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

004483

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUN 7 1985

MEMORANDUM

SUBJECT: KRENITE - Miscellaneous mutagenicity data submitted under Accession #256247

EPA Registration No. 352-376 Caswell No. 465G

FROM: Irving Mauer, Ph.D., Geneticist
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Richard Mountfort, PM 23
Registration Division (TS-767)

THRU: Jane E. Harris, Ph.D., Head
Section VI, TB/HEB (TS-769)

Registrant: E.I. du Pont de Nemours & Company

Action Requested:

Review and evaluate the following mutagenicity studies:

A. Unscheduled DNA Synthesis/Rat Hepatocytes in vitro HLR 680-82. (UDS/HPC)

B. CHO/HGPRT Assay for Gene Mutation HLR 676-82. (CHO/HGPRT)

C. In Vitro Assay for Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells HLR 683-82. (CHO/CA)

D. In Vivo Bone Marrow Cytogenetic Assay in Rats, Final Report HLO-724-82. (Rat BM/CA)

TB Evaluation/Conclusions: Data Reviews for these studies are attached to this memo.

Study	Type	Evaluation
A	UDS/HPC	[Note (1)]
B	CHO/HGPRT	ACCEPTABLE
C	CHO/CA	[Note (2)]
D	Rat BM/CA	ACCEPTABLE

Note (1): This study cannot be evaluated because pages 2, 4, and 6 (and possibly others?) are missing from the submission.

Note (2): This study cannot be evaluated because the report is missing pages 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 (and possibly others?).

TOXICOLOGY BRANCH: DATA REVIEW

Caswell 465G
Chem. # (N/A)
EPA Reg# 352-376

Chemical: KRENITE

Study Type: Mutagenicity: Gene mutation (HGPRT) in mammalian cells (CHO)

Citation: (B) "CHO/HGPRT Assay for Gene Mutation"

Accession No.: 256247

Sponsor/Testing Lab: DuPont/Haskell Laboratory

Study No./Date: HLR 676-82/November 3, 1982

Test Material:

INR-1108 [phosphonic acid, (aminocarbonyl)-, monoethyl ester, ammonium salt], Lot #560406-86 (41.5% ai), a water-soluble yellow liquid.

Procedures:

The materials and methods (a copy from the study report is attached) were adapted from generally acceptable methodology developed at Oak Ridge National Laboratory (Hsie et al., see GENE-TOX. Report: Mutation Research 86:193-214, 1981).

Briefly, following preliminary cytotoxicity experiments to select dosages, duplicate cultures of CHO-K1 cells (BH4 clone) were exposed to test material (undiluted) in increasing amounts up to cytotoxic levels of 40 uL/ml for 5 hours in cultures containing a rat hepatic microsome activation system (S-9), and to levels up to 33.3 uL/ml for 18 to 19 hours in nonactivated cultures. Reference mutagens tested as concurrent positive controls were ethylmethanesulfonate (EMS) for nonactivated assays, and dimethylbenzanthracene (DMBA) for activated assays. After the 7-day expression time, cells

were plated to assess survival and frequency of 6-thioquanine-resistant cells (mutants). Mutation frequencies (mf) were expressed as number of mutant colonies per 1 x 10^6 surviving cells, and transformed data analyzed by a two-variable (dose and experiment) ANOVA and a t-test of significance for both significant increases in mf and dose-response relationship; linear and quadratic (and/or higher order effects) were tested by the F-Test.

Results:

Krenite was toxic (<50% cell survival) to both nonactivated (3 separate trials) and activated cultures (2 experiments) at concentrations above 20 uL/ml and 30 uL/ml, respectively. At a level of 26.7 uL/ml Krenite in one of the nonactivation trials, a mf approximately two-fold over concurrent control was found, but statistical analyses of the 3 individual trials showed no indication of a positive dose-response. In neither of the activated assays was a significant mf observed even at concentrations into the cytotoxic range.

The investigators conclude that Krenite was not mutagenic in this CHO/HGPRT assay.

Conclusions/TB Evaluation:

Since this test was conducted according to procedures adequate to provide valid data (negative for HGPRT mutants in CHO cells), the study is ACCEPTABLE.

EPA Registration Number 7834-87

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TOXICOLOGY BRANCH: DATA REVIEW

Chemical: KRENITE

Caswell: 465G
EPA Chem.# (N/A)
EPA Reg. No. 352-376

Study Type: Mutagenicity -- Cytogenetics in rats

Citation: (D) In vivo Bone Marrow Cytogenetic Assay in Rats with H# 14,506. Final Report.

Accession No./MRID No.: 256247/NA

Sponsor/Testing Lab: DuPont/Hazleton Laboratories

Study No./Date: HLA 201-572/November 1, 1982.

Test Material: H# 14,506, ammonium ethyl carbamoylphosphonate, a yellow liquid supplied by the sponsor (presumed to be the technical).

Procedures:

A copy of the MATERIALS AND METHODS is appended to this review.

Briefly, groups of 12 male and 12 female Sprague-Dawley CD rats were gavaged once with the test material (in saline, and assumed to be 100% ai for dosing purposes) at levels of 0 (0.9% saline), 1000, 3,000, and 10,000 mg/kg (volume of 15 ml/kg for all groups). One-quarter of each group was sacrificed 6, 12, 24, and 48 hrs later, and bone marrows processed according to standard (referenced) procedures. At least 50 cells in metaphase per animal were analyzed for both structural (clastogenesis) and numerical (modal number) chromosome abnormalities. A group of six rats (three males, three females) were given 40 mg/kg cyclophosphamide (CP), and sacrificed 24 hrs later (positive control).

A Quality Assurance/Good Laboratory Practices statement was included in the Final Report, signed October 26, 1982, by Frederick G. Snyder, Manager, QA.

Results:

No animals died during this study, and except for soft feces observed shortly after treatment in two mid-dose animals (one male, one female) and three at the HDT (two males, one female), no adverse clinical signs were evident. No significant body weight changes were recorded in any Krenite-treated group.

Compared to saline controls (with 0.8 to 1.0 percent aberrant cells), no significant increases in structural chromosome aberrations or modal number (42 chromosomes) were found in any Krenite-treated group, whereas the positive controls (C) exhibited 36.6 percent aberrant metaphases ($p < 0.0000$ (1)), containing 1.948 aberrations per cell ($p < 0.0011$), more than one-half of which were complex rearrangements. Mean mitotic indices in the Krenite groups were not significantly different from controls.

The authors conclude that the test material was not clastogenic at any dose level tested.

Conclusions/TB Evaluation:

Under the conditions of this study, acute oral administration of the test materia_ apparently had no cytogenetic activity, even at high levels up to 10 grams/kg. ACCEPTABLE.

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