DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Clariant Corporation
Ben Durham, Jr., Product Safety Manager
Functional Chemicals Division
625 East Catawba Avenue
Mount Holly, North Carolina 28120

RE: Docket No. 75N-183H
Comment No. PR9

Dear Mr. Durham:

This letter is in response to your submission dated September 13, 2002, filed as PR 9 under Docket Number 75N-183H in the Dockets Management Branch. This submission contains (1) the results of a 13-week dermal toxicity study of chloroxylenol (PCMX) in mice, and (2) a draft protocol for a 24-month dermal carcinogenicity study of PCMX in mice. The 13-week dermal toxicity study was conducted according to the agency's review and comments.

We have reviewed your submission and have the following advice for conduct of your planned 24-month dermal carcinogenicity study of PCMX in mice:

1. We recommend that the proposed study be conducted using Crl:CD-1®(ICR)BR mice that are 4 weeks of age at receipt, and that you begin dosing when mice are approximately 6 weeks of age, using 60/sex/dose group.

2. We recommend that the following doses be used: 0 (acetone), 3%, 10%, and 20%. After examining the data provided on mice dosed with 30% PCMX in the 13-week dermal toxicity study, we have concluded that is unlikely mice could be dosed for the length of the study at this dose level with acceptable survival.

3. For the histopathology portion of the study, please collect tissues from the larynx and pharynx in addition to the tissues you have already proposed.

4. Mice should be housed individually. This is recommended to prevent inadvertent oral exposure to the test article.

5. Acetone should be used as the vehicle.

6. We recommend that you do not perform interim sacrifices. These sacrifices would not provide additional important information and would limit the number of animals available for evaluation at 24 months.

75N-183H LET 39

7. You should notify the Division of Over-the-Counter Drug Products promptly, by telefax or a telephone call to the project manager, if the survival of any treatment group, especially the high-dose group, declines to 20 in order to discuss early termination of the affected dose group.

8. The schedule for in-life clinical observations appears to be acceptable.

Any comment you may wish to make on the enclosed information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

If you have any questions, please contact Tia Frazier, Project Manager, at 301-827-2271.

Sincerely yours,

Charles J. Ganley, M.D.

Charles J. Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V

Cc: HFD-305/Docket No. 75N-183H/PR9
HFD-520/Soreth/Sheldon/Bostwick/Dillon-Parker/Mulinde/Hastings
HFD-560/Ganley/Rosebraugh/Shetty/Lumpkins/Jackson/Hilfiker
OTC Tracking: #3210

PHARMACOLOGY/TOXICOLOGY COVER SHEET

Docket number: 75N-183
Sequence number/date/type of submission: 9/13/02; toxicology study and carcinogenicity protocol
Information to sponsor: Yes after the Exec CAC has discussed the protocol
Sponsor and/or agent: Clariant Corporation, Mt. Holly, NC
Manufacturer for drug substance: Same
Reviewer name: Terry S. Peters, D.V.M.
Division name: Anti-Infective Drug Products
HFD #: 520
Review completion date: 12/11/02

Drug:

Generic name (list alphabetically): Chloroxylenol
Code name: PCMX, Nipacide PX-R, parachlorometaxylenol, UN: 3077 or BX-K95-3
Chemical name: Phenol,4-chloro-3,5- dimethyl-4-chloro-3,5-xylenol
CAS registry number: 88-04-0
Molecular formula/molecular weight: C_8H_9ClO; 156.61

Relevant NDAs: 19128, 9004, 1668

Drug class: Active ingredient in topical antimicrobicide

Indication: Antisepsis of skin

Study title: A 13-Week Dermal Toxicity Study of PCMX in Mice

Key study findings: The NOAEL for this study is <30% PCMX applied dermally. The NOEL for this study is <15% PCMX. Signs and lesions were consistent with a mild dermal irritant.

Study no: WIL-304003
Conducting laboratory and location: WIL Research Laboratories, Inc., Ashland, OH
Date of study initiation: 10/30/01 for animal receipt; 11/12/01 for initiation of dosing
GLP compliance:
QA report: Yes except for the Certificate of Analysis performed by the sponsor
Drug, lot #, and % purity: Nipacide PX-R, parachlorometaxylenol, UN: 3077 or BX-K95-3 at 99.5% purity
Formulation/vehicle: Acetone, Lot #QN0014

Dosing:

Species/strain: Crl:CD®-1(ICR)BR mice
#/sex/group or time point (main study): 10
Satellite groups used for toxicokinetics or recovery: None
Age: 28 days on receipt by the laboratory
Weight: Males: 22.7- 29.6 g; females: 19.8- 24.0 gms
Doses in administered units: 0 (naïve), 0 (vehicle), 15%, 30% or 60% corresponding to approximately 0, 0, 250, 500 or 1000 mg/kg/d on the basis of a 30 gm mouse
Route, form, volume, and infusion rate: 50 μL/dose topically

Observations and times:

Clinical signs: Twice daily with detailed dermal examinations (according to the Draize methodology) once/week
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Weeks -1 and 12. The examinations were done by different ophthalmologists at the 2 timepoints
EKG Not performed

Hematology: First 5 animals euthanized at study termination. In the protocol review (DAIDP, 11/8/00), it was suggested that all control and high dose animals be evaluated and the remaining dose groups should be examined if effects were noted.

Clinical chemistry: Remaining animals at study termination. In the protocol review (DAIDP, 11/8/00), it was suggested that all control and high dose animals be evaluated and the remaining dose groups should be examined if effects were noted.

Urinalysis: Not performed

Gross pathology: All animals at study termination

Organs weighed: Adrenals, brain, epididymides, heart, kidneys, liver, ovaries with oviducts, spleen, testes, thymus, thyroid with parathyroid and uterus.

Histopathology: Histopathologic evaluation was performed by PAI, West Chester, OH by Dr. R. Bruner. Selected tissues from all animals were evaluated. Selected tissues were identified as all tissues in the list below from the vehicle control and high dose animals and skin (treated and untreated) and gross lesions from all animals. In the protocol review (DAIDP, 11/8/00), it was suggested that the "tissues listed below from control and high dose animals and skin and gross lesions from all others" be examined. In addition, from the same review, "It is recommended that any target tissues identified in the high dose animals be examined from all animals. Special attention should be paid to kidney and liver based upon the PK study."

Toxicokinetics: None were performed.

Results:

Mortality: All animals survived until study termination.

Clinical signs: In the high dose animals, very slight to moderate erythema and edema were noted during the entire dosing period. In the mid dose animals, very slight to moderate erythema and lesser edema were noted. At 15%, very slight to slight erythema and very slight edema were found. The sponsor stated that the "irritation was often sporadic and transient in nature and did not increase proportionately with repeated applications beyond study day 14." While the erythema persisted ("sporadically") in PCMX-treated animals throughout the study, the edema was not observed after day 42. The scabs were noted on day 14 in one/sex in the mid dose group and 4/10 males and 3/10 females in the high dose group. No scabs were noted after day 72 of the study. "Desquamation was noted on all animals in the PCMX groups" but the sponsor did not consider this finding to be indicative of test article irritation/adverse.

In the males at all doses, a yellow 'material' was found on the urogenital area. The sponsor concluded that this finding was not related to systemic toxicity.

Body weights: No treatment-related effects were reported.

Food consumption: No treatment-related effects were reported.

Ophthalmoscopy: No treatment-related effects were reported

Hematology: No treatment-related effects were reported.

Clinical chemistry: No treatment-related effects were reported.

Organ weights: In females, thymic weights were slightly increased with treatment but no differences from controls were appreciated in males. No histologic correlates were found in the females.

Gross pathology: Dermatologic findings included thickening and scabbing of the skin in 2 males and one female from the high dose PCMX-treatment group. Severity did not exceed moderate but did increase with increasing dose. Desquamation was reported for all PCMX-treated animals.

Histopathology: Microscopic changes were noted in all PCMX-treated animals, consistent with findings expected with a mild dermal irritant. They included epidermal hyperplasia (all dosed animals) and hyperkeratosis (6/10, 10/10 and 7/10 for respective male PCMX groups, and 6/10, 8/10 and 7/10 for the respective female PCMX groups), inflammation of the superficial dermis (most treated animals), serocellular crust formation and necrosis of epidermal cells. All findings ranged from minimal to moderate. As the dose increased, the lesions became more significant and in the high dose group, additional findings included hyperplasia of the bone marrow and increased extramedullary hematopoiesis in the spleen to respond to the increasing demand for leukocytes in the inflammatory reaction.

Although it was recommended that the livers and kidneys should receive 'special attention' on the basis of the PK study, they were not evaluated in the low and mid dose groups

Observations and times:

Clinical signs: Twice daily with detailed dermal observation once/week

Body weights: At least once weekly for the first 13 weeks, then every 4 weeks

Food consumption: As for body weights

Hematology: At study termination for all animals and when possible, all moribund and premature decedent animals.

Clinical chemistry: Not to be performed

Organ weights: Adrenals, brain, epididymides, heart, kidneys, liver, ovaries with oviduct, spleen, testes, thyroid with parathyroid, thymus, uterus

Gross pathology: All animals

Histopathology: All tissues on the tissue list for all premature decedents and all control and high dose animals. All gross lesions and tissue masses from all animals will be examined. Remaining tissues will be retained for possible evaluation. Reviewer comment: At least treated and untreated skin should be evaluated from all groups. Additionally, any and all target tissues identified in the high dose animals should be evaluated from all dosed animals.

Toxicokinetics: Not to be performed

Addendum/appendix listing:

Dose-ranging study report: 13 Week Study reviewed above

Executive CAC conclusions:

Tissue list: To include an adequate list and 3 sections of treated skin and nasal cavity

Reviewer signature: Terry S Peters, D.V.M.

Deputy Division Director Signature: 12/23/02

Summary of individual study findings: The NOEL for this study is <15% PCMX when dermally applied This was the lowest dose tested. At best, a NOAEL might approximate 30% PCMX. However, given the desquamation noted at all dose levels, in addition to the inflammatory response and necrosis of epidermal cells, it seems unlikely that the animals would tolerate any dose >15% for the 2 year period of the carcinogenicity study.

Histopathology Inventory for IND #

Adrenals	X
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	X
Cecum	X
Cervix	X
Colon	X
Duodenum	X
Epididymis	X
Esophagus	X
Eye	X
Fallopian tube	X
Gall bladder	X
Gross lesions	X
Harderian gland	X
Heart	X
Ileum	X
Injection site	
Jejunum	X
Kidneys	X
Lachrymal gland	
Larynx	
Liver	X
Lungs	X
Lymph nodes, cervical	
Lymph nodes mandibular	
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	X
Ovaries	X
Pancreas	X
Parathyroid	X
Peripheral nerve	X
Pharynx	
Pituitary	X
Prostate	X
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X

Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X
Sternum	X
Stomach	X
Testes	X
Thymus	X
Thyroid	X
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X

X, tissues collected and preserved

Carcinogenicity Protocol

Study title: A 24-Month Dermal Carcinogenicity Study of PCMX in Mice
Study number: None identified
Conducting laboratory and location: WIL Research Laboratories, Ashland, OH
Date of study initiation: None specified
GLP compliance: To be conducted in compliance
Drug, lot #, and % purity: None specified
CAC concurrence: Taken to Exec. CAC on 1/14/03

Study Type (2 yr bioassay, alternative model etc.)**: 2 year dermal bioassay**
Species/strain: Crl:CD-1®(ICR)BR mice
Number/sex/group; age at start of study: 60; 4 weeks at receipt
Animal housing: Individually
Formulation/vehicle: Acetone
Drug stability/homogeneity: To be determined by the sponsor
Methods:

Doses: 0 (acetone), 3, 10 and 30% PCMX in 50 μL volume
Basis of dose selection: 13 week dermal toxicity study
Restriction paradigm for dietary restriction studies: Not applicable
Route of administration: Dermal
Frequency of drug administration: Daily
Dual controls employed: No
Interim sacrifices: None. The sponsor will be notified if the number of survivors in any group "appears to be approaching 20" to discuss termination of the group. Additionally, the high dose group "may be terminated before 24 months if survival reaches 20 animals without terminating the other groups." This should only be done after consultation with the OTC division.
Statistical methods: In life data will be evaluated by one-way analysis of variance (ANOVA). Pairwise comparisons will be made by Dunnett's Test if the ANOVA is statistically significant.

A Kaplan-Meier survival curve will be calculated for each sex and group. A generalized Wilcoxon test for survival will compare the homogeneity across groups at the p= 0.05 level.

Tumor incidence data will be analyzed by Peto's method with standard fixed time intervals. For each tumor type, tumors may be grouped at the discretion of the study director. A 1-sided trend test will be conducted using dose coefficients.
An exact permutation test will be used for low incidence tumors. Trend tests will be conducted at the 0.025 and 0.005 significance levels.

Carcinogenicity Assessment Committee (CAC/CAC-EC) Minutes
Review of Carcinogenicity Study Design/Dose Selection Proposals

Application (IND/NDA) number: 75N-183H, Consult from OTC to HFD-520
Submission date and number: 9/23/02 to OTC; received HFD-520 on 11/1/02
Division: HFD-560 with consult to HFD-520
Project manager: Tia Frazier/ Frances Lesane
CAS#: 88-04-0
Drug name: Chloroxylenol, also known as Nipacide
Pharmacological Classification: Active ingredient in topical antimicrobicide. Included in the TFM
Sponsor/Applicant: Clariant Corporation, Mt. Holly, NC
Sponsor/Applicant contact name: Ben Durham, Jr., Product Safety Manager
Sponsor/Applicant telephone and fax number: (800) 548-6902
Date submitted (stamp date): 9/25/02
45-day date (from submission stamp date): Not applicable
P/T Reviewer(s): Terry S. Peters, D.V.M.
Date Review Completed: 12/11/02
Date of ExecCAC review: 1/14/03
CAC members: Contrera, Jacobs, Osterberg

Summary of Proposal for Review:

Species/strain: Crl:CD-1®(ICR)BR mice
Number/sex/dose: 60
Route: Dermal

	male	female
Doses proposed:	0, 3, 10 and 30%	same
(Approximate doses: 0, 50, 167 and 500 mg/kg/d)		
Basis of dose selection:		
MTD	x	x
AUC ratio		
saturation		
MFD		
PD		
other		

Kinetics submitted: None in current submission	rodent	human
pharmacokinetics		
metabolism		
protein binding		

Notable design features: Previous ^{14}C-labeled study in mice showed significant absorption (~50% of applied dose).

Summary of Recommendations to CAC

	male	female
Doses recommended by reviewer:	0, 3, 10 and 20%	Same

Basis for recommendation (details): The 13 Week Dermal Toxicity Study in Mice (doses: 0 (naïve), 0 (acetone vehicle), 15%, 30% and 60%) showed significant histologic dermal lesions (hyperplasia, thickening, hyperkeratosis, inflammation, serocellular crust formation). Additionally, desquamation was noted in all dosed animals. Bone marrow hyperplasia and increased extramedullary hematopoiesis were reported in the high dose animals. The NOEL was ≤15% PCMX with a NOAEL <30%.

CAC Concurrence (y/n): The Exec. CAC concurred with the reviewer's recommendations for the reduced dose regimen.

CAC Recommendations: To include the larynx and pharynx in the list of tissues examined.

Comments: This product was reviewed as a consult from OTC. A review of the 13-week study and the carcinogenicity protocol have been forwarded to OTC.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, HFD 520
/TPeters, HFD-X520
/CSO/PM, HFD-520
/ASeifried, HFD-024