820K88129

August, 1987

PARAQUAT

DRAFT

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

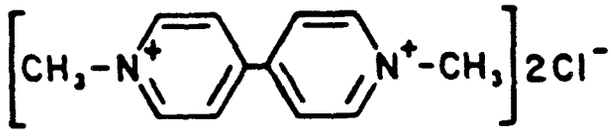
Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

Paraquat, with a chemical name 1,1'-dimethyl-4,4'-dipyridinium ion, is present mostly as the dichloride salt (CAS No. 1910-42-5) or as the dimethyl sulfate salt (CAS No. 2074-50-2, molecular weight 408.48) (Meister, 1987). Contents discussed below pertain to paraquat dichloride.

CAS No. 1910-42-5

Structural Formula



1,1'-Dimethyl-4,4'-bipyridinium-dichloride

Synonyms

- o-Paraquat dichloride, Gramixel, Gramonol, Gramoxone, Gramuron, Pathclear, Totacol, Weedol (Meister, 1985).

Uses

- Contact herbicide and desiccant used for desiccation of seed crops, for noncrop and industrial weed control in bearing and nonbearing fruit orchards, shade trees, and ornamentals, for defoliation and desiccation of cotton, for harvest aid in soybeans, sugarcane, guar, and sunflowers, for pasture renovation, for use in "no-till" or before planting or crop emergence, dormant alfalfa and clover, directed spray, and for killing potato vines. Paraquat is also effective for eradication of weeds on rubber plantations and coffee plantations and against paddy bund (Meister, 1985).

Properties (ACGIH, 1980; Meister, 1985; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_{12}H_{14}N_2.2Cl$
Molecular Weight	257.18
Physical State	Colorless to yellow crystalline solid
Boiling Point	175 to 180°C
Melting Point	--
Vapor Pressure	No measurable vapor pressure
Specific Gravity	1.24 at 20°C/20°C
Water Solubility	Very soluble
Log Octanol/Water Partition Coefficient	2.44 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Paraquat was found in only one sample, at a concentration level of 20 ug/L, from 721 ground water samples analyzed (STORET, 1987). Samples were collected at 715 ground water locations, with paraquat found in one location in California. No surface water samples were collected for analysis.

Environmental Fate

- ^{14}C-Paraquat dichloride (>96.5% pure) at 91 mg/L was stable to hydrolysis at 25 and 40°C at pH 5, 7 and 9 for up to 30 days (Upton et al., 1985).

- Uniformly ring-labeled ^{14}C-paraquat (99.7% pure) at approximately 7.0 ppm in sand did not photodegrade when irradiated with natural sunlight for 24 months (Pack, 1982). No degradation products were detected at any sampling interval. After 24 months of irradiation, >84% of the applied radioactivity was extractable and <4% was unextractable.

- Paraquat was essentially stable to photolysis in soil (Day and Hemingway, 1981). Four degradation products, 1-methyl-4,4'-bipyridylium ion, 4-(1,2-dihydro-1-methyl-2-oxo-4-pyridyl)-1-methyl pyridylium ion, 4-carboxy-1-methyl pyridylium ion, and an unknown, individually constituted <6.0% of the total radioactivity in either irradiated (undisturbed) or dark control soils.

- Paraquat (test substance uncharacterized) at 0.05 to 1.0 ppm in water plus soil declined with a half-life of >2 weeks (Coats et al., 1964). In water only, paraquat declined with a half-life of approximately 23 weeks.

- ^{14}C-Paraquat (test substance uncharacterized) was immobile in silt loam and silty clay loam (R_f 0.00), and slightly mobile in sandy loam (R_f 0.13) soils, based on soil thin-layer chromatography (TLC) tests (Helling and Turner, 1968).

- Methyl-labeled ^{14}C-paraquat (test substance uncharacterized) at 1.0 ppm was stable to volatilization at room temperature over a 64-day period (Coats et al., 1964).

- In a pond treated with paraquat (test substance uncharacterized) at 1.14 ppm (Frank and Comes, 1967), paraquat residues (uncharacterized) declined from 0.55 ppm 1 day after treatment to nondetectable (<0.001 ppm) 18 days after treatment. The dissipation of paraquat residues (uncharacterized) in water was accompanied by a concomitant increase of paraquat residues (uncharacterized) in the soil. Paraquat (test substance uncharacterized) at 0.04 ppm dissipated in pond water with a half-life of approximately 2 days (Coats et al., 1964). For more details, see Calderbank's chapter on paraquat in Herbicides (Calderbank, 1976).

III. PHARMACOKINETICS

Absorption

- In Wistar rats given single oral doses of ^{14}C-paraquat dichloride or dimethyl sulfate by gavage (0.5 to 50 mg/kg, purity not stated), 69 to 96% was excreted unchanged, mostly in feces, and no radioactivity appeared in bile (Daniel and Gage, 1966). Some systemic absorption of the degradation products that were produced in the gut was noted. Approximately 30% of the administered dose appeared in feces in a degraded form.

- ^{14}C-Methyl-labeled paraquat (99.7% purity) was administered orally to a cow in a single dose of approximately 8 mg cation/kg (Leahey et al., 1972). A total of 95.6% of the dose was excreted in feces in the first 3 days. A small amount, 0.7% of the dose, was excreted in the urine, 0.56% during the first 2 days. Only 0.0032% of the dose appeared in the milk.

- A goat was administered ^{14}C-ring-labeled paraquat dichloride (>99% purity) orally at 1.7 mg/kg for 7 consecutive days (Leahey et al., 1976a). At sacrifice, 2.4% and 50.3% of the radioactive dose had been excreted in the urine and feces, respectively, and 33.2% was recovered in the contents of the stomach and intestines. The radioactivity was associated with unchanged paraquat.

- In studies with pigs, ^{14}C-methyl-labeled (Leahey et al., 1976b) and ^{14}C-ring-labeled (Spinks et al., 1976) paraquat (>99% purity) at dose levels of 1.1 and 100 mg ion/kg/day, respectively, was given for up to 7 days. At sacrifice, 69 to 72.5% and 2.8 to 3.4% of the total radioactive dose had been excreted in the feces and urine, respectively.

Distribution

- Pigs were given oral doses of ^{14}C-methyl-labeled (Leahey et al., 1976b) and ^{14}C-ring-labeled (Spinks et al., 1976) paraquat dichloride (>99% purity) for up to 7 consecutive days at dose levels of 1.1 and 100 mg ion/kg/day, respectively. At sacrifice, radioactivity associated mostly with unchanged paraquat was identified in the lungs, heart, liver and kidneys, with trace amounts in the brain, muscle and fat.

- The distribution of radioactivity was studied in a goat fed ^{14}C-ring-labeled paraquat dichloride (1.7 mg/kg/day, 99.7% purity) in the diet for 7 consecutive days (Hendley et al., 1976). Most of the radioactivity was found in the lungs, kidneys and liver. The major residue was unchanged paraquat.

Metabolism

- Paraquat dichloride or paraquat dimethyl sulfate (radiochemical purity: 99.3 to 99.8%), labeled with ^{14}C in either methyl groups or in the ring, was poorly absorbed from the gastrointestinal tract of a

cow (Leahey et al., 1972), goats (Hendley et al., 1976), pigs (Leahey et al., 1976b; Spinks et al., 1976) and rats (Daniel and Gage, 1966), and was excreted in the feces mostly as unchanged paraquat. However, after an oral dose, there was microbial degradation of paraquat in the gut. In one study with rats (Daniel and Gage, 1966), 30% of a dose of paraquat appeared in the feces in a degraded form. A portion of these microbial degradation products can be absorbed and excreted in the urine, whereas the remainder is excreted in the feces.

Excretion

- In studies with a cow (Leahey et al., 1972) and rats (Daniel and Gage, 1966), about 96% and 69 to 96%, respectively, of the administered radioactivity (single oral doses, ^{14}C-labeled) from paraquat was excreted in the feces within 2 to 3 days as unchanged paraquat.

- Goats (Hendley et al., 1976) and pigs (Leahey et al., 1976b; Spinks et al., 1976) that received single oral doses of ^{14}C-labeled paraquat (1.7 and 1.1 or 100 mg ion/kg/day, respectively) for up to 7 days excreted 50 and 69%, respectively, of the total administered dose in feces unchanged.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- The Pesticide Incident Monitoring System (U.S. EPA, 1979) indicated numerous cases of poisoning from deliberate or accidental ingestion of paraquat or by dermal and inhalation exposure from spraying, mixing and loading operations. Generally, the concentrations of the ingested doses or of amounts inhaled or spilled on the skin were not specified. Symptoms reported following these exposures included burning of the mouth, throat, eyes and skin. Other effects noted were nausea, pharyngitis, episcleritis and vomiting. No fatalities were reported following dermal or inhalation exposure. Deliberate and accidental ingestion of unspecified concentrations of paraquat resulted in respiratory distress and subsequent death. See also Cooke et al. (1973).

Long-term Exposure

- No information was found in the available literature on long-term human exposure to paraquat.

Animals

Short-term Exposure

- Acute oral LD_{50} values for paraquat (99.9% purity) were reported as 112, 30, 35 and 262 mg paraquat ion/kg in the rat, guinea pig, cat and hen (Clark, 1965). Signs of toxicity included respiratory distress

and cyanosis among rats and guinea pigs, blood-stained droppings among the hens, and muscular weakness, incoordination and frequent vomiting of frothy secretion among the cats.

- Acute (4-hour) inhalation LC_{50} values for paraquat ranged from 0.6 to 1.4 mg ion/m^3 paraquat (McLean Head et al., 1985).

Dermal/Ocular Effects

- Acute dermal LD_{50} values for rabbits (Standard Oil, 1977) were 59.9 mg/kg and 80 to 90 mg paraquat ion/kg for rats (FDA, 1970).

- Paraquat concentrate 3 (34.4% paraquat ion) was applied (0.5 mL or 172 mg paraquat ion) to intact and abraded skin of six male New Zealand White rabbits for 24 hours (Bullock, 1977). Very slight, moderate or severe erythema and slight edema were noted during the 7-day observation period for both intact and abraded skin.

- Paraquat concentrate 3 (0.1 mL, 34.4% paraquat ion) was instilled into the conjunctival sac of one eye in each of six male New Zealand White rabbits (Bullock and MacGregor, 1977). Untreated eyes served as controls. Unwashed eyes were examined for 14 days. Complete opacity of the cornea was reported in three of six rabbits. Roughened corneas, severe pannus, necrosis of the conjunctivae, purulent discharge, severe chemosis of the conjunctivae and mild iritis were also reported.

Long-term Exposure

- Beagle dogs (three/sex/dose) were fed technical o-paraquat (32.2% cation) in the diet for 90 days at dose levels of 0, 7, 20, 60 or 120 ppm (Sheppard, 1981). Assuming that 1 ppm is equivalent to 0.025 mg/kg/day, these levels correspond to doses of 0, 0.18, 0.5, 1.5 or 3 mg paraquat ion/kg/day (Lehman, 1959), respectively. Increased lung weight, alveolitis and alveolar collapse were observed at 60 ppm. The No-Observed-Adverse-Effect-Level (NOAEL) identified for this study was 20 ppm (0.5 mg paraquat ion/kg/day).

- Alderley Park beagle dogs (six/sex/dose) were fed diets containing technical paraquat (32.3%) cation daily for 52 weeks at dietary levels of 0, 15, 30 or 50 ppm (Kalinowski et al., 1983). Based on actual group mean body weights and food consumption, these values correspond to doses of 0, 0.45, 0.93 and 1.51 mg/kg/day for male dogs and 0, 0.48, 1.00 or 1.58 for females. Clinical and behavioral abnormalities, food consumption, body weight, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology were comparable for treated animals and controls at 15 ppm (the lowest dose tested). An increased severity and extent of chronic pneumonitis occurred at 30 ppm in both sexes, but especially in the males. Based on the results of this study, the NOAEL identified was 15 ppm (0.45 mg paraquat cation/kg/day).

- Technical paraquat dichloride (32.7% paraquat ion) was fed to Alderley Park mice (60/sex/dose) for 97-99 weeks at levels of 0, 12.5, 37.5

and 100/125 ppm (100 ppm for the initial 35 weeks and then 125 ppm until termination of the study) (Litchfield et al., 1981). Based on the assumption that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.87, 5.6 and 15/18.75 mg/kg. The animals were observed for toxic signs, and body weights, food consumption and utilization, urinalysis, gross pathology and histopathology were evaluated. Renal tubular degeneration in the males and weight loss and decreased food intake in the females, were the only effects observed, and occurred in the 37.5-ppm dose group. Based on these findings, a NOAEL of 12.5 ppm (1.87 mg/kg/day) was identified.

° Fischer 344 rats (70/sex/dose) were fed diets containing 0, 25, 75 or 150 ppm of technical paraquat (32.69% cation) for 113 to 117 weeks (males) and 122 to 124 weeks (females) (Woolsgrove et al., 1983). Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.25, 3.75 or 7.5 mg/kg/day. Clinical signs, food and water consumption, clinical chemistry, urinalysis, hematology, ophthalmoscopic effects, gross pathology and histopathology were evaluated. Increased incidences of slight hydrocephalus were noted in the female rats dying between week 53 and termination of the study; these incidences were 5/60, 8/30, 9/27 and 9/30 rats in the control, low, mid and high dose, respectively. Also, increased incidences of spinal cord cysts and cystic spaces were noted in the male rats dying between week 53 and termination of the study. These incidences were 0/53, 6/36 and 4/35 rats at the control, low and mid-level doses, respectively; no incidence was reported at the high dose. Eye opacities, cataracts and nonneoplastic lung lesions (alveolar macrophages and epithelialization, and slight peribronchiolar lymphoid hyperplasia) were observed at 75 ppm and above. Similar eye lesions occurred at 25 ppm (the lowest dose tested). These effects did not appear to be biologically significant, since they were either minimal or occurred after 104 weeks of treatment and appeared, therefore, to be only an acceleration of the normal aging process. Based on these results, an approximate NOAEL of 25 ppm (1.25 mg/kg/day) was identified.

Reproductive Effects

° Lindsay et al. (1982) fed Alderley Park rats technical paraquat dichloride (32.7% cation w/w) in unrestricted diet for three generations at dose levels of 0, 25, 75 or 150 ppm paraquat ion. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.25, 3.75 or 7.5 mg/kg/day. No adverse reproductive effects were reported at 150 ppm (the highest dose tested) or less. An increased incidence of alveolar histiocytosis in the lungs of male and female parents (F_0, F_1 and F_2) was observed in the 75- and 150-ppm dose groups. Based on these results, a reproductive NOAEL of >150 ppm (7.5 mg/kg/day, the highest dose tested) and a systemic NOAEL of 25 ppm (1.25 mg/kg/day, the lowest dose tested) were identified.

Developmental Effects

- Young adult Alderley Park mice (number not stated) were administered paraquat dichloride (100% purity) orally by gavage at dose levels of 0, 1, 5 or 10 mg paraquat ion/kg/day on days 6 through 15 of gestation (Hodge et al., 1978a). No teratogenic responses were reported at 10 mg ion/kg/day (the highest dose tested) or lower. Partially ossified sternebrae in 26.3% of the fetuses in the high-dose group (10 mg ion/kg/day) and decreased maternal weight gain in the 5-mg ion/kg/day dose group were observed. Based on these results, the developmental NOAEL identified for this study was 5 mg/kg/day, while the maternal NOAEL was 1 mg/kg/day.

- Hodge et al. (1978b) dosed Alderley Park rats (29 or 30/dose) by gavage with paraquat dichloride (100% purity) on days 6 through 15 of gestation at dose levels of 0, 1, 5 and 10 mg paraquat ion/kg/day. No teratogenic effects were reported at 10 mg ion/kg/day (the highest dose tested). Maternal body weight gain was significantly decreased ($p \leq 0.001$) at 5 mg ion/kg/day and above. Fetal body weight gain was significantly ($p = 0.05$) decreased at the mid-dose (5 mg/kg/day) and above. Based on these findings, the developmental and maternal NOAEL of 1 mg paraquat ion/kg/day was identified.

Mutagenicity

- Analytical-grade paraquat dichloride (99.6% purity) was weakly mutagenic in human lymphocytes, with and without metabolic activation, at cytotoxic concentrations (1,250 to 3,500 ug paraquat dichloride/mL) (Sheldon et al., 1985).

- Technical-grade, 45.7% active ingredient (a.i.) and analytical-grade (99.6% a.i.) paraquat dichloride were weakly positive in the L5178Y mouse lymphoma assay with and without metabolic activation in studies by Clay and Thomas (1985) and Cross (1985), respectively. Statistically significant increases in mutant colonies were observed only at doses below 29% cell survival (Cross, 1985).

- Analytical-grade paraquat dichloride (99.4% a.i.) increased sister-chromatid exchanges (SCE) at nontoxic doses ($\leq$124 ug/mL in non-activated cultures and $\leq$245 ug/mL in S9-supplemented cultures. The induction of increased SCE was more marked in the absence of the S9 fraction (Howard et al., 1985).

- Mutagenic activity was detected in various assays with Salmonella typhimurium (Benigni et al., 1979), human embryo epithelial cells (Benigni et al., 1979) and Saccharomyces cerevisiae (Parry, 1977).

Carcinogenicity

- Technical paraquat dichloride (32.7% paraquat ion) fed to Alderley Park mice (60/sex/dose) for 99 weeks did not induce statistically significant dose-related oncogenic responses at dose levels of 0, 12.5, 37.5 or 100/125 ppm (100 ppm for the initial 35 weeks and then

125 ppm until termination of the study) (Litchfield et al., 1981). Based on the assumption that 1 ppm in food in mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.87, 5.6 and 15/18.75 mg/kg. The study appeared to have been conducted properly, except that hematological and organ weight determinations were not performed. The absence of these parameters do not compromise the results, since the occurrence of certain toxicological end points (e.g., leukemia) detected by these tests are rare in mice. The results, therefore, provide evidence that paraquat is not oncogenic at the dose levels tested.

- Woolsgrove et al. (1983) fed Fischer 344 rats (70/sex/dose) diets containing technical paraquat (32.69%) for 113 to 117 weeks (males) and 122 to 124 weeks (females) at dietary levels of 0, 25, 75 and 150 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.25, 3.75 and 7.5 mg paraquat cation/kg/day. The predominant tumor types noted in this study were tumors of the lungs, endocrine glands (pituitary, thyroid and adrenal) and of the skin and subcutis. Both the lung and endocrine tumors occurred at a frequency similar to the incidence of these kinds of tumors in the historical control. Only the squamous cell neoplasia of the skin and subcutis were determined to be treatment-related. The squamous cell carcinoma was a predominant tumor in the head region of the male and female rats. This uncommon tumor occurred in 51.6% of all rats with skin and subcutis tumors in the head region. The incidence of these tumors in this study was 2, 4, 0 and 8% in the control, low-, mid- and high-dose male groups, respectively and 0, 0, 4 and 3% in the control, low-, mid- and high-dose female groups, respectively. When these incidences were compared with incidences in historical controls (0 to 2.0% in males and 1.9 to 4.0% in females) the high-dose male group reflected a significant increase ($p = 0.01$). Also when squamous cell carcinoma and papilloma (including those of the head region) were combined, only the tumor incidence in the high-dose male group exceeded the historical and concurrent controls (U.S. EPA, 1985 and 1986a).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for the determination of the One-day HA value for paraquat. It is therefore recommended that the Ten-day HA value for the 10-kg child of 0.1 mg/L (100 ug/L), calculated below, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rat developmental study (Hodge et al., 1978b) has been selected to serve as the basis for the determination of the Ten-day HA value for paraquat. In this study, Alderley Park rats were administered paraquat (100% purity) during gestation days 6 through 15 at dose levels of 0, 1, 5 or 10 mg paraquat ion/kg/day. There was a statistically significant ($p \leq 0.001$; $p = 0.05$) decrease in maternal and fetal body weight gain at the 5-mg paraquat ion/kg/day dose; also at 5 mg/kg/day, there was a slight retardation in ossification. The fetotoxic and maternal NOAEL identified in this study was 1 mg paraquat ion/kg/day. An adequate study of comparable duration reported a NOAEL that was higher than that in the study selected for derivation of the Ten-day HA. A NOAEL of 5 mg/kg/day was identified for developmental effects, while the maternal NOAEL was similar (1 mg/kg/day) (Hodge et al., 1978a).

Using a NOAEL of 1 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(1 \text{ mg/kg bw/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.1 \text{ mg/L } (100 \text{ ug/L})$$

where:

1 mg/kg/day = NOAEL, based on the absence of fetotoxic and maternal effects in rats exposed to paraquat by gavage on days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No studies were found in the available literature that were suitable for deriving the Longer-term HA value for paraquat. The 90-day oral study of dogs (Sheppard, 1981) reported a NOAEL (0.5 mg ion/kg/day) which is similar to the NOAEL (0.45 mg ion/kg/day) of the 52-week oral dog study (Kalinowski et al., 1983) used to derive the Lifetime HA. It is, therefore, recommended that the Drinking Water Equivalent Level (DWEL) of 0.16 mg/L (160 ug/L), calculated below, be used for the Longer-term HA value for an adult, and that the DWEL adjusted for a 10-kg child, 0.045 mg/L (45 ug/L), be used for the Longer-term HA value for a child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Kalinowski et al. (1983) has been selected to serve as the basis for the Lifetime HA value for paraquat. In this 52-week feeding study in beagle dogs, a NOAEL of 15 ppm (0.45 mg paraquat ion/kg/day) was identified based on the absence of hematological, biochemical, gross pathological and histological effects as well as the absence of any significant changes in food consumption, or in body and organ weights for treated and control groups. Adequate studies of comparable duration reported NOAELs higher than those of the critical study selected for derivation of the Lifetime HA. A lifetime oral study in rats (Woolsgrove et al., 1983) reported a NOAEL of 25 ppm (about 1.25 mg/kg/day); a NOAEL of 12.5 ppm (about 1.87 mg/kg/day) was identified for mice (Litchfield et al., 1981).

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.45 \text{ mg ion/kg/day})}{(100)} = 0.0045 \text{ mg/kg/day}$$

where:

0.45 mg ion/kg/day = NOAEL, based on the absence of biochemical, hematological, gross pathological and histopathological effects in dogs fed paraquat in the diet for 52 weeks.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0045 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.16 \text{ mg/L } (160 \text{ ug/L})$$

where:

0.0045 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Calculation of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.16 \text{ mg/L})\ (20\%)}{10} = 0.003 \text{ mg/L } (3 \text{ ug/L})$$

where:

0.16 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- In studies with mice, technical paraquat dichloride (32.7% paraquat ion) did not induce significant oncogenic responses at dose levels of 0, 12.5, 37.5 or 100/125 ppm (0, 1.87, 5.6 or 15/18.75 mg/kg, respectively) (Litchfield et al., 1981). The oncogenic potential of paraquat has been determined in studies in which rats were fed technical paraquat for 113 to 124 weeks at dose levels of 0, 25, 75 and 150 ppm (0, 1.25, 3.75 and 7.5 mg/kg/day), respectively. The incidences of pulmonary, thyroid, skin and adrenal tumors were not clearly associated with treatment; however, the incidence of skin carcinomas was significantly increased ($p = 0.01$) in the high-dose males (Woolsgrove et al., 1983).

- The International Agency for Research on Cancer has not evaluated the

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), paraquat may be classified in Group C: possible human carcinogen. This group is used for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The Office of Pesticide Programs (OPP) has established tolerances on raw agricultural commodities for paraquat ion derived from either the bis(methyl sulfate) or dichloride salt ranging from 0.01 to 5 ppm (U.S. EPA, 1984). The tolerances are based on an ADI of 0.0045 mg/kg/day derived from a 1-year feeding study in dogs, with a NOAEL of 0.45 mg/kg/day and a safety factor of 100.

- The National Academy of Sciences (NAS, 1977) has a Suggested-No-Adverse-Response-Level (SNARL) of 0.06 mg/L. This was calculated using an uncertainty factor of 1,000 and a NOAEL of 8.5 mg/kg/day identified in the 2-year rat study by Chevron Chemical Company (1975), with an assumed consumption of 2 L/day of water by a 70-kg adult, with the assumption that 20% of total intake of paraquat was from water.

- American Conference of Governmental Hygenists has presented a threshold limit value of 0.1 mg/m^3 for paraquat of respirable particle sizes (ACGIH, 1980).

VII. ANALYTICAL METHODS

- There is no standarized method for the determination of paraquat in water samples. A method has been reported for the estimation of paraquat residues on various crops (FDA, 1979). In this method, paraquat is reduced by sodium dithionite to an unstable free radical that has an intense blue color and also a strong absorption peak at 394 nm.

VIII. TREATMENT TECHNOLOGIES

- Weber et al. (1986) investigated the adsorption of paraquat and other compounds by charcoal and cation and anion exchange resins and their desorption with water. They developed Freundlich adsorption-desorption isotherms for paraquat on charcoal. When 250 mg of charcoal was added to paraquat solutions, it exhibited the following adsorptive capacities: 37.3 and 93.2 mg paraquat/g charcoal at concentrations of 0.373 mg/L and 37.3 mg/L, respectively. Paraquat was also adsorbed by IR-120 exchange resins (H^+ and Na^+ forms). The IR-120-H resin showed more affinity towards paraquat than the IR-120-Na resin. When 665 mg of paraquat in solution was added to 15 mg of resin, IR-120-H adsorbed 70% of paraquat while the IR-120-Na adsorbed 66% of paraquat.

- MacCarthy and Djebbar (1986) evaluated the use of chemically modified peat for removing paraquat from aqueous solutions under a variety of

experimental conditions. Paraquat sorption isotherms on treated Irish peat were determined by equilibrating 100-mL volumes of 3.66 mg/L paraquat with 0.1 g of peat at ambient conditions. Tests indicated that equilibrium for paraquat was achieved after 6 days. Peat exhibited the following paraquat sorption capacities: 40, 55 and 60 mg paraquat/g peat at concentrations of 2, 4 and 6 mg/L, respectively. The effects of pH, ionic strength and flow rate on paraquat removal efficiency were also investigated. When 45 mL of 16-mg/L paraquat solution was gravity fed to a column with a diameter of 6 mm that had been packed with 700 mg treated peat, 95 to 99% paraquat removal efficiency was reported without a significant effect by variations in pH, ionic strength or flow rate.

° In summary, several techniques for the removal of paraquat from water have been examined. While data are not unequivocal, it appears that adsorption of paraquat by charcoal, ion exchange and modified peat are effective treatment techniques. However, selection of individual or combinations of technologies for paraquat removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

IX. REFERENCES

ACGIH. 1980. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values for substances in workroom air, 4th ed. Cincinnati, OH: ACGIH.

Benigni, R., M. Bignami, A. Carere, G. Conti, L. Conti, R. Crebelli, E. Dogliotti, G. Gualandi, A. Novelletto and V. Ortali. 1979. Mutational studies with diquat and paraquat *in vitro*. Mutat. Res. 68:183-193.

Bullock, C.H.* 1977. The skin irritation potential of ortho paraquat 3 lbs/gal concentrate. Standard Oil Company of California, Report No. SOCAL 1061/30:71, August 1. MRID 00054576.

Bullock, C.H. and J.A. MacGregor.* 1977. The eye irritation potential of ortho paraquat 3 lbs/gal concentrate. Standard Oil Company of California, Report No. SOCAL 1060/30:70, August 1. MRID 00054575.

Calderbank, A. 1970. The fate of paraquat in water. Outlook Agric. 6(3):128-130.

Calderbank, A. 1976. *In* Herbicides: Chemistry, degradation and mode of action. 2nd ed. G. Kearney, C. Phillips and D. Kaufman, eds. New York: Marcel Dekker.

CHEMLAB. 1985. The Chemical Information System, CIS, Inc, Bethesda, MD.

Chevron Chemical Company. 1975. Paraquat poisoning; a physician's guide for emergency treatment and medical management. San Francisco, CA: Chevron Environmental Health Center. (Cited in NAS, 1977)

Clark, D.G.* 1965. The acute toxicity of paraquat. Imperial Chemical Industries Limited. Report No. IHR/170, January 1. MRID 00081825.

Clark, D.G., T.S. McElligott and E.W. Hurst. 1966. The toxicity of paraquat. Brit. J. Ind. Med. 23(2):126-132.

Clay, P. and M. Thomas.* 1985. Paraquat dichloride (technical liquor): Assessment of mutagenic potential using L5178Y mouse lymphoma cells. Imperial Chemical Industries PLC, England. Report No. CTL/P/1398, September 24. MRID GS 0262-009.

Coats, G.E., H.H. Funderburk, Jr. and J.H. Lawrence et al.* 1964. Persistence of diquat and paraquat in pools and ponds. Proceedings, Southern Weed Control Conference. 17:308-320. Also in Unpublished submission received Apr. 7, 1971 under unknown admin. no.; submitted by Chevron Chemical Co., Richmond, CA; CDL:180000-I. MRID 00055093.

Cooke, N.J., D.C. Flenley and H. Matthew. 1973. Paraquat poisoning. Serial studies of lung function. Q. J. Med. New Ser. 42:683-692.

Cross, M. 1985.* Paraquat dichlorde: Assessment of mutagenic potential using L5178Y mouse lymphoma cells. Imperial Chemical Industries PLC, England. Report No. CTL/P/1374, September 17. MRID GS 0262-009.

Daniel, J.W. and J.C. Gage.* 1966. Absorption and excretion of diquat and paraquat in rats. Imperial Chemical Industries Limited, England. Brit. J. Ind. Med. 23:133-136. MRID 00055107.

Day, S.R. and R.J. Hemingway.* 1981. ^{14}C-Paraquat: Degradation on a sandy soil surface in sunlight. Report No. RJ 01688. Unpublished study submitted by Chevron Chemical Co. under Accession No. 257105.

FDA. 1970. Food and Drug Administration. Acute LD_{50} - rat. Project No. stated. Chambers, GA. MRID GS 0262-003.

FDA. 1979. Food and Drug Administration. Pesticide analytical manual, revised June 1979, Food and Drug Administration, Washington, DC.

Frank, P.A. and R.D. Comes.* 1967. Herbicidal residues in pond water and hydrosoil. Weeds. 15:210-213.

Helling, C. and B. Turner.* 1968. Pesticide mobility: Determination by soil thin-layer chromatography. Science. 167:562-563.

Hendley, P., J.P. Leahey, C.A. Spinks, D. Neal and P.K. Carpenter.* 1976. Paraquat: Metabolism and residues in goats. Huntingdon Research Centre, England. Project No. AR 2680A, July 16. MRID 00028597.

Hodge, M.C.E., S. Palmer, T.M. Wright and J. Wilson. 1978a. Paraquat dichloride: teratogenicity study in the mouse. Imperial Chemical Industries Limited, England. Report No. CTL/P/364, June 12. MRID 00096338.

Hodge, M.C.E., S. Palmer, T.M. Wright and J. Wilson. 1978b. Paraquat dichloride: teratogenicity study in the rat. Imperial Chemical Industries Limited, England. Report No. CTL/P/365, June 5. MRID 00113714.

Howard, C.A., J. Wildgoose, P. Clay and C.R. Richardson. 1985. Paraquat dichloride: An *in vitro* sister chromatid exchange study in Chinese hamster lung fibroblasts. Imperial Chemical Industries PLC, England. Report No. CTL/P/1392, September 24. MRID GS 0262-009.

Kalinowski, A.E., J.E. Doe, I.S. Chart, C.W. Gore, M.J. Godley, K. Hollis, M. Robinson and B.H. Woollen. 1983. Paraquat: One-year feeding study in dogs. Imperial Chemical Industries, England. Report No. CTL/P/734, April 20. MRID 00132474.

Leahey, J.P., R.J. Hemingway, J.A. Davis and R.E. Griggs. 1972. Paraquat metabolism in a cow. Imperial Chemical Industries Ltd, England. Report No. AR 2374A, November 17. MRID 00036297.

Leahey, J.P., C.A. Spinks, D. Neal and P.K. Carpenter. 1976a. Paraquat metabolism and residues in goats. Huntingdon Research Centre, England. Project No. AR 2680 A, July 16. MRID 00028597.

Leahey, J.P., P. Hendley and C.A. Spinks. 1976b. Paraquat metabolism and residues in pigs. Huntingdon Research Centre, England. Project No. AR 2694 A, October 4. MRID 00028598.

Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Assoc. Food and Drug Off. U.S., Q. Bull.

Lindsay, S., P.B. Banham, M.J. Godley, S. Moreland, G.A. Wickramaratue and B.H. Woollen. 1982. Paraquat multigeneration reproduction study in rats: Three generation. Imperial Chemical Industries PLC, England. Report No. CTL/P/719, December 22 and Report No. CTL/P/719S, MRID 00126783. Chevron response to EPA comments on rat reproduction study. No date. Received by EPA on 9/10/85.

Litchfield, M.H., M.F. Sotheran, P.B. Banham, M.J. Godley, S. Lindsay, I. Pratt, K. Taylor and B.H. Woollen. 1981. Paraquat lifetime feeding study in the mouse. Imperial Chemical Industries Limited, England. Report No. CTL/P/556, June 22. MRID 00087924.

MacCarthy, P. and K.E. Djebbar. 1986. Removal of paraquat, diquat and amitrole from aqueous solution by chemically modified peat. J. Environ. Qual. 15(2):103-107.

McLean Head, L., J.R. Marsh and S.W. Millward. 1985. Paraquat: 4-hour acute inhalation toxicity study in the rat. Imperial Chemical Industries. Report no. CTL/P/1325 and CTL/P/1325, September 24.

Meister, R., ed. 1985. Farm chemicals handbook. Willoughby, OH: Meister Publishing Company.

Meister, R., ed. 1987. Farm chemicals handbook. Willoughby, OH: Meister Publishing Company.

NAS. 1977. National Academy of Sciences. Drinking water and health. Washington, DC: National Academy Press.

Pack, D.E.* 1982. Long term exposure of ^{14}C-paraquat on a sandy soil to California sunlight. Unpublished submission by Chevron Chemical Co. under Accession No. 257105.

Parry, J.M. 1977. The use of yeast cultures for the detection of environmental mutagens using a fluctuation test. Mutat. Res. 46:165-176.

Sheldon, T., C.A. Howard, J. Wildgoose and C.R. Richardson. 1985. Paraquat dichloride: A cytogenetic study in human lymphocytes in vitro. Imperial Chemical Industries PLC, England. Report No. CTL/P/1351, September 3. MRID GS 0262-009.

Sheppard, D.B. 1981. Paraquat thirteen week (dietary administration) toxicity study in beagles. Hazleton Laboratories Europe Ltd, England. Report No. CTL/C/1027. HLE Project No. 2481-72/111A, February 17. MRID 00072416.

Spinks, C.A., P. Hendley, J.P. Leahey and P.K. Carpenter. 1976. Metabolism and residues in pigs using ^{14}C-ring-labelled paraquat. Huntingdon Research Centre, England. Project No. AR 2692 A, October 1. MRID 00028599.

Standard Oil Company. 1977. Acute dermal LD_{50} - rabbit. Project No. SOCAL 1059/29:40. MRID 00054574.

STORET. 1987.

TDB. 1985. Toxicology Data Bank. MEDLARS II. National Library of Medicine's National Interactive Retrieval Service.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Summary of reported pesticide incidents involving paraquat. Pesticide Incident Monitoring System. Report no. 200. July.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.205. July 1.

U.S. EPA. 1985. U.S. Environmental Protection Agency. Registration standard for paraquat. Memo from K. Locke. December 20.

U.S. EPA. 1986a. U.S. Environmental Protection Agency. Peer reviews of Paraquat oncogenic potential. Memo from E. Rinde. September 18.

U.S. EPA. 1986b. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003. September 24.

Upton, B.P., P. Hendley and M.W. Skidmore.* 1985. Paraquat: Hydrolytic stability in water pH 5, 7 and 9. ICI Plant Protection Division. Report series RJ0436B. Submitted Sept. 3, 1985. Chevron Chemical Co., Richmond, CA.

Weber, J.B., T.M. Ward and S.B. Weed. 1986. Adsorption and desorption of diquat, paraquat, prometone. Proc. Soil Sci. Soc. Amer. 32:197-200.

Windholz, M., S. Budvari, R.F. Blumetti and E.S. Otterbein, eds. 1983. The Merck Index, 10th edition. Rahway, NJ: Merck and Co., Inc.

Woolsgrove, B., R. Ashby, P. Hepworth, A.K. Whimmey, P.M. Brown, J.C. Whitney and J.P. Finn. 1983. Paraquat: Combined toxicity and carcinogenicity study in rats. Life Sciences Research, England. Report No. 82/1LY217/328, October 27. MRID 00138637.

Worthing, C.R. 1983. The pesticide manual. Published by the British Crop Council.

---

*Confidential Business Information submitted to the Office of Pesticide Programs.