UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

06601

DATE: March 10, 1980

SUBJECT: EPA Reg.#239-2186; Three-Week Inhalation Study in rats exposed to an aerosol of paraquat. CASWELL#634 Accession#241818

WHD 3/10/80 WSW

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Recommendations:

1. The report is acceptable only as supplementary data. The report stated all remaining animals (terminal kills) were killed at the end of the series of exposures or following a 3 week recovery period. A macroscopic examination was performed and tissues were fixed as described for interim kills. No histopathological examination was carried out. In view of the fact that no macroscopic findings were detected in the interim kill high dose rats but microscopic lesions were present, Toxicology Branch requests that microscopic examination of the terminal kill low dose rats be performed in order to determine if a NOEL for the study exists. The data as presented in the report precludes the establishment of a NOEL for the study, although the objective of the sponsor is supported.

2. There was no adverse effect on body weight gain in the treatment groups.

Review:

Three-Week Inhalation Study in Rats Exposed to an aerosol of paraquat (Huntingdon Research Center, ICI 279/79476, Dec. 6, 1979)

Test Material: Paraquat technical liquor diluted with distilled water; 40% A.I.; brown liquid.

Two-hundred and ninety-four albino rats (147 male and 147 female) of the Sprague-Dawley CD strain were obtained from Charles River UK Limited. The weight ranges were 106-126 gm and 112-138 gm for females and males respectively. One hundred and forty-four male and 128 female rats were used during the study. The groups and dose levels as shown below:

EPA FORM 1320-6 (REV. 3-76)

Group	Number of Animals Males	Females	Treatment
1 (control)	36	32	No aerosol
2 (control)	36	32	Saline aerosol
3 (low dose)	36	32	0.01 ug paraquat ion/L
4 (high dose)	36	32	0.10 ug paraquat ion/L

The rats were exposed six hours a day, 5 days a week for 3 weeks (total 15 exposures) in a whole - body exposure in a 6 m^3 inhalation chamber. Aerosol (0.7 microns) was produced by ultrasonic nebulisation of a solution of paraquat.

The concentration of paraquat ion in each chamber was determined twice and the particle size destribution once during each exposure. The saline aerosol was not analyzed. The mean (Standard deviation) aerosol concentration analyzed for each chamber twice during each exposure was as follows:

Group	mean aerosol Concentration (S.D.) ug paraquat ion/L	No. of analyses
3 (low dose)	0.012 (0.002)	30
4 (high dose)	0.110 (0.001)	30

Particle size analysis (cascade inpactor) indicated that all particles in the aerosol were < 0.7 microns in mean aerodynamic diameter.

Each animal was weighed twice weekly (Monday and Thursday) throughout the study except for the first 7 days following the start of exposures, when all animals were weighed daily. Food consumption was measured weekly. Water consumption for each cage of rats daily over a 5 day period (Monday to Friday). Clinical signs were recorded twice daily.

Three days after the first exposure and 1 day after the third exposure 4 male and 4 female rats from each group (total 64 animals) were killed and examined both macroscopically and microscopically. Histopathological examination was restricted to nasal passages, pharynx, larynx and lungs. An additional 4 male rats from each group (16 animals) were killed 1 day after the third exposure for macroscopic examination of the nasal passages, including turbinates, only.

All remaining animals killed either at the end of the series of exposures or following a 3 week recovery period were examined macroscopically only.

Results: There were no treatment-related effects on body weight, food consumption, water consumption and clinical signs.

The macroscopic examination revealed no treatment-related abnormalities. The histopathological examination revealed changes only in the larynges rats from group 4 (0.10 ug paraquat ion/liter). In animals examined 3 days after the first exposure in group 4, there was squamous metaplasia and/or hyperplasia predominantly in the ventro-lateral aspect at the base of the epiglottis in all 8 rats. Focally, in some rats, the original respiratory epithelium overlay the metaplastic type.

In animals examined 1 day after the third exposure to 0.10 ug paraquat ion/liter there were areas of ulceration, often associated with necrosis, acute inflammatory cell infiltration, and sometimes squamous metaplasia and/or hyperplasia of adjacent epithelia in all 8 rats examined. These changes were most marked at the level corresponding with the base of the epiglottis and the arytenoid projections.

Macroscopic examination of the nasal turbinates in the 4 male rats from each group killed specifically for this purpose revealed no abnormalities. No treatment-related macroscopic abnormalities were seen in terminal kills.

Conclusion: Since the object of the study was to determine whether the reduction in body weight gain seen in a previous study (HRC No. ICI/245/7949) in male rats exposed at 0.10 and 0.01 ug paraquat ion/L was repeatable and whether this effect could be related to pathological changes in the respiratory tract seen after exposure to 0.1 ug paraquat ion/L, the conclusion that no adverse effect on body weight gains in treatment groups supports the objective of the study. However, the NOEL for the present study, as presented in recommendation #1, has not been establishmed.

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Chemical:	**4,4'-Bipyridinium, 1,1'-dimethyl-, dichl**
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