top surface of this frame using the Skin-bond cement was used to cover the dosed area. Glue application was initiated at least one-half hour before application of the dose to allow the cement to adequately cure. Upon dose application, the nylon screen was affixed to the "frame" with cement and the rat was returned to its (metabolism) cage to recover from anesthesia."

Dose application

"The amount of ^{14}C-hydramethylnon applied was determined by weighing the syringe prior to and after application of the dose, and 15-25 uCi was applied to the skin of each animal over a 2 X 5 cm area. Dose concentrations of ^{14}C were checked prior to and after dosing by liquid scintillation spectrometry (LSS)"

Washing of the application site

The ^{14}C-hydramethylnon was kept on the skin for 10 hr, then washed off with a waterless soap (D-TAM skin cleanser, Colormetric laboratories Inc, Des Plaines IL) to absorb the residual chemical, followed by a water rinse. After washing, the containment device was left in place and a porous bandage was used to cover the dose site for the ballance of the study. The skin washings and the containment device were assayed at the end of the experiment and included in the final ^{14}C recovery totals.

Sample Collection

Test animals were indvidually caged in Roth-type metabolism cages during the 10-hour exposure period and the post-wash period. Total urine and feces were collected. Excreta collections were 0-10 hours, 10-24 hours and for subsiquent 24 hour periods dependent upon the total duration of the individual animal. At termination the cages were washed with 50:50 methanol:water.

Termination

At the end of the study the animals were anesthetized and a blood sample was taken by cardiac puncture. The animals were sacrificed by anesthetic overdose. Urine from the bladder was collected and added to the last urine collection. Application site skin, the skin border under the frame of the containment device, the remaining skin and the skinned carcass were collected for separate analysis.

Results

The 24 hour stability determination of hydramethylnon in the gel gave an initial mean concentration of 2.00 % and a 24 hour concentration of 1.96 %

For treatment groups 1 and 2 the dermination of hydramethylnon in the gel gave an initial mean concentration of 1.96 % and a 24 hour mean concentration of 2.04 %.

For treatment groups 3 and 4 the dermination of hydramethylnon in the gel gave an initial mean concentration of 1.86 % and a 13 day mean concentration of 1.87 %.

The actual dose applied was as follows (data from tables 2 and 4 of Appendix 1);

	Group 1	Group 2	Group 3	Group 4
Formulation(g)	1.4763	1.4830	1.9857	1.992
Hydramethylnon(mg)	30.3	30.1	37.1	37.5

Dose distribution, as percent of applied dose, is summarized below and is presented in detail in tables 1 and 3 from Appendix 1 of the report.

Group	Not absorbed[a]	Absorbed[b]	Skin residue (absordable)[c]	Total Recovered
1	89.060	0.414	0.902	90.330
2	89.230	0.861	0.926	92.017
3	94.418	0.413	0.215	95.046
4	91.436	0.587	0.039	92.062

a. Total of soap, skin rinse, water rinse and containment device.
b. Total of plasma, RBC, urine, feces, cage wash, carcass and pelt
c. Amount in/on washed skin of application site.