TXR-4055
10-17-84

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: DX-T6376; PP#3G2834: Du Pont response dated May 8, 1984.

TO: Robert Taylor/V. Walters
Product Manager #25
Registration Division (TS-767C)

FROM: W. Thomas Edwards, Pharmacologist W. Thomas Edwards 10-17-84
Section III, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Robert P. Zendzian, Acting Section Head
Section III, Toxicology Branch/HED (TS-769C) 10/18/84
and
William L. Burnam, Chief
Toxicology Branch/HED (TS-769C)

Responses are commented on by numbers:

Item 2, mutagenicity evaluation in Salmonella typhimurium: The additional data is adequate and satisfies deficiences. The study is acceptable.

Item 3; CHO/HPRT assay: The explanation is adequate. The study is now acceptable.

Item 4, in vivo cytogenic studies: Animal toxicity is not an indication that CINCH was absorbed (orally) in concentrations sufficient to affect target tissue. Therefore we recommend a repeat assay and suggest using parenterial administration.

Item 5, UDS assay in rat hepatocytes in vitro: The explanation is adequate the study is now acceptable.

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DATA REVIEW

Study Type: CHO/HGPRT Assays for gene mutation.

Accession Number: 071435 (1/1) MRID 125826-125841

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 612-82.

Date: October 27, 1982.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, Technical).

Protocol:

The Chinese Hamsters Ovary (CHO) cell line was used to detect mutations in a gene coding for the enzyme hypoxanthineguanine phosphoribosyl transferase (HGPRT).

Two assay trials were made without S-9 activation and 3 trials with S-9 activaiton. Dosage levels were 0, 0.5, 1.0, 2.0, 3.5, and 7.0 mM. The positive control without S-9 was methanesulfonic acid, ethyl ester (EMS). The positive control with S-9 was 7,2-dimethylbenz[a]anthracene. Additional plates were prepared for determining survival data for each trial.

Results:

All test results were negative i.e., no difference in change of enzyme activity, but survival results for exposed cells did not reach or closely approach criteria stated in experimental design (i.e., 10% of control survival).

Conclusions:

Results provisionally accepted, but testing with higher concentrations to meet stated criterion is required.

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DATA REVIEW

Study Type: Mutagenicity evaluation in Salmonella typhimurium.

Accession Number: 071435 (1 2)

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 927-80.

Date: November 14, 1980.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-11, approximately 100%).

Protocol:

The following tests were performed according to the Ames procedure.

Salmonella typhimurium strain	Activation, S-9	Concentration ug/plate	Plates per concentration	Positive control ug/plate
TA 1535	no	0 to 50.0	4	MNNG 4
TA 1535	yes	0 to 50.0	4	2AA 10
TA 1537	no	0 to 5.0	3	9AAc 50
TA 1537	yes	0 to 10.0	3	2AA 10
TA 98	no	0 to 5.0	3	2NF 25
TA 98	yes	0 to 10.0	3	2AA 10
TA 100	no	0 to 5.0	3	MNNG 4
TA 100	yes	0 to 10.0	3	2AA 5

Test solvent and negative control: Dimethylsulfoxide
positive controls:

MNNG, N-methyl-N'-nitro-N-nitrosoquanidine
2AA, 2-aminoanthracene
9AAc, 9-aminoacridine
2NF, 2-nitro-fluorene

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Results:

Results as reported were all negative i.e., no increase in revertents over negative control. Additional data are needed. - (1) Cytotoxicity data. (2) Mutant frequency data. Also exposure of TA 98 and TA 100 did not extend into the toxic range. Activated Cell used.

Conclusion:

Results provisionally accepted. Additional data are required. See above.

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DATA REVIEW

Study Type: Unscheduled DNA synthesis (UDS) assay, rat hepatocytes in vitro.

Accession Number: 071435

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 770-82.

Date: January 6, 1983.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, technical).

Protocol:

Freshly isolated hepatocytes from the livers from an unstated number of eight-week old male Charles River Sprague-Dawley rats were treated with DPX-T6376 in vitro and the incorporation of ^{3}H-thymidine measured as a measure of unscheduled DNA repair. Detection of 5 grains or more (after background correction) over a nucleus is considered a positive response.

Solvent was DMSO, present in all tests, as well as in negative and positive controls. Positive control substance was 7,12dimethylbenz[a]anthacene (DMBA).

Test compound concentrations were 0, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 0.1, and 1.0 mM DPX-T6376 in trial I, and 0, 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 0.1, and 1.0 mM in trial 2.

Results:

Negative, i.e., <5 grains/nucleus at any concentrations tested.

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Conclusions:

Unacceptable data, since

1. No cytotoxicity data.
2. At least 3 animals of each sex are required.
3. Treatment to toxicity levels must be performed.
4. Suggest that hepatocytes isolated from treated animals be sampled for UDS.

Explanation acceptable.
Not mutagenic in concentration tested.

Core classification:

acceptable

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Thomas Edwards