(6-14-1998)

DATA EVALUATION RECORD

DIMETHYL DODECYLAMINE OXIDE (UDX-7577)

Study Type: 84-2; Dominant Lethal Assay in Mice

Work Assignment No. 3-27 (MRID 44475204)

Prepared for

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Disclaimer

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DATA EVALUATION RECORD

STUDY TYPE: Dominant lethal assay in mice
OPPTS Number: 870.5450 OPP Guideline Number: §84-2

DP BARCODE: D244775 SUBMISSION CODE: S538885
P.C. CODE: 000439

TEST MATERIAL (PURITY): Dimethyl dodecylamine oxide (purity not provided)

SYNONYMS: UDX-7577

CITATION: Harris, C.J. and Pieper, K.M. (1975) The Evaluation of Dimethyl Dodecylamine Oxide (UDX-7577) in the Dominant Lethal Assay. The Proctor & Gamble Company, Cincinnati, Ohio. Laboratory Notebook No. V8192, October 1, 1975. MRID 44475204. Unpublished.

SPONSOR: The Proctor & Gamble and Company, Cincinnati, Ohio.

EXECUTIVE SUMMARY:

In a dominant lethal assay (MRID 44475204), groups of 20 male $C_3D_2F_1/J$ mice were exposed orally to dimethyl dodecylamine oxide (DDAO) in water for 5 consecutive days at dose levels of 0, 10, 100, or 1,000 mg/kg, then mated sequentially to groups of untreated female mice (1 male:2 females) for seven 7-day periods. Females were sacrificed 13 or 14 days from the midpoint of the mating periods and assessed for total implantations, resorptions, and dead embryos. The incidence of pregnancy, average total implantations per pregnant female, average number of fetal deaths per pregnant female, and the mutagenic index were calculated for each mating period and the collective (except mutagenic index) mating periods. Between control and treated animals, no reduced fertility nor variations in any determined dominant lethal parameter were detected.

This study is classified as **unacceptable according to FIFRA Test Guideline §84-2 (not upgradable)** because (i) there was no evidence that the compound penetrated to the target tissue, as in the form of reduced fertility, (ii) positive concurrent controls were not included in the study, (iii) the test substance was neither tested to the limit dose (5,000 mg/kg) nor was it reported whether toxicity occurred at the highest dose tested (1,000 mg/kg) and (iv) the purity of the test substance was not provided.

COMPLIANCE: A signed and dated statement that the study was conducted prior to January 28, 1984 and, therefore, was not subject to GLP compliance requirements was provided. A signed and dated No Data Confidentiality statement was also provided.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Dimethyl dodecylamine oxide (UDX-7577; DDAO)
   Description: None provided
   Lot/Batch #: Not provided
   Purity: Not provided (see Other Comments)
   Stability of compound: Not provided
   CAS #: Not provided
   Structure: Not provided
   Solvent used: Water
   Other comments: The test substance was in the form of a 27.7% aqueous solution. It is unknown whether this refers to the percent active ingredient or the percent used to prepare dose formulations.

2. Control materials:

   Vehicle/Final volume/Route of administration:
   Water/final volume not reported/oral

   Positive/Final dose(s)/Route of administration:
   Positive controls were not included.

3. Test compound administration:

   Volume of test substance administered: Volume not reported

   Route of administration: Oral

   Dose levels used: 10, 100, or 1,000 mg/kg body weight in water. The rationale for dose selection was not indicated.

4. Test animals: Species: Mouse
   Strain: $C_3D_2F_1/J$
   Age and weight at start of treatment: Not provided
   Source: Jackson Labs, Bar Harbor, Maine
   Acclimation period: One week
   Diet: Not reported
   Water: Not reported

B. STUDY DESIGN

Table 1: Study design.

Test Group	Dose to Animal (mg/kg)[a]	Animals Assigned	
		Males	Females
Untreated Control	0	20	280
Vehicle Control	0	20	280
Low	10	20	280
Mid	100	20	280
High	1,000	20	280

a Administered to males only once daily for 5 consecutive days. Females were not treated.

1. Animal assignment and environmental conditions: Animals were housed individually except during mating (1 male:2 females) and males were assigned randomly to the treatment groups shown in Table 1. Environmental conditions and caging description were not reported.

2. Compound preparation: The test substance was used as a 27.7% aqueous solution. The method of achieving dose levels of 10, 100, or 1,000 mg/kg was not reported. Compound concentration and homogeneity of the dosing mixtures were not analyzed.

3. Test compound administration: The test substance was administered to males once daily for five consecutive days prior to mating.

4. Animal observations: Not reported

5. Dominant lethal assay:

   a. Mating: Beginning on the last day of treatment, each male was individually housed with two untreated virgin females for seven sequential mating periods lasting seven days each. The mating procedure was designed to encompass all testicular germ cell stages during a 49 day period to ensure that groups of females were inseminated with sperm from males during each stage of spermatogenesis. Vaginal smears were not prepared and no check was made for vaginal

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plugs. Positive controls were not included.

b. Examination and scoring of uteri: At 13 or 14 days of pregnancy (as measured from the mid-week of presumptive mating) the females were sacrificed. The uterine contents were examined and scored for total implantations, resorptions, and dead embryos. Corpora lutea were not counted. Early and late fetal deaths were scored individually for each pregnant mouse and weekly averages were determined for each test group. The following weekly calculations were made:

1. Incidence of pregnancy = number of pregnant females/total females x 100%

2. Average total implantations per pregnant female = total implantations/# pregnant females

3. Average # fetal deaths per pregnant female = total fetal deaths/# pregnant females

4. Mutagenic index = (resorptions + dead embryos)/total implantations x 100%

c. Statistical methods: The Chi-Square test was used to compare values obtained from each test group to the concurrent control group. Statistical significance was reported at $p \leq 0.05$.

d. Evaluation criteria: In this dominant lethal assay, the test substance was considered positive if there was a statistically significant (1) increase in the frequency of dead implantations, (2) reduction in the average number of living embryos, (3) reduction in the average number of implantations, and (4) reduction in the frequency of fertile matings.

II. REPORTED RESULTS:

A. Animal observations

Clinical signs of toxicity were not reported.

B. Dominant lethal assay

No significant differences were observed in the pregnancy rate, average number of total implants, average number of total resorptions, or average number of fetal deaths per pregnancy. The number of implantations, resorptions, and dead fetuses in the controls and treated mice are presented as an attachment (Attachment I) to this DER (study report Table V, page 13). The data also indicate no dose response or treatment-related

mutagenic effects when expressed as the mutagenic indices. The mutagenic indices for weeks 1 through 7 are presented as an attachment (Attachment II) to this DER (study report Table IV, page 12).

III. DISCUSSION/CONCLUSIONS

A. Investigator's conclusions

There were no significant differences observed between treated and control animals in regard to the number of dead implants per pregnant female, living implants per pregnant female, percentage of fertile matings, and/or average number of implantations. The study authors concluded that in this dominant lethal assay, DDAO showed no evidence of mutagenesis in germinal cells following oral doses of 10, 100, or 1,000 mg/kg on five consecutive days to male mice.

B. Reviewer's discussion

Following administration of oral doses of DDAO to male mice on five consecutive days, there was no indication of a mutagenic effect at any stage of spermatogenesis based on indirect mating evidence. At 10, 100, or 1,000 mg/kg there were no significant differences ($p \leq 0.05$) in dead implants per pregnant female, living implants per pregnant female, percentage of fertile matings, and/or average number of implantations. However, there was no evidence presented (no positive control included) that a positive mutagenic agent would induce dominant lethal mutations in the mouse strain used. In addition, the purity of the test substance was not provided, DDAO was not tested to the limit dose (5,000 mg/kg) and, since animal observations were not reported, it could not be determined whether any toxicity occurred at the highest dose tested (1,000 mg/kg). Therefore, there is no evidence that mutagenic effects of DDAO could be manifested in this strain under the conditions of this test.

C. Study deficiencies

This study is judged to be unacceptable because neither evidence for transport of the test compound to the target tissue (resulting in at least reduced fertility) nor a positive concurrent control group was included to evaluate the sensitivity of the test strain to mutagenicity. Also, the purity of the test substance was not provided, the actual concentrations and the homogeneity of the dosing solutions were not tested, the highest dose level tested was only 20% of the recommended limit dose, and clinical observations to indicate the presence of a toxic effect were not reported. Other deficiencies noted were the absence of the following: individual animal data, lot/batch number, physical description and stability of the test substance, rationale for dose

selection, volume of dose administered to the animals, animal ages and weights, animal husbandry, and environmental conditions.

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ATTACHMENT 1

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY
SEE THE FILE COPY

Table V

Composite Group Data For Entire Study

DDAO Dominant Lethal Assay

Implantations, Resorptions and Dead Fetuses

Group	% Pregnant	Implants Total/Average	Resorptions Total/Average	% Resorptions	Total Dead Fetuses
No Dose Control	86.7	2182/8.98	96/0.40	4.39	5
H_2O Control	86.4	2156/8.91	73/0.30	3.38	11
DDAO 1000 mg/kg	86.0	2273/9.43	73/0.30	3.21	5
DDAO 100 mg/kg	88.2	2296/9.30	77/0.31	3.35	13
DDAO 10 mg/kg	87.1	2352/9.64	94/0.38	3.99	8

ATTACHMENT 2

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY
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Table IV

DDAO Dominant Lethal Assay

Mutagenic Indices

Week Post Treatment	No Dose Control	H_2O Control	DDAO 1000 mg/kg	DDAO 100 mg/kg	DDAO 10 mg/kg
1	6.4	4.1	4.5	5.6	7.3
2	6.5	6.5	4.6	4.8	2.8
3	5.0	4.9	3.7	5.5	3.6
4	4.4	2.4	2.4	2.4	3.7
5	4.5	5.1	4.4	4.0	4.3
6	2.5	3.1	2.3	2.4	3.6
7	3.4	3.0	2.3	2.5	3.0