11 10 pages

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

013491

Chemical Name: Paraquat (1,1'-Dimethyl-4,4'-bipyridinium ion; present as the dichloride salt)

PC Code: 061601

The Health Effects Division Less-Than-Lifetime/Peer Review Committee considered the toxicity data available for this chemical at meetings held on July 25 and August 1, 1995. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: Krystyna K. Locke Krystyna K. Locke Date: 8/7/95

Section Head: Roger Gardner Roger Gardner Date: 8/9/95

Acting Branch Chief: Marion P. Copley Marion P. Copley Date: 8/9/95

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Dermal Absorption Data (consideration of oral and dermal data in same species for comparison of toxicity by each route)

Studies Selected - Guideline Nos.: 85-2

MRID: 00153439 (Dermal absorption study with adult male volunteers)

% absorbed: 0.3

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Acute Dietary Endpoint (One Day)

Studies Selected - Guideline Nos.: None available

Endpoint and dose for use in risk assessment: None

Comments about study and/or endpoint: No data are available that suggest a need for an acute dietary endpoint.

This risk assessment is not required.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Studies Selected - Guideline Nos.: 82-4 Three-week inhalation study with rats and 83-3a Developmental toxicity study with rats.

MRIDs: 00113718 and 00113714

Summaries: (1) In a repeated dose inhalation toxicity study, Sprague-Dawley rats were exposed (whole body) to respirable aerosols of paraquat dichloride (cation content: 40%; particle size: < 2 um in diameter) for 3 weeks (6 hours/day, 5 days/week). The concentrations of paraquat cation in the inhalation chambers were 0, 0.01, 0.1, 0.5 and 1.0 ug/L (nominal) or 0, 0.012, 0.112, 0.487 and 1.280 ug/L, respectively, (analytical). The numbers of rats of each sex assigned to these groups were as follows: 32 (control group), 16 (0.5 ug/L group) and 36 (remaining groups). Parameters examined included observations for toxic signs, body weights and food consumption. One-half of the rats in each group were examined grossly and microscopically after 15 exposures and the remaining rats were examined 2 weeks after the termination of the exposures (recovery period). These examinations were restricted only to the respiratory tract (nasal passages, pharynx, tongue, larynx, trachea and lungs). The 1.0 ug/L group was abandoned after the first exposure because 28 males (78%) and 29 females (80%) died from respiratory failure after that exposure.

Toxic signs were not observed in the 0.01 ug/L group and there was no mortality in this or the other test groups. All rats in the 0.1 ug/L group had nasal discharge and squamous keratinizing metaplasia, and/or hyperplasia of the epithelium of the larynx. The changes in the epithelium were still observed in 69% of the rats sacrificed at the end of the recovery period. The following findings were reported for the 0.5 ug/L group examined after 3 weeks of

treatment: (1) extensive ulceration, necrosis, inflammation and squamous keratinizing metaplasia, and marked/moderate hyperplasia of adjacent epithelia---in the larynx of all rats; and (2) aggregations of foamy macrophages in the bronchioles or alveoli, hypertrophy of the epithelium and thickened alveolar walls---in the lungs of most or all rats. After a 2-week recovery period, no ulceration or necrosis was observed in the larynx, but changes in the lungs were still seen. In addition, disruption of bronchiolar epithelium, adjacent to the macrophage aggregation, was noted.

Considering the above findings, the NOEL and LOEL for sub-chronic (3 weeks) inhalation toxicity, for both sexes, are 0.01 ug/L and 0.10 ug/L, respectively, expressed as paraquat cation. **(MRID 00113718)**

(2) Paraquat dichloride (purity: 100%) was administered by gavage in 0.5% aqueous Tween 80 to groups of 29-30 Alderley Park SPF rats at dose levels of 0, 1, 5 or 10 mg/kg/day, expressed as paraquat cation, from gestation day 6 through 15. The test solutions were administered in a volume of 1 ml/100 g of body weight. Control females received the same volume of 0.5% Tween 80 alone. Females were observed for changes in appearance or behavior and body weights were determined at intervals during gestation. The rats were sacrificed on gestation day 21 and reproductive observations were made and uteri examined for live fetuses and intra-uterine deaths. Fetuses were weighed, sexed, and examined for external, visceral and skeletal alterations. Doses used in this study were based on the results of a range-finding study in which doses (paraquat cation) of 5, 10, 20 or 40 mg/kg/day were tested and which was briefly summarized in this submission. (In the range-finding study, all rats died in the 40 mg/kg group and one rat died in the 20 mg/kg group. The nonsurvivors had dark red lungs or dark red patches on the lungs).

Maternal toxicity was reported at the two highest doses and included (1) deaths (2 and 6 in the mid-dose and high-dose groups, respectively, compared with none in the control group); (2) clinical signs such as piloerection, thin and hunched appearance, and decreased body weight gain (24% and 29% less than controls for the mid-dose and high-dose groups, respectively); (3) respiratory distress in 3 high-dose females; and (4) histopathological findings in the lungs (edema in the alveoli and polymorph infiltration) and in the kidneys (degenerative changes in the proximal tubules) of the nonsurvivors. Treatment-related developmental effects (delayed ossification in the forelimb and hindlimb digits) were observed only in the mid-dose and high-dose groups. It was reported that 41.9% of the control

group fetuses had good forelimb digit ossification compared with 28.8% and 23.0% of the mid-dose and high-dose fetuses, respectively. Similar results were noted for the hindlimb digit ossification.

Based on the above findings, the NOEL and LOEL for maternal toxicity are 1 mg/kg/day and 5 mg/kg/day, respectively, expressed as paraquat cation. The NOEL and LOEL for developmental toxicity are also 1 mg/kg/day and 5 mg/kg/day, respectively. **(MRID 00113714)**

Endpoints and doses for use in risk assessment:

(1) 0.01 µg/L, expressed as paraquat cation (NOEL for subchronic inhalation toxicity, based on nasal discharge and squamous keratinizing metaplasia and/or hyperplasia of the epithelium of the larynx).

(2) 1 mg/kg/day, expressed as paraquat cation (NOEL for maternal toxicity, based on unscheduled deaths, thin and hunched appearance, decreased body weight gain, and histological changes in the lungs and kidneys of the nonsurvivors.)

Comments about studies and/or endpoint: Exposure by inhalation and by the dermal route, extrapolating data (NOEL) from the rat developmental toxicity study and correcting for dermal absorption (0.3%), seemed appropriate for short term occupational and residential exposure.

This risk assessment is required.

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Intermediate Term Occupational or Residential Exposure (1 Week to Several Months)

Studies Selected - Guideline Nos.: 82-4 Three-week inhalation study with rats and 83-3a Development toxicity study with rats.

MRIDs: 00113718 and 00113714

Summaries: The same as for the Short Term Occupational or Residental Exposure (1 to 7 Days)

Endpoints and doses for use in risk assessment:

(1) 0.01 µg/L, expressed as paraquat cation (NOEL for subchronic inhalation toxicity, based on nasal discharge and squamous keratinizing metaplasia and/or hyperplasia of the epithelium of the larynx).

(2) 1 mg/kg/day, expressed as paraquat cation (NOEL for maternal toxicity, based on unscheduled deaths, thin and hunched appearance, decreased body weight gain, and histological changes in the lungs and kidneys of the nonsurvivors.)

Comments about studies and/or endpoint: Exposure by inhalation and by the dermal route, extrapolating data (NOEL) from the rat developmental toxicity study and correcting for dermal absorption (0.3%), seemed appropriate for intermediate term occupational and residential exposure.

This risk assessment is required.

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Chronic Occupational or Residential Exposure (Longer Than Several Months)

Study Selected - Guideline No.: 83-1b

MRID: 00132474

Summary: Groups of 6 male and 6 female Alderley Park beagle dogs were fed diets containing technical grade paraquat dichloride (cation content: 32.3%) for 52 weeks. The amount of food offered daily each dog was 400 g. The dose levels used were 0, 15, 30 or 50 ppm, expressed as paraquat cation. Based on the actual group mean body weights and food consumption, these doses corresponded to 0, 0.45, 0.93 or 1.51 mg of paraquat cation/kg/day, respectively, in the case of male dogs. For female dogs, these doses corresponded to 0, 0.48, 1.00 or 1.58 mg or paraquat cation/kg/day, respectively. The doses used in this study were based on the results obtained in the 90-day feeding study (MRID 00072416) which had been discussed in the subchronic toxicity section of this document.

The major effect of paraquat was a dose-related increase in the severity and extent of chronic pneumonitis in the mid-dose and high-dose male and female dogs. This effect was noted also in the low-dose male group, but was minimal when compared with the male controls. Chronic pneumonitis was less severe in the low-dose female group than in the female controls. Because 44 dogs (out of 48 studied), including 6 male and 5 female controls, had some degree of chronic pneumonitis, paraquat had no effect on the incidence of this lesion. Other findings observed only in the high-dose dogs were (1) significant ($P<0.01$) increases in the group mean lung weights (absolute or adjusted for body weight, 36% in males and 61% in females) and in spleen weights (absolute or adjusted for body weights, 50-55% in males and 38-43% in females), when the paraquat-treated dogs were compared with

the controls; (2) hyperpnea in 67% males and females; and (3) increased vesicular sound in 50% males and 67% females. Only one lenticular cataract (minimal, in a mid-dose female) was observed in this study. Based on the above findings, the systemic NOEL is 15 ppm (males: 0.45 mg/kg/day and females: 0.48 mg/kg/day, expressed as paraquat cation). The systemic LOEL is 30 ppm (males: 0.93 mg/kg/day and females: 1.00 mg/kg/day, expressed as paraquat cation). **(MRID 00132474)**

Endpoint and dose for use in risk assessment: 0.45 mg/kg/day, expressed as paraquat cation (NOEL for systemic toxicity, based on the severity and extent of chronic pneumonitis in both sexes).

Comments about study and/or endpoint: None

This risk assessment is required.

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Cancer Classification and Basis: Group E, based on a lack of evidence of carcinogenicity in acceptable studies with two animal species, rat (83-1a/83-2a; MRIDs 00138637, 00153223, 40202401, 40202402, 41317401, 40218001) and mouse (83-2b; MRIDs 00087924, 40202403), by the Toxicology Branch Peer Review Committee (now Carcinogenicity Peer Review Committee) on June 15, 1988, and (again) on March 15, 1989.

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RfD and Basis: 0.0045 mg/kg/day, expressed as paraquat cation, based on the results of the one-year dog feeding study and the uncertainly factor (UF) of 100.

NOEL for critical study: 0.45 mg/kg/day, expressed as paraquat cation (based on the severity and extent of chronic pneumonitis in both sexes).

Study Type - Guideline No.: 83-1b Chronic feeding in the non-rodent.

MRID: 00132474

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Acute Toxicity Endpoints

The table below summarizes the acute toxicity studies on paraquat dichloride and the toxicity categories for the different routes of administration. Because there were differences in the toxicity categories in some instances, both sets of data---old studies and studies submitted in July, 1995---have been included in this document.

ACUTE TOXICITY DATA FOR PARAQUAT DICHLORIDE

Test	OLD STUDIES		NEW STUDIES ###	
	RESULTS	CATEGORY	RESULTS	CATEGORY
Acute oral LD_{50} (rat)	189 mg/kg ♂ # 125 mg/kg ♀	II[1]*	344 mg/kg ♂ 283 mg/kg ♀	II[2]
Acute Dermal LD_{50} (Rabbit)	174 mg/kg ♂ #	I[3]*	> 2000 ♂+♀	III[4]
Acute Inhalation LC_{50} (Rat)	1 µg/L ♂+♀ ##	I[5]*	No new study	--
Eye Irritation (Rabbit)	Severe irritation #	I[6]*	Moderate irritation	II[7]
Dermal Irritation (Rabbit)	Slight to severe irritation; PIS = 2.1 #	III[8]*	Slight irritation	IV[9]
Dermal Sensitization (Guinea pig)	Negative #	--[10]	Negative	--[11]

* Indicates results used for regulatory purposes. The new studies were considered in this Reregistration Eligibility Decision Document at the request of the registrant.

[1] MRID No. 00054573
[2] MRID No. 4368501
[3] MRID No. 00054574
[4] MRID No. 4368502
[5] MRID No. 00046105
[6] MRID No. 00054575
[7] MRID No. 43685003
[8] MRID No. 00054576
[9] MRID No. 43685004
[10] MRID No. 00155289
[11] MRID No. 43685005

\# The test material used in these studies was paraquat dichloride in the form of ORTHO Paraquat Concentrate 3 (end-use product containing 34.4% of paraquat cation). The LD_{50} values are expressed in terms of the test material (and not the cation).

\## The test material used in this study was crystalline paraquat dichloride. Purity was not specified, but crystalline paraquat dichloride used in other studies was 99.9% pure. The LC_{50} value is expressed as paraquat dichloride (and not as paraquat cation).

\### The test material used in these studies was paraquat technical concentrate which is 45.6% paraquat dichloride (cation content: 33% w/w). The LD_{50} values are expressed in terms of paraquat dichloride (and not as paraquat cation).