Chevron Chemical Company

[redacted]

Richmond, Califor[redacted]
July 14, 1982

JUL 20 1982
REGISTRATION & REGULATORY AFFAIRS

PARAQUAT RPAR

RPAR TASK FORCE

Enclosed is the EPA Paraquat Decision Document. It reaches the conclusion that available data do not support a RPAR (p. 28) and therefore, paraquat will be returned to the re-registration process.

It will be several weeks before EPA officially publishes this document and makes formal transmission to Chevron. At that time, we expect them to make specific requests for additional data as indicated in the document. By then I will expect we will have completed a technical review to surface comments and questions. If needed, a meeting of our toxicologists with EPA will be arranged.

For your information, I have the following observations:

- Reproductive Effects. The data reviewed did not include the multi-generation rat study submitted April 2, 1982.

- Oncogenicity - Chronic Feeding. The Agency did not include the mouse lifetime study submitted December 10, 1981. The rat and dog studies being requested are well along and we expected to have Final Reports by early 1983.

- Mutagenicity. We need toxicology review and recommendations regarding the request for point mutation and DNA damage tests.

- Acute Inhalation. As above, we need input on the request for another rat study.

- Subchronic Toxicity.
  Note the requests for:
  a) 21-Day rabbit dermal toxicity study.
  b) Dermal absorption rate assessment study.
  c) Field worker/applicator exposure study.
  d) Investigation of face mask filtering capabilities. Seiber's published work; Akesson's recent study and the CTL exposure studies are not cited.

I think it noteworthy that the document states: "Current paraquat labeling is explicit in directing those involved in mixing and loading in proper handling procedures." (p. 4), that the label is consistent with Agency regulations (p. 14) and that precautionary labeling is adequate for prevention of dermal acute toxicity (p. 29).

The Agency clearly intends that the emetic be added to our formulation (pp. 13, 29) and it is my understanding that will be accomplished for product produced for 1983 sales.

[redacted]

LRS:df
Enclosure

cc: [redacted]

PARAQUAT

DECISION DOCUMENT

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July 1, 1982

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Environmental Protection Agency

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I. Introduction

Section 3(a) of the Federal Insecticide Fungicide and Rodenticide Act [FIFRA] requires all pesticide products to be registered by the Administrator of EPA before they may be sold or distributed. Section 6(b) of FIFRA authorizes the Administor to issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears that the pesticide or its labeling "does not comply with the provisions of [FIFRA] or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus the Administrator may cancel the registration of a pesticide whenever he or she determines that it no longer satisfies the statutory standard for registration, which requires, among other things, that the pesticide not cause "unreasonable adverse effects on the environment" [Section 3(c)(5) of FIFRA]. These "unreasonable adverse effects" are defined in Section 2(bb) of FIFRA to include "any unreasonable adverse effects to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide."

The Environmental Protection Agency, hereafter referred to as the Agency, created the Rebuttable Presumption Against Registration [RPAR] process to facilitate the identification of pesticide uses which may not satisfy the statutory standard for registration and to provide a public, informal procedure for the gathering and evaluation of information about the risks and benefits of these uses. The regulations governing the RPAR process are set forth in 5 40 CFR 162.11. These regulations set forth certain criteria of risk and provide that an RPAR shall arise against a pesticide if the Agency determines that the ingredient(s), metabolite(s), or degradation product(s) of the pesticide in question meet or exceed any of these risk criteria.

In administering the RPAR process, the Agency adheres to the standard for initiating the RPAR process established by Section 3(c)(8), one of the 1978 amendments to FIFRA, which provides that the Agency may not start an RPAR unless it has "a validated test or other significant evidence rising prudent concerns of unreasonable adverse risk to man or the environment."

When the Agency publishes a notice indicating that an RPAR has arisen, the regulations (40 CFR 162.11) require that an opportunity then be provided for registrants, applicants, and interested persons to submit evidence to rebut the presumption, or evidence relating to the economic, social, and environmental benefits for any use of the pesticide. If the presumptions of risk are not rebutted, the evidence on the benefits of the pesticide is evaluated and considered along with the information on the risks. The Agency then analyzes various methods of reducing the amount of risk from the pesticide together with their costs and determines whether the pesticide can be regulated so that the benefits of continued use outweigh the risks. If measures short of cancellation cannot reduce the risks associated with any given use of the pesticide to a level which is outweighed by benefits, the use in question must be cancelled.

Paraquat first came under intensive Agency review due to the widely held belief that neither an antidote nor a commonly accepted first aid treatment existed. In addition, paraquat's potential for exceeding 40 CFR 162.11 risk criteria in relation to both its dermal and inhalation toxicity was to be reviewed. The Federal Register Notice announcing the Agency's intent to iniate the scientific review of paraquat (43 FR 30613) cited

"...teratogenicity, lack of emergency treatment, chronic effects, reproductive effects, oncogenicity (data gap), mutagenicity (data gap) and acute effects" as areas of concern. Although the above noted criteria formed the primary concerns, the Agency additionally initiated a review of all available fish and wildlife data as well as those human health effect data not specifically addressed within 43 FR 30613.

This decision document is divided into five sections. Section I is this introduction. Section II discusses general information on the product's chemistry, uses, and tolerances. Section III addresses the primary purpose of the review; it compares data on potential adverse effects of paraquat with the Agency's criteria for a Rebuttable Presumption Against Registration. Section IV summarizes the conclusions of this review of paraquat and recommends actions to be taken as a result of these conclusions. Section V is a bibliographical listing of the studies cited.

II. Chemical Profile

A. Chemical Identity

Paraquat is the common name for 1,1'-dimethyl-4,4'-bipyridinium ion, the active ingredient of the contact herbicides paraquat dichloride and paraquat bis(methylsulfate). The structural formula of paraquat dichloride is shown below:

B. Registered Products and Uses

Paraquat is a nonselective contact herbicide which kills annual broadleaf weeds and grasses and inhibits perennial broadleaf weeds and grasses. Although the mode of action is not completely understood, Summers (1980) attributed the effect to a process by which the diquaternary salts undergo reduction to radical cations during photosynthesis and respiration. The radical cations are then rapidly auto-oxidized by air, generating the superoxide radical anion, hydrogen peroxide and possibly other associated radicals which are the toxic agents responsible for the dessication of plant tissue and loss of color.

Paraquat is used as a pre-emergent and preplant herbicide for some food and feed crops. In the management of fruit, nut, and ornamental tree orchards and certain small fruits, paraquat is applied as a directed spray to the interspaces between the plants. Paraquat is used as a desiccant or harvest aid for cotton, potatoes, soybeans, guar, sunflowers and sugarcane. Noncrop sites such as highway margins, commercial buildings and storage yards are sprayed to control weeds. Paraquat is applied to pine trees (by bark streaking, boring or injection) for the purpose of increasing the resin content. Paraquat also has uses as a spot treatment for walks, driveways, shrubs and flower beds.

Two principal paraquat formulations, other than the manufacturing use product, are Federally registered for use within the United States. These products are comprised of low concentration pressurized liquids for home use [Ortho Spot Weed and Grass Killer - 0.276% paraquat dichloride] and restricted use soluble concentrates which contain 29.1% paraquat dichloride.

C. Tolerances

Tolerances have been established for residues of paraquat (1,1'-dimethyl-4,4'-bipyridinium-ion) resulting from the application of either the bis(methylsulfate) or the dichloride salt (both calculated as the cation)

in or on raw agricultureal commodities. The tolerances for paraquat are as follows:

5 parts per million in or on alfalfa, birdsfoot trefoil, clover, pasture grass, and range grass.

2 parts per million in or on sunflower seeds.

0.5 parts per million in or on almond hulls, cottonseed, guar beans, hop vines, potatoes, sugar beets, sugar beet tops, and sugarcane.

0.2 parts per million in or on passion fruit

0.1 parts per million in or on hops

0.05 parts per million (negligible residue) in or on apples, apricots, avocadoes, bananas, barley grain, cherries, citrus fruit, coffee beans, fresh corn including sweet corn (kernels plus cob with husk removed), corn fodder and forage, corn grain, figs, guava, lettuce, melons, nectarines, nuts, oat grain, olives, papayas, peaches, pears, peppers, pineapples, plums (fresh prunes), rye grain, safflower seed, small fruit, sorghum forage and grain, soybeans, soybean forage, tomatoes, and wheat grain.

0.01 parts per million (negligible residue) in eggs, milk, and the meat, fat, and meat by-products of cattle, goats, hogs, horses, poultry, and sheep.

D. Exposure

Althouth the Agency has not undertaken a comprehensive review of those residue chemistry data available for paraquat, this to be accomplished in conjunction with the Registration Standards Program, human dietary exposure to paraquat is considered by the Agency to be negligible. In the most severe case, that of direct application to food crops as a harvest aid, photochemical degradation, adsorption and processing of the crop have been identified as mechanisms whereby final residues are reduced (Slade, 1966; and Calderbank, 1975). While significant residues may be present in harvested rice, very low residue levels may be found in dehusked or polished rice. Residue analysis has indicated that no detectable residues may be found in the oil of either sunflower or cotton having been desiccated with paraquat.

Althouth limited dietary exposure may be anticipated, human exposure to paraquat is largely restricted to individuals involved in either the mixing and loading or application of the compound. A wide variety of application equipment is used for paraquat. It is applied as a liquid by boom sprayers, knapsack sprayers, pressurized hand sprayers and aircraft. Both dermal and inhalation exposure may be anticipated to occasionally occur as a result of inadvertant spillage on exposed skin or clothing and applicator exposure to spray mist. Current paraquat labeling is explicit in directing those involved in mixing and loading in proper handling proceedures.

III. Paraquat as a Potential RPAR Candidate

A. Introduction

As previously noted, paraquat was suspected by the Agency of meeting the risk criteria established under 40 CFR 162.11. 43 FR 30613 identified those individual areas of Agency concern. Those health effect triggers listed were teratogenicity, lack of emergency treatment, chronic effects, reproductive effects, oncogenicity (data gap), mutagenicity (data gap), and acute effects. Subsequent to the publication of the Federal Register notice identifying those areas of Agency concern, the comprehensive review of available paraquat data revealed that an additional trigger relating to mammalian toxicity was also potentially exceeded. Although not specifically identified as exceeding a risk criterion, potential avian reproduction effects were also noted as a possible cause for concern (Stevens, 1980 and Stevens et al., 1982). The individual areas of concern and the relevant data are discussed below.

B. Teratogenicity

40 CFR 162.11(a)(3)(ii)B) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s)...produce any other chronic or delayed toxic effect [i.e., other than oncogenic or mutagenic effects] in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account an ample margin of safety."

The Agency, in evaluating the open literature data relevant to paraquat's potential for teratogenicity, found that the data were inadequate. The studies generally involved inadequate numbers of test animals, or were incompletely reported (Gregorio, 1982a). Often the focus of the study was not directed toward either morphological effects or reproductive impairment. In nearly all cases, paraquat was not administered orally and dams were not dosed daily throughout gestation. The following open literature studies were reviewed by the Agency: Khera et al. (1970), Rus et al. (1975), Gibson (1975 and 1976). Although these were found to be inadequate, they provided no evidence of any teratogenic effect.

Data, submitted by Chevron Chemical Corp. in support of product registration, contained two studies pretaining to paraquat's teratogenic potential. The first of these studies was Hodge et al. (1978b). In this study, rats were orally dosed (20/dose) from days 6-15 of pregnancy with the following doses of paraquat dichloride: 0, 1, 5, and 10 mg (paraquat ion) per kg body weight. Most of the dams in the 5 and 10 mg/kg groups showed adverse reaction to the paraquat treatment. The following effects were recorded: piloerection, weight loss (average body weights for all groups were 158.5, 155.6, 120.4, 112.5 grams respectively for the above noted dosages), and hunched appearance.

The number of implants, viable fetuses, fetal survival, resorptions, and mean litter weights were comparable to control animals. There was evidence that mean fetal weight was reduced in the 5 and 10 mg/kg groups when compared to the control ($p = 0.05$). This effect, however, is thought to be attributable to maternal toxicity rather than to any direct action upon the fetus by the compound. This fetal weight loss,

therefore, is not considered by the Agency to be an indicator of teratogenicity. Additionally, this effect would be indirectly mitigated with the establishment of a No Observed Effect Level (NOEL) resulting from chronic feeding data. The significantly reduced dose established from the NOEL would offer a practical margin of safety for pregnant mothers and, hence, for the fetus. No gross skeletal or soft tissue abnormalities were reported. The No Observable Effect Level (NOEL) established by this study is 1.0 mg/kg (Gregorio, 1982a).

In the second study by Hodge et al. (1978a) mice were dosed (20/dose) from day 6 through 15 of pregnancy with the following doses of paraquat dichloride: 0, 1, 5 and 10 mg/kg (PQ ion) per kg body weight.

No pathological or clinical evidence of maternal poisoning was observed in dams. The number of implantations, viable fetuses and resorptions were not statistically different from the control. Neither the sex ratio nor fetal litter weights varied significantly from control litters. No gross skeletal or soft tissue abnormalities were reported in any groups. The No Observable Effect Level (NOEL) derived from this study is higher than 10 mg/kg.

The Agency has concluded that those studies submitted by Chevron are adequate. The Agency has further concluded that these data indicate paraquat to be non teratogenic (Gregorio, 1982a).

C. Reproductive Effects

Applying those 40 CFR 162.11(a)(3)(ii)(B) criteria described under (A.) above, the Agency evaluated all available data dealing with paraquat's potential for causing adverse reproductive effects in mammals. Although no multi-generation studies on rodents appear available, three single generation studies dealing with this effect were located for Agency review.

In a reproduction study conducted by McElligott (1966) rabbits were treated with paraquat. Ten rabbits were retained untreated as a control. Ten rabbits received 30 ppm paraquat in the diet. The third group, comprised of 5 rabbits, received 2.4 mg/kg intraveneous (IV) injections (8 times) followed by 1.2 mg/kg IV injections until term. A single rabbit in this group received only the 1.2 mg/kg IV injections. The forth group of 5 rabbits recived 1.2 mg/kg iv injections (10 tomes) followed by 12 mg/day in drinking water.

Due, however, to an inadequate description of the experimental design, an inadequate reporting of the data and an unusual dosing schedule, the McElligott study can not be used in the establishment of a No Observable Effect Level (NOEL) (Gregorio, 1982a).

Griffiths et al. (1960) fed rats 0, 30 and 100 ppm (paraquat ion) for one generation. The study indicated no effects at either dose level. Reference was made within the paper to "definite toxic" effects at 250 ppm (producing "pulmonary lesions within a period of several weeks"). No data, however, were reported and no NOEL may be established (Gregorio, 1982a).

In the third study reviewed by the Agency (Fletcher, 1972), rats were fed

0, 30, and 100 ppm (paraquat ion) for one generation. The highest dose tested (100 ppm) was indicated to have produced no reproductive impairment. This finding, however, could not be substantiated due to inadequacies in the data presentation (i.e., no individual animal data for pathology, not all tissues listed to be examined were reported, no reporting of the number of dead and live offspring per litter). Additionally, no explanation or data was provided in relation to such statements as "significantly fewer progeny were reared in the 30 ppm paraquat group (in the F_{1b} litters) due to an unusually high incidence of maternal neglect." The aforementioned data reporting deficiencies, coupled with the study being limited to a single generation, precludes Agency utilization of the data in the establishment of a NOEL (Gregorio, 1982b).

The Agency, finding that the available studies relating to reproductive effects are inadequate, can make no conclusion with regard to this criteria. Data will, therefore, will be requested of the registrant. The Agency will require a two generation reproduction study.

D. Oncogenicity - Chronic Feeding

40 CFR 162.11(a)(3)(ii)(A) provides that a pesticide product shall undergo a Rebuttable Presumption Against Registration should it be found to induce "oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure..."

The Agency process, identified and reviewed four feeding studies involving paraquat. The Agency's Carcinogen Assessment Group (CAG) (CAG, 1977) found the data base, in aggregate, to be insufficient. The review findings are summarized as follows:

1. ICI, 1972

   The CAG found that the controls had a very poor survival rate (80% and 76% mortality for male and female mice, respectively) and the 80-week duration of the study was considered "somewhat shorter than desirable." Furthermore, the doses used - 25, 50 and 75 ppm (3.75, 7.5 and 15 mg/kg/day, respectively) - were "well below the maximum tolerated dose of 90-120 mg/kg/day.

2. IBT, 1964c

   In an invalid study (by data audit) CAG noted that the number of missing rats and rats for which no histopathological examinations were performed were so large that it was impossible to draw conclusions concerning the carcinogenicity of paraquat. Histological examinations were performed on only a few surviving controls and rats ingesting 250 ppm of paraquat. The absence of tumors was, in CAG's view, "an extremely unlikely occurrence for any stock or strain of rats."

3. IBT, 1964b

   This invalid (by data audit) study, undertaken with Beagles, could not be evaluated due to the short duration of the study. Poor selection of dosage levels resulted in both too few animals and

levels being tested. Of the three levels initially tested (50, 125 and 250 ppm), only dogs at the two lowest levels survived the 27-month testing period. Dogs at the 250 ppm dosage all died within 11-53 days. A new level, 10 ppm (2 animals/sex/dose) was added one month after the study began. No concurrent control group was added. The four animals in the 10 ppm group were sacrificed at 26 months. Based upon the noted deficiencies, the Agency has concluded that this study may be considered as supplemantary data in relation to chronic feeding, but is insufficient with regard to an assessment of paraquat's potential for oncogenicity.

4. IBT, 1965
In an invalid study (by data audit) CAG determined that the study duration was, again, far too short "for a bioassay study to determine carcinogenicity." Additionally, CAG found that only one level of paraquat, 75 ppm, had been administered to the study dogs and no controls were used.

With the absence of acceptable data, the Agency cannot make a determination as to either the oncogenic or chronic effect potential of paraquat (CAG, 1977). The Agency will, therefore, request that additional studies be performed by paraquat registrants.

E. Mutagenicity

40 CFR 162.11(a)(3)(ii)(A) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s) metabolite(s), or degradation product(s)—induce mutagenic effects, as determined by multitest evidence." Section 162.3(y) defines mutagenicity as "the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations." Mutagenic chemicals are recognized as posing a potential risk to human health due to their ability to cause heritable changes in genes and chromosomes. Germline changes can, for example, lead to birth defects or to the accumulation of deleterious mutations which may be involved in the etiology of cancer.

The Agency has obtained and reviewed several pertinent mutagenicity studies. These studies, aggregated by study type, are described below.

1. Bacterial Systems

Imperial Chemical Industries (1977) tested paraquat dichloride in an assay using S. typhimurium strains TA-1535 and TA-1538, with and without the presence of rat liver postmitochrondrial supernatant (PMS) with cofactor (S-9) mix from rats administered phenobarbitol. Paraquat was also tested using TA-1535, TA-1538, TA-98, TA-100 strains with S-9 mix made from rats administered Aroclor with PMS, but without cofactor and without S-9 mix. Paraquat concentrations tested ranged from 0.16 to 5000 ug. Vehicle controls and positive controls [N(-2 acetylaminofluorine (AFF) and nitrofluorene (2NF), 2-(1-chloro-2-2-isopropyl-aminoethyl) napthalene (CPE), Meclorethamine, nitrogen mustard and dimethyl sulfoxide (DMSO)]. The study results indicated paraquat was not mutagenic under the conditions of the test.

Inveresk International (1977) tested paraquat dichloride (99.9%

pure) and 2-aminoanthracene dissolved in DMSO (positive control) in a S. typhimurium assay using strains TA-1535, TA-1537, TA-1538 and TA-100. Tests were conducted on agar plates in the presence and absence of rat liver preparation prepared by treating male rats with Aroclor 1254 and the cofactors required for mixed function oxidase reactions. Paraquat dosages ranged from 1 ug to 1 mg per plate. Paraquat and the positive control chemical (2-aminoanthracene) were not mutagenic when tested without activation. However, when the S. typhimurium systems were activated with rat liver cells and co-factors, 2-aminoanthracene (positive control) was mutagenic. The results of this study indicated that paraquat was not mutagenic under the described test conditions (Gregorio, 1982a).

Anderson et al. (1972) tested paraquat using spot tests for its ability to revert eight strains of S. typhimurium to histadine independence. Paraquat was described as giving negative results, but no quantitative data were reported, no metabolic activation system was used, and the strains used were not specified. Furthermore, paraquat did not produce zones of inhibition of cell growth. It is, therefore, unclear whether a sufficient number of cells were exposed to the chemical (Gregorio, 1982a).

Benigni et al. (1979b) tested paraquat in a conventional Ames assay in the presence and absence of a rat liver- extract metabolic activation system. Paraquat did not increase the number of histidine-independent revertants in any of the S. typhimurium strains used (GA-1535, TA-1537, TA-1538, TA-98, TA-100).

Benigni et al. (1979b) also performed a zone of inhibition test using ultraviolet excision repair-proficient and repair-deficient strains of S. typhimurium (TA-1978, and TA-1538, respectively) in the presence and absence of metabolic activation. Paraquat at 100 ug/plate caused larger zones of inhibition in the repair-deficient than in the repair-proficient strain. This suggests that paraquat caused DNA damage reparable by the S. typhimurium excision repair pathway. In both strains, the zone of inhibition was larger in the absence than in the presence of metabolic activation (Gregorio, 1982a).

Benigni et al. (1979b) tested paraquat in an incompletely validated forwarded mutation system to detect 8-azaganine (8-AG) resistant mutants in S. typhimurium . The bacteria were plated in agar containing both paraquat and 8-AG. There was an apparent increase in the number of mutants on the paraquat treated plates. However, this assay appears to be rather subjective. The authors stated that "colonies smaller than 0.1 mm were not counted as mutants." In addition, the presence of both paraquat and the selective agent (8AG) on the plates at the same time is of some concern. It is possible that the two might interact to reduce the effective concentration of 8-AG. This would tend to increase the number of surviving colonies, which might not all be true mutants (Gregorio, 1982a).

2. Fungal Systems

Benigni et al. (1979b) tested the mutagenic potential of paraquat in the fungus A. nidulans using 8-AG resistance and the induction of

methionine suppressor mutations. Both test systems were used in plate incorporation assays and in suspension assays. Positive results were obtained with the 8-AG-resistance system in the plate incorporation assay; however, this assay suffers from the same defects as the S. typhimurium assay. The negative results obtained in the suspension assay suggest that the apparent positive results obtained in the plate incorporation assay may have been an artifact, possibly caused by interaction between paraquat and 8-AG reducing the toxicity or preventing the uptake of 8-AG (Gregorio, 1982a).

In the methionine suppressor assay, no mutants were detected in the plate incorporation assay, but there was a slight increase in mutation frequency in the suspension assay. The negative results in the plate incorporation asay may have been produced because the plating medium contained none of the required nutrient, methionine. In "reversion" assays, a small amount of the required nutrient in the plating medium is often required to allow expression of induced mutations (Ames et al. 1975). Benigni et al. (1979b) also performed an assay designed to detect the induction of recessive lethal mutations in yeast. However, this assay system has not been characterized well enough to ensure that the scored recessive lethal "mutations" were true mutants (Gregorio, 1982a).

Three studies report the ability of paraquat in the form of Gramoxone® to induce mitotic gene conversion in Saccharomyces cerevisiae . Gene conversion may be considered as a type of nonreciprocal recombination that occurs in diploid fungi during mitosis. The mechanism is not completely understood, but it appears to involve the replacement of a small number of nucleotide pairs from the chromosome of the pair, and replacement by the corresponding sequence from the other chromosome. Hence, if the organism is heteroallelic at the site of gene conversion, the product of gene conversion is homoallelic (Gregorio, 1982a).

Siebert and Lemperle (1974) exposed cells of S. cerevisiae strain D4 to 1,000 ppm of Gramoxone® for 2 hours and observed slight, but not significant, increase in the frequency of convertants to the ade 2 and trp 5 loci. In concurrent experiments with other chemicals, the convertant frequency in control cells varies up to 10-fold, suggesting that this assay may have low sensitivity (Gregorio, 1982a).

With a different strain of S. cerevisiae and using 16-hour treatments with concentrations of Gramoxone® between 100 and 900 ppm, Parry (1973) observed dose-related increases in convertant frequency at doses up to 600 ppm at the his 1 locus and up to 700 ppm at the ade 2 locus. At higher doses, the convertant frequencies declined. The convertant frequencies reached maxima of 820 + 30 in 10^6 space survivors at the his 1 locus with Gramoxone® concentrations between 400 and 600 ppm, and 2,540 + 110 in 10^6 survivors at the ade 2 locus with Gramoxone® concentrations between 600 and 700 ppm. Although Parry did not report the results of tests with negative controls, the positive dose responses and the high frequencies of convertants strongly suggest that Gramoxone® induced gene conversion (Gregorio, 1982a).

Parry (1977) used a modified fluctuation test to test for gene conversion in a third strain, S. cerevisiae exposed to paraquat at doses between 0.02 and 6 ug/ml. He obtained results strongly suggestive of gene conversion at the trp and his 4 loci at concentrations between 0.02 and 2.0 mug/ml. It is likely that gene conversion caused the positive results, but Parry did not demonstrate unequivocally that gene conversion was induced by paraquat (Gregorio, 1982a).

3. Mammalian Studies

Benigni et al. (1979b) performed an unscheduled DNA synthesis (UDS) assay with human embryonic cells in culture. The cells exposed to paraquat at 20, 100, 1,000 and 2,000 ug/ml had higher numbers of grains per nucleus than did control cells. Although the increase in grains per nucleus with all doses tends to support the author's conclusion that paraquat induced UDS, insufficient detail was provided with respect to the experimental proceedure. UDS is a reflection of DNA repair; therefore, this apparently positive result supports the result of the zone of inhibition test with bacteria. As both of these studies, however, contained defects which did not permit validation, additional confirmation will be required before any conclusion may be drawn.

Anderson et al. (1976) conducted a dominant lethal assay with a positive control, three dose levels of paraquat, and 15 male CD-1 mice per treatment group. This study revealed no evidence of dominant lethal mutagenicity of suppression of fertility in mice receiving paraquat orally 0.04, 0.4, or 4 mg paraquat ion/kg/day for five days (Gregorio, 1982a).

Pasi et al. (1974) intraperitoneally injected five male Swiss-Webster mice at 66 mmole/kg (sic). The authors observed no significant reduction in the numbers of implants per pregnancy or increase in the numbers of early deaths per pregnancy resulting from matings occurring during any of the eight weeks after treatment. The incidence of pregnancy among females mated to treated males was significantly lower ($p < 0.01$) than in the control group during the third week after mating (33% versus 80%) and averaged 51 versus 70 percent over the eight week duration. However, the small number of animals and the relatively low pregnancy rate, even in the controls, reduced the sensitivity of the assay so that increases of more than twofold in the number of early deaths per pregnancy were not statistically significant. No positive control was run to ensure that the assay system was functioning properly. Additionally, there is an obvious error in the reporting of the dose of paraquat administered: 66 mmole/kg, approximately 17 g/kg, is about 500 times the intraperitoneal LD_{50}. It is more probable that the actual dose was 66 umole/kg (Gregorio, 1982a).

As indicated in the preceding data summaries, both positive and negative responses in mutagenic testing systems have been reported in the literature. There is evidence that paraquat does not cause dominant lethal mutations in mice and does not induce reversion to histidine independence in the Ames strains of S. typhimurium . The data suggest that paraquat may cause reparable DNA damage in bacteria, induce forward

mutations in bacteria and A. nidulans induce gene conversion in yeast and induce unscheduled DNA synthesis in human cells in vitro . These apparently positive findings, however, have all resulted from studies which were flawed. The Agency, therefore, cannot come to any conclusion concerning the potential mutagenicity of paraquat (Gregorio, 1982a) The Agency will require that additional mutagenic testing be performed by paraquat registrants.

F. Lack of Emergency Treatment

40 CFR 162.11(a)(3)(iii) provides that a rebuttable presumption shall arise if a pesticide has "no known antidotal, palliative or first aid treatments for amelioration of toxic effects in man resulting from a single exposure." The Agency, in considering this criteria, evaluates not only the simple presence or absence of an antidote or first aid treatment, but must also consider the mechanism and potential for exposure. The Agency's Pesticide Incident Monitoring System (PIMS) has indicated that death due to paraquat poisoning can result from either oral or dermal exposure. These two exposure routes, therefore, form the principal basis of Agency concern. The Agency has evaluated available case histories and treatment regimes and has developed the following analysis:

1. Oral Exposure

The PIMS reports indicate that the majority of the poisoning incidents involving paraquat have resulted from the purposfull ingestion of the chemical in apparent suicide attempts. Case histories from accidental poisonings indicate that varing amounts of paraquat are lethal (a sip to several mouthfuls), death is generally caused by pulmonary insufficiency, and accidents are frequently the result of storage in unmarked bottles.

The current emergency treatment for paraquat has been directed at preventing absorption, promoting rapid excretion and modifying possible tissue effects (Cavalli and Fletcher, 1977). This treatment is based on the following criteria (1) ingestion of less than 50 ml of paraquat, (2) treatment is initiated within 24 hours of ingestion, and (3) treatment consists of the following:

- o induced vomiting
- o administion of clay absorbents
- o administration of cathartics
- o perform hemodialysis, peritoneal dialysis or forced diuresis.

An analysis was conducted on the available case histories which complied, in part, with the Cavalli and Fletcher criteria. Sixteen cases were screened from the literature which were treated with the recommended criteria (ingesting 50 ml or less, treatment within 24 hours and at least one of the suggested accompanying treatments). As shown in Table 1, adherance to the treatment regime resulted in an 81 percent survival rate (13/16).

TABLE 1
HUMAN EXPOSURE - ORAL ROUTE

Dose	Time to Treatment	Treatment Type I	II	III	IV	V	VI	VIII	Outcome	Reference
2 mouthfuls	<2 hr.			X					S	Anderson, 1970[1]
30 ml	<2 hr.	X							S	Douglas et al., 1973[1]
1 mouthful	9-24 hr.	X	X						S	Douglas et al., 1973[2]
50 ml	24-48 hr.	X				X	X		S	Douze et et al., 1975[3]
1 mouthful	24-48 hr.					X		X	S	Eliahou et al., 1973[1]
30 ml	<2 hr.			X		X			D	Farr, 1977[1]
50 ml	<48 hr.				X	X			S	Grabensee, 1974[5]
45 ml	<2 hr.			X		X			S	Kerr et al., 1968[1]
<20 ml	>48 hr.					X			S	Laithwaite, 1976[1]
20 ml	<2 hr.			X		X	X		S	Mahieu et al., 1977[2]

Treatment type: I Fuller's earth
II Bentonite
III Gastral lavage
IV Induced Vomiting
V Forced diuersis
VI Peritoneal dialysis
VII Haemodialysis

S = Survived
D = Died

1/ Steroids/Immunosuppressants, Antibiotics
2/ Steroids/Immunosuppressants, Cytotoxic Agents
3/ Antibiotics
4/ Cytotoxic Agents
5/ Cytotoxic Agents, D-Propanol
6/ Activated Charcoal

TABLE 1 - Continued
HUMAN EXPOSURE - ORAL ROUTE

Dose	Time to Treatment	Treatment type Type I	II	III	IV	V	VI	VIII	Outcome	Reference
4 ml	3-8 hr.			X					D	Masterson & Roche, 1970[3]
30 ml	<2 hr.	X		X	X				S	McCormack, 1976[4]
10 gm	<2 hr.			X		X			S	McDonagh & Martin, 1970[2]
10 ml	>48 hr.					X	X		S	Pasi & Hine, 1971
1 mouthful	<2 hr.					X			D	Oreopoulos et al., 1968[5]
30 ml	<2 hr.	X	X	X	X	X		X	S	Thomas et al., 1977[6]

Treatment type: I Fuller's earth
II Bentonite
III Gastral lavage
IV Induced Vomiting
V Forced diuersis
VI Peritoneal dialysis
VII Haemodialysis

S = Survived
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1/ Steroids/Immunosuppressants, Antibiotics
2/ Steroids/Immunosuppressants, Cytotoxic Agents
3/ Antibiotics
4/ Cytotoxic Agents
5/ Cytotoxic Agents, D-Propanol
6/ Activated Charcoal

It should be noted that the Agency, on April 14, 1982, issued an exemption from tolerance for 2 amino-4,5-dihydro-6-methyl-4-propyl- S -triazolo(1,5-alpha)pyrimidin-5-one in raw agricultural commodities. This compound is for use as an emetic at not more than 0.1 percent in formulations of paraquat dichloride. The added emetic will rapidly induce vomiting, thereby, lessining absorption time and exposure.

2. Dermal Exposure

The available case histories resulting from accidental dermal exposure (see Table 2) demonstrate that paraquat can be percutaneously absorbed in amounts sufficient to cause death. Although the reporting of fatal paraquat dermal absorption cases was inadequate, the reports did indicate that accidental application of "large amounts" to the body will initially result in sores and burns of the exposed area and subsequent pulmonary insufficiency. In addition, nail damage (bands of white discoloration or complete nail loss) resulted in instances where no precautions (i.e. rubber gloves) were taken while diluting paraquat concentrates.

None of these reported cases can be analyzed by the previously described Cavalli and Fletcher criteria. The significance of the treatment, therefore, cannot be established (Gregorio, 1982a).

3. Inhalation Exposure

No cases of acute inhalation toxicity resulting in human death have been reported. The Agency, therefore, has not considered the need or adequacy of emergency treatments in relation to inhalation exposure.

G. Acute Toxicity

40 CFR 162.11(a)(3)(i) provides that a rebuttable presumption shall arise if a pesticide "(A) Has an acute dermal LD_{50} of 40 mg/kg or less as formulated; or (2) Has an acute dermal LD_{50} of 6 g/kg or less as diluted for use in the form of a mist or spray; (3) Has an inhalation LC_{50} of 0.04 mg/liter or less as formulated."

The Agency has reviewed numerous papers dealing with paraquat's acute toxicity. Paraquat administration has been demonstrated to cause lung effects in experimental animals by oral, dermal and inhalational routes. These toxic effects have been seen following both acute and subchronic administration,

Studies reviewed by the Agency and determined to be germaine are discussed below, categorized by study type (i.e. route of administration):

1. Acute Oral Toxicity

The results of animal studies on the acute oral toxicity of paraquat are summarized in Table 3. Although the data show variation in the reported values, the LD_{50} results indicate a very high acute oral toxicity. These studies demonstrate that

TABLE 2
HUMAN EXPOSURE - DERMAL ROUTE

Dose	Treatment time	Treatment type										Outcome	Reference
		1	2	3	4	5	6	7	8	9	10		
U	>48 hr.										X	S	Barber, 1971
U	>48 hr.									X		D	Binns, 1976
U	U										X	S	Dobbelaere & Bouffioux, 1974
U	>48 hr.				X				X	X		D	Jaros et al., 1978
U	U										X	S	Samman & Johnston, 1969
U	U										X	S	"
U	U										X	S	"
U	>48 hr.								X			D	Waight & Wheather, 1979
U	>48 hr.							—			X	D	Weston et al., 1971
U	>48 hr.									X		S	Withers et al., 1979

U = Unspecified

1 - Fuller's Earth
2 - Bentonite
3 - Gastric Lavage
4 - Induced Vomiting
5 - Forced Diuersis
6 - Peritoneal Dialysis
7 - Hemodialysis
8 - Steroids
9 - Antibiotics
10 - Unspecified Treatment

TABLE 3
ACUTE ORAL TOXICITY

Animal	Sex	Material	LD_{50} (PQ ion)	Reference
SD-Rat	M	Ortho Spot Weed and Grass Killer	106 (68-164) mg/kg (Lungs Consolidated)	Chevron Chemical Company, 1969
SD-Rat	F	Ortho Spot Weed and Grass Killer	82 (71-94 mg/kg) (Lungs Consolidated)	Chevron Chemical Company, 1969
SD-Rat	M/F	Ortho Spot Weed and Grass Killer	No deaths, signs of toxicity, gross pathology at 50 mg/kg (14-day observation)	Rittenhouse, 1978
Rat	F	99% Pure Pq Dichloride	112 (104-127) mg/kg (Lungs Consolidated)	Clark, 1965
Rat	F	Pq Dichloride	150 mg/kg	Clark, 1965
SD-Rat	M	Pq Dichloride	126 (102-156) mg/kg (Lung hemorrhage, fibrosis; liver kidney tubular necrosis)	Murray and Gibson, 1972
SD-Rat	M	Pq Dichcloride	115 (90-150) mg/kg	Sharp et al., 1972
Wilson Rat	M	Pq Dichloride	95 (79-114) mg/Kg	Sharp et al., 1972
Monkey	-	Pq Dichloride	50 mg/kg (tubular necrosis in liver, kidney; lung fibrosis)	Murray and Gibson, 1972
Rat	F	99% Pure Pq Dimethosulfate	141 (140-142) mg/kg (Lung Consolidation)	Clark, 1965
Rat	F	99% Pure Pq Dimethosulfate	112 mg/kg (21-day observation)	Clark, 1965

TABLE 3 - Continued
ACUTE ORAL TOXICITY

Animal	Sex	Material	LD_{50} (PQ ion)	Reference
Rat	F	JF-1824	127 mg/kg	Clark, 1965
Rat	F	JF-1824 (with surface active agent)	150 mg/kg	Clark, 1965
Rat	F	Paraquat LTS	120 mg/kg	Clark, 1965
Sherman Rat	M/F	Paraquat	100 mg/kg	Kimbrough and Gaines, 1970
SD-Rat	M	Paraquat	189 (90-398) mg/kg [Slope was 1.7 (0.73—3.8]	Rittenhouse, 1978
SD-Rat	F	Paraquat	125 (62-251) mg/kg [Slope was 2.0 (0.93-4.2]	Rittenhouse, 1978

paraquat produces a very steep dose-response curve indicating that the range of doses producing 0-100 percent mortality is very narrow (Gregorio, 1982a).

The reported toxic signs were hyperexcitability, uncoordination and, in some reports, convulsions. The major target organs are the lungs, kidney and liver.

The Agency does not routinely take regulatory action based upon the acute oral toxicity of any pesticide, other than to ensure proper labeling, use restrictions and packaging. Current paraquat labeling is consistant with Agency regulations governing warnings and precautionary statements [40 CFR 162.10(h)] and with those regulations governing use classification [40 CFR 162.11(c)].

2. Acute Dermal Toxicity

The results of animal studies on the acute dermal toxicity of paraquat are summarized in Table 4. The data indicate a moderate to severe acute dermal toxicity (Toxicity Category II or III) [40 CFR 162.10(h)(1)(B)].

The reported toxic signs were salivation and skin erythema; the major target organs were the lungs, kidney and liver.

3. Acute Inhalation Toxicity

Gage (1968) exposed Rats (4 animals/sex) to varying concentrations of paraquat (purity unspecified) for a single 6-hour exposure period. Approximately 90 percent of the particles were 2.4 microns in diameter. The results of the study are summarized in Table 5.

Pathological examination of the survivors of the 4.8, 13.7 and 32.5 ug/liter exposures showed congested lungs with occasional petechial hemorrhages. Histopathological examination of these animals demonstrated congestion and an increase in the number of polymorphs and histiocytes around the bronchi and vessels. In addition, the kidneys of these animals were pale and showed cloudy swelling. No other details were given as to the pathology/histopathology of other animals. These results suggest that the LC_{50} for paraquat is 1.0 ug/liter.

In several varying short term exposure trials utilizing varying particle sizes, Gage demonstrated the effect of particle size on lethality (See Table 5a).

IBT (1964d) determined an LC_{50} value for rats (4 animals/sex) exposed to paraquat (unspecified formulation). Particle size was reported to be within a 0.5 to 3 micron range. Exposure was for 4 hours. The LC_{50} value derived from the study results was reported as 6.4 mg/liter, well above that LC_{50} established by the Gage study. This study, however, in addition to being an unvalidated Industrial Biotest study, has been found deficient in

TABLE 4
ACUTE DERMAL TOXICITY

Animal	Sex	Material	LD_{50} (PQ ion)	Reference
Rabbit	-	Ortho Spot Weed and Grass Killer	1 animal died on day-14 at 5 g/kg (no gross pathology in surviving animals)	Chevron Chemical Company, 1969
Rabbit	M	Ortho Spot Weed and Grass Killer	No deaths, gross pathology at 5 g/kg (14-day observation)	Cavalli, 1969
Rabbit	M	Ortho Paraquat	174 (80-376) mg/kg (lung hemorragic; grainy livers, soft kidneys)	Bullock, 1977b
Rabbit	M	Pq Dichloride	No deaths at 480 mg/kg (mild erythema; animals wearing plastic collars to prevent oral ingestion)	McElligott and Swanston, 1966
Rabbit	-	Paraquat LTS (with spreader)	236 mg/kg (lung congestion, pale kidneys)	McElligott, 1965
RatM/F	M/F	Spray concentrate	80 mg/kg	Gaines, 1968

Table 5
ACUTE INHALATION TOXICITY
Gage, 1968

PQ Concentration (ug/liter)	Mortality	
	Males	Females
32.5	2[1]	1[1]
13.7	4	4
4.8	3[1]	2[1]
2.6	3[1]	2[1]
1.5	3[1]	1[1]
1.3	2	4
0.75	0 (at 15 days)	0 (at 15 days)
0.4	0 (at 20 days)	0 (at 20 days)

1/ Survivors were judged to be in poor condition and were killed for autopsy

TABLE 5a
ACUTE INHALATION TOXICITY
Gage, 1968

Particle Size (u)	Time (hr)	PQ Concentration (ug/liter)	Mortality (#animals died/ #animals tested)
2.5	2.0	3.3	4/4
2.5	2.0	2.77	4/4
2.5	2.0	2.40	0/4
10.0	2.0	9.80	3/4
2.5	1.0	3.1	0/4
2.5	1.0	2.1	0/4
2.5	1.0	1.1	0/4
10.0	1.1	9.0	0/4

the reporting of results. Additionally, the test substance was not adequately identified (Gregorio, 1982a).

The Agency, based upon its finding that both available acute inhalation toxicity studies are inadequate and that considerable disparity exists between the reported test results, has determined that insufficient data are available with which to provide a definitive conclusion. The Agency will, therefore require the submission of additional data relative to paraquat's acute inhalational toxicity.

4. Eye Irritation

The results of animal primary eye irritation studies for paraquat are summarized in Table 6. Although the data show variability, it indicates that paraquat is a moderate to severe eye irritant.

5. Dermal Irritation

The results of animal studies conducted to assess primary dermal irritation potential are summarized in Table 7. The data indicate that paraquat is a moderate to severe skin irritant.

6. Summary of Acute Toxicity Data

As evidenced by the acute toxicity animal data, paraquat has a very steep dose-response curve which indicates that the range of doses which produce 0-100 percent mortality is very narrow (small increases in the doses resulted in large increases in response). Death usually occurs within ten days of exposure as a result of intraalveolar hemorrhage. Animals which die within 24 hours of dosing show no remarkable pathology. Animals that died within two to five days of dosing, demonstrate severe lung congestion, edema and variable inflammatory infiltrate. Animals that died within five to ten days show lungs characterized by hemorrhage and fibrosis. (Gregorio, 1982a).

H. Subchronic Toxicity

Although specific 40 CFR 162.11 risk criteria do not exist in relation to subchronic toxicity data, the Agency reviewed such studies related to paraquat for potential adverse effects.

1. Subchronic Oral Toxicity

The results of animal subchronic oral toxicity studies are summarized in Table 8.

These data suggest a dietary NOEL of 0.5 mg/kg/day (20 ppm) paraquat ion in dogs.

2. Subchronic Dermal Toxicity

McElligott (1965) treated rabbits (3 animals per dose level with 116, 58, 29, 14.5, 7.25 and 2.8 mg/kg (paraquat cation)

TABLE 6
EYE IRRITATION

Animal	Material	Dose	Results	Reference
Rabbit	Ortho Spot Weed and Grass Killer (Pq Dichloride 0.94%)	0.1 ml	Mild conjunctival irritation in 3/6 rabbits at 24 hrs; 1/6 at 72 hrs. All normnal at 72 hours.	Cavalli and Hallesy, 1969
Rabbit	Ortho Spot Weed and Grass Killer (Pq Dichloride 0.94%)	1-second spray	Mild to moderate conjunctival irritation in 6/6 rabbits at 24 hrs; normal at 72 hours.	Bullock, 1976
Rabbit	Tech. Pq. Hydrochloride	0.2 ml of 6.25 100% Solution	12-50% showed increasing corneal damage; 100% (5/5) rabbits died.	Snow and Wei, 1973
Rabbit	Ortho Paraquat (3 lb/gal. Conc.)	0.1 ml	Complete opacity of cornea, roughened cornea, necrosis conjunctivae, purulent discharge; severe chemosis mild iritis in all animals.	Bullock and MacGregor, 1977

TABLE 7
PRIMARY DERMAL IRRITATION

Animal	Material	Dose	Results	Reference
Rabbit	Ortho Spot Weed and Grass Killer	0.5 ml	Well confined erythema and slight edema observed at 7-days	Ford and Forchini, 1976
Rabbit	Ortho Paraquat (3 lb/gal conc.)	-	Slight to severe erythema and slight edema	Bullock and McGregor, 1976
Rabbit	Gramoxone (25% Paraquat)	0.1,0.5, 1.0,2.5, 5.0 and 10.0%	No irritation observed in animals with intact skin. Mild swelling and erythema in animals with abraded skin at 2.5% and higher.	Fodres et al., 1978

as paraquat dichloride on shaved backs. The material was dried in a stream of warm air and the site of application covered with light gauze and after 24 hours, washed with warm water and gently dried on 20 consecutive days. Grooming was prevented by wearing plastic collars. After final treatment, surviving animals were observed for 14 days without restraining collars.

The skin was affected at all dose levels except the 2.4 mg/kg dose, and histologic changes consisted of parakeratosis and occasional intraepidermal pustules. Animals receiving 14.5 mg/kg and higher, exhibited respiratory distress, extreme weight loss (30-40%), gastric hemorrhage and kidney damage (degenerative changes in the renal proximal convoluted tubules). Post mortem showed congested lungs with thickened alveolar walls and polymorph infiltrate. Deaths were as follows: 0/3 at 2.8 mg/kg; 0/3 at 7.25 mg/kg; 2/3 at 14.5 and 29 mg/kg; 3/3 at 58 and 116 mg/kg.

The conduct of the study (removal of restraining collars) along with the severe weight loss causes speculation that the annimals were licking the treated areas and causing ulceration in the oral cavity therefore not permitting the animals to eat. With these considerations a NOEL cannot be established from this study (Gregorio, 1982a).

McElligott, in the second phase of the above cited trial, dermally treated rabbits (3 animals/sex) with 2.4 mg/kg (paraquat cation) as paraquat dimethosulphate (JF 1824) on shaved backs in the same manner as described above.

Lungs showed mild congestion and histological examination revealed mild thickening of alveolar walls and polymorphonuclear leukocytes.

A NOEL cannot be established due to possible oral contamination as discussed and explained in the above study (Gregorio, 1982a).

In a separate study, McElligott and Swanston (1966) dermally treated rabbits (3 animals/sex/dose) with 192, 96, 48, 24 and 0 mg/kg paraquat cation as paraquat dichloride on shaved backs. The material was dried in a stream of warm air and site of the application covered with light gauze and after 24 hours, washed with warm water and gently dried on 20 consecutive days. Grooming was prevented by wearing plastic collers throughout dosing and the 14 day observation period.

Local erythema and hyperkeratosis with some necrosis was observed at all dose levels. Animals at the 192, 96, and 48 mg/kg doses showed some weight loss (10-20%), which was explained by the investigator as "this may have been due to the large amounts of paraquat on the skin with the escape of paraquat in dust and squames with subsequent oral contamination." Microscopic evidence of renal damage was observed in all the animals at the 192 mg/kg dose, but only

TABLE 8
SUBCHRONIC ORAL TOXICITY

Animal	Sex	Material	NOEL (PQ ion)	LEL (PQ ion)	Reference
Rat (90-day)	F	Pq Dichloride	None[1/]	None[1/]	Kimbrough and Gaines, 1970
Beagle Dog (90-day)	M/F	Technical PQ (32.2% w/w PQ cation)	0.5 mg/kg/day	1.5 mg/kg/day[2/]	Sheppard, 1981

[1/]Areas of fibrosis were identified in all surviving animals, lowest dose tested was 9 mg/kg/day.

[2/]Beagle dogs (3 animals/sex/dose) were fed 0, 7, 20, 60 and 120 PPM of paraquat in the diet for 13 weeks. There were no distinct changes in the hematological, clinical chemistry or urinalysis. Respiratory rasping was observed in 4/6 animals at the 120 PPM dose, however no other evidence of respiratory distress were described for any other dose level. The results of the necropsy showed large lung lesions, described as grey and red depressed areas involving several lobes (involving 10-100% of the affected lobe) in the 60 and 120 PPM dose groups. Small focal changes were observed one female (control group) and one male (20 group). Histopathological the lung lesions seen in the 60 and 120 groups were classified as alveolitis (inter-stitial hypercellularity, and alveolar collapse). Pale swollen segments of cortical tubules were seen in male (60 group) and one female and one male (120 group).

males receiving 96 mg/kg. Renal changes described as "cloudy swellings" was reported at the 48 mg/kg dose. Lung examination was described as follows:" in all animals there was an interstitial pneumonitis of varying intensity, characterized by peribronchial lymphoid hyperplasia, and swollen hypercellular alveolar walls in which macrophages were conspicuous." This was seen even in the control animals. A NOEL cannot be established due to a respiratory disease within the entire rabbit colony (Gregorio, 1982a).

3. Subchronic Inhalation

Hardy et al. (1979) exposed rats (whole body) to aerosolized paraquat ion for six hours/day, five days/week, for three weeks (total of 15 exposures). The dose levels were as follows: Group 1 consisted of 32 rats per sex exposed to 0 paraquat as a control; Group 2 consisted of 36 rats per sex exposed to 0.01 ug paraquat ion/liter; Group 3 consisted of 36 rats per sex exposed to 0.10 ug paraquat ion/liter; Group 4 consisted of 36 rats per sex exposed to 1.00 ug paraquat ion/liter; and Group 5 consisted of 16 rats per sex exposed to 0.50 ug paraquat ion/liter. The 1.00 ug exposure group was aborted following a single exposure due to 79 percent of the animals having died from respiratory exposure. Group 5 was subsequently added as a replacement for the aborted Group 4.

All the animals in Group 1, 2, 3, and 5 survived the exposure time. At the 0.5 and 0.1 ug/liter dose groups, a few animals had brown staining around their noses and/or brown nasal discharge, lasting for 1-2 days following the first exposure; no clinical symptoms were observed in the 0.01 ug/liter group. The following pathology was reported:

Dose (ug/liter)	Description of Effects[1]
0.01	No effect
0.10	16 rats showed squamous keratinising metaplasia and/or hyperplasia of the epithilium of the larynx after 3-week exposure.

These changes were observed in 11 rats after 2-week recovery period.

0.50	1) Focal ulceration of the pharynx in 2 male rats after 3-week treatment.
	2) All rats showed areas of ulceration and acute inflammatory cell infiltration of the larynx after 3-week exposure. No ulceration or necrosis was observed in the rats after a 2-week recovery period.

3) Aggregations of foamy macrophages, thickening of the alveolar walls were observed in rats exposed for 3-weeks. These changes were still observed after a 2-week recovery period, in addition, distribution of bronchiolar epithilium adjacent to macrophage aggregations was noted.

1/ Tissues other than the respiratory tract were not observed.

The indicated NOEL is 0.01 ug paraquat ion/liter.

Grimshaw et al. (1979) exposed rats (whole body) to aerosolized paraquat ion for 6 hours/day, 5 days/week for 3 weeks (total of 15 exposures) at concentrations of 0, 0.01, and 0.1 ug/liter. The generated particle size was 2 u. The results from this repeat study are identical for the 0.01 and 0.1 ug/liter dose levels described in the experiment done by Hardy et al. (1979). The indicated NOEL is 0.01 ug paraquat ion liter.

Wyatt et al. (1979) instilled paraquat dichloride (99 percent pure) or ^{3}H-paraquat in concentrations of 10^{-5} to 10^{-12} directly into the left lung lobe of male Alderly Park (Wistar) rats. Instillation of 10^{-5} g of paraquat in 0.1 ml of saline resulted in macroscopic damage ot the left lobe within 24 hours after dosing. Approximately 50 percent of each left lobe was damaged, and the damage increased with time. At 72 hours, the left lobes of all treated rats were plum-colored and of a jelly-like consistency. The lesion was much less extensive in the group that received 10^{-6} g of paraquat or less and did not increase in severity between 24 and 72 hours.

Instillation of 10^{-5} g of paraquat increased wet weights (of the left lobe) over time. Wet weights in treated animals were significantly heavier than controls at 24, 48 and 72 hours ($p < 0.01$). This was also true at 48 and 72 hours for the rats treated with 10^{-6} of paraquat. No changes in lung weight were noted after instillation of 10^{-8} or 10^{-10} g paraquat.

This study demonstrated that instillation of 10^{-5} or 10^{-5} g of paraquat into the lung lobe of the rat causes macroscopic and microscopic lesions and increased weight. The results indicate, as indicated in other studies, paraquat does affect the lung (Gregorio, 1982a).

Kimbrough and Gaines (1970) found that intrabronchial injections of paraquat (marked with India ink) induced lung fibrosis and epithelial proliferation at a dose of 0.05 mg/kg. Direct intrabronchial injection of paraquat produced pulmonary edema, congestion and intraalveolar hemorrhage.

Laird et al. (1979) determined by radioimmunoassay the paraquat concentrations (ug/g wet weight) in rat lungs

following the 5th and 15th inhalation exposures to H^3-paraquat. At a dose level of 0.01 ug/liter the lung concentrations averaged 0.11 ± 0.12 ug/g following the 5th exposure and 0.09 ± 0.13 ug/g following the 15th exposure. A concentration of 0.01 ± 0.10 ug/g was observed following a one day recovery period. At a dose level of 0.10 ug/liter, the lung concentrations averaged 2.08 ± 0.46 ug/g following the 5th exposure and 1.66 ± 0.35 ug/g following the 15th exposure. Concentrations at one, two and three days into recovery were 1.34 ± 0.24, 0.65 ± 0.09, and 0.35 ± 0.12 ug/liter respectively.

These data indicate that paraquat does not accumulate in the lungs between the 5th and 15th exposure, and that paraquat disappears after termination of exposure (Gregorio, 1982a).

4. Conclusions on Subchronic Toxicity

The available subchronic oral, dermal and inhalation data indicate that paraquat has an effect on the lung.

In an adequate subchronic feeding study in dogs (Sheppard, 1981), the NOEL is 20 ppm (0.5 mg/kg/day) of paraquat ion. The lung effects seen at doses of 60 (1.5 mg/kg/day) and 120 ppm (3.0 mg/kg/day) doses were alviolar collapse.

In several inadequate subchronic dermal studies using rabbits, a NOEL cannot be established (See Subchronic Dermal Toxicity for details). However these studies do suggest that paraquat absorbed through the skin can result in lung effects described as thickening of the alveolar walls and congestion.

In two supplementary subchronic inhalation studies using rats, the NOEL is 0.01 ug paraquat ion/liter (0.00145 mg/kg). The reported lung effects were irritation of the nasal passages and larynx (0.1 ug/liter) and alviolar wall thickening with aggregatious of foam macrophages (0.5 ug/liter). Both these studies were conducted with a generated particle size or 2-3 microns, therefore, these studies simulate a situation where the generated paraquat is 100% respirable. Other rat studies (Gage, 1968) suggest that paraquat generated at coarser size (10 microns) is not as respirable (Gregorio, 1982a).

I. Fish and Wildlife

Although the Agency did not specifically address fish and Wildlife concerns when identifying paraquat as an RPAR candidate (43 FR 30613), the subsequent comprehensive scientific evaluation of paraquat data revealed potential adverse effects. The findings of the Agency review are presented below:

1. Acute Toxicity to Aquatic Organisms

40 CFR 162.11(a)(3)(i)(B)(3) provides that an RPAR risk criteria shall have been met should a "maximum calculated concentration following direct application to a 6-inch layer of water (result in) more than 1/2 the acute LC_{50} for

aquatic organisms representative of the organisms likely to be exposed as measured on test animals specified in the Registration Guidelines."

The acute toxcicity of paraquat to fish species was evaluated by the Agency (US EPA, 1977 & 1979a) in studies utilizing Ortho Paraquat CL Concentrate containing 29.1% active ingredient. The 96-hour LC_{50} values for bluegill(Lepomis macrochirus)and rainbow trout(Salmo gairdneri)were found to be 156 (68-356) and 29 (20-41) ppm, respectively. These data demonstrate that 29.1 percent paraquat is slightly toxic to certain species of fish, but that the toxicity range falls below that which might cause critical concern by the Agency.

Wheeler (1978) studied the toxicity of technical paraquat dichloride (92.3%) to 1st instar Daphnia magna . The 48-hour LC_{50} was reported to be 1.2 (0.67-2.2) ppm. In a study conducted by the Agency (US EPA, 1979) the 48-hour EC_{50} for 29.1% paraquat dichloride was found to be 8.0 (3.4-18.7) ppm. These data indicate that paraquat is moderately toxic to a representative aquatic invertebrate species (Stevens et al, 1980).

Benjits-Claus and Persoone (1975) studied the effects of a commercial brand of paraquat, Gramoxone (200 g. active parts per liter), with and without wetters (Lissapol NX and Ethomone 525) on larval development, mortality and the number of molts of an estuarine mud crab (Rithropanopeus harrisii) at concentrations ranging from 0.1 to 1000 ppb. The ED_{50}'s (pre-crab stage) over a 20 day period are reported as 0.86 ppb for paraquat without wetters and 4.6 ppb for paraquat with wetters. The effects of paraquat on larval development became significant at 10 ppb with a delay of 3.09 and 5.76 days respectively for paraquat with and without wetters (Stevens et al., 1980).

No data were located with respect to paraquat's potential acute toxicity to aquatic insects.

In addition to laboratory studies, the Agency reviewed several field studies and incident reports relating to paraquat toxicity to aquatic organisms. Yeo (1967) treated six reservoirs in California with paraquat (unknown formulation) at concentrations ranging up to 2500 ppb. Additionally, ten plastic growth pools were treated with 1000, 2000 and 3000 ppb paraquat. Dissipation of paraquat in the reservoirs 24-hours post treatment averaged 73% among all concentrations. Certain of the aquatic weeds in the reservoirs were controlled adequately with paraquat. In the growth pools, treatment with paraquat did not appear to significantly affect the number of green sunfish (Lepomis cyanellus) or smallmouth bass (Micropterus dolomieui). The condition of the fish in the reservoirs was not, however, reported.

In two lake experiments at Oxton, Nottinghamshire, England (Way et al., ?), in which a commercial formulation of

paraquat [Gramoxone JF 1341 (20% a.i.)] was applied at 0.5 mg/l, there was reportedly excellent control of many aquatic plants without any appreciable adverse effects to some 16 species of invertebrates. It was additionally reported that neither fish nor breeding birds in and around the lakes appeared to suffer obvious changes in species composition or population density during the 22-week post-treatment observation period. Water and mud samples were taken up to 32 days and 110 weeks, respectively. The residues in water fell rapidly over the first 48 hours and were not detectable (0.01 ppm) by the sixteenth day. Mean residues in water were 0.31 ppm, 0.16 ppm, 0.12 ppm and 0.045 ppm after 1, 2, 4 and 8 days.

A gradual accumulation of paraquat residues in mud samples was reported from one lake. Generally, residues in mud showed a logarithmic increase over the first four post-treatment days (1.23, 2.42 and 7.82 ppm for 1, 2 and 4 days, respectively) followed by a slower increase up to the 32nd day (11.24 ppm). Thereafter, there appeared to be a slightly more rapid increase to 197 days (17.68 ppm) followed by a loss to a one-year post-treatment level of 7.95 ppm). The first two periods coincided with the collapse and disintegration of plant material. Paraquat residues appeared to accumulate in weed tissues (25.5, 38.3 and 27.8 ppm at 2, 4 and 32 days) up to eight days at which time disintegration took place and residues appearently began settling out to the bottom (Stevens et al., 1980).

Newman (1966) reported satisfactory weed control in several types of aquatic environments (drainage canals, larger canals, and lakes) treated with up to 1 mg/l (unknown formulation). Severe deoxygenation occurred in one lake that was treated wholly. Another lake that was partially treated had no apparent serious deoxygenation. No major direct effects on any of the various groups of invertebrates sampled were evident in the study (Stevens et al., 1980)

Earnest (1971) studied the effect of paraquat on fish in a Colorado farm pond. Paraquat (2 lb a.i./gal formulation) was applied to a 0.44 acre pond at 5.4 gal to achieve a desired concentration of 1.14 ppm. Five months before treatment, 150 bluegills and 100 rainbow trout were released into the pond to add to an already existing population of green sunfish. Fifty bluegill were added to the pond three weeks before treatment, and 350 each bluegill and catfish were added five days before treatment. Five days prior to treatment an additional 250 bluegill and 150 catfish were placed in live-cages. Residue analyses were conducted on 10 green sunfish exposed to 1.0 ppm paraquat for 4, 8 and 16 days each and on samples of mud, water and algae.

The results indicated the bluegill to be the more sensitive of the fish species tested. At least 34 percent of the 400 free swimming bluegills died within 48 hours; 67 percent of the 250 bluegills in the live-cages were dead the day after

treatment. One trout and 25 catfish were found dead at various times which seemed to correspond to periods of low dissolved oxygen (DO) (1.8 ppm bottom and 4.0 ppm surface). DO fell from approximately 7.0 ppm overall to 7.0 ppm at the surface and 5.0 ppm at the bottom one day post-treatment. This is the time period (1-2 days after application) when most of the mortality occurred. Most mortality seemed to occur in the live cages, but their locations with respect to bottom or surface was not specified.

Paraquat levels in fish, one day post-treatment, ranged from 0.58 ppm in green sunfish to 1.86 ppm in rainbow trout. Residue levels in bluegills reached a maximum of 1.58 ppm after eight days and then declined. The aquatic vegetation, Chara and Spirogyra , were reportedly controlled effectively. Paraquat residues were concentrated up to 2300 ppm in the plants until they disintegrated. Residues in water were highest (1.52 ppm bottom) three hours after treatment. The residues fell off rapidly following the three hour high concentraton. Paraquat was more persistent in mud. The residue concentration reached a maximum level of 15.9 ppm after 16 days and was still fairly elevated (3.0 ppm) at 99 days (Stevens et al., 1980).

Treatment of drainage ditches with paraquat at 0.6 ppm caused a marked but temporary decrease in the numbers of plankton or protist organisms (Hewss, 1972). All populations recovered to pre-treatment levels in about two weeks.

In a study concerning the effects of paraquat on invertebrates in a New Zealand stream, paraquat was applied at 2 ppm a.i. for 30 minutes, adjusting for stream flow and delivery rate (Burnett, 1972). Drift-net samples showed significant (2-8X) numbers of amphipods during the first 2.5 hour period following application, indicating a direct toxic effect. Drift-net samples for six other invertebrate species did not show significant changes. Surber samples one year later showed increased numbers of invertebrates in the stream, particularly Trichoptera. Brooker and Edwards (1974) reported that paraquat (Gramoxone S and W) applied to a reservoir at 1 mg/l eliminated the angiosperms. Planktonic invertebrates were either eliminated or survived at lower densities. Many invertebrates which intimately associate with angiosperms (Trichoptera, Lepidoptera, Gastropoda) were eliminated or colonized the replacement growth of Chara globularis at reduced densities. The authors attributed the reduction in invertebrates to the destruction of plants, particularly angiosperms, and not to the direct toxic effect of the paraquat. This study indicates that changes in community structure can result from the destruction of macrophytes. Reductions in populations of some nontarget aquatic invertebrates may, therefore, be expected following paraquat applications of 1 mg/l (Stevens et al., 1980).

The Agency has not located any incident data involving aquatic species

2. Toxicity to Terrestrial Wildlife

40 CFR 162.11(a)(3)(i)(B) establishes certain RPAR criteria in relation to hazards to wildlife. Such critera are exceeded when a pesticide "(1) occurs as a residue immediately following application in or on the feed of a mammalian species representative of the species likely to be exposed to such feed in amounts equivalent to the average daily intake of such represntative species, at levels equal to or greater than the acute oral LD_{50} measured in mammalian test animals as specified in the Registration Guidelines. (2) Occurs as a residue immediately following application in or on avian feed of an avian species, representative of the species likely to be exposed to such feed in amounts equivalent to the average daily intake of such representative species, at levels equal to or greater than the subacute dietary LC_{50} measured in avian test animals as specified in the Registration Guidelines."

40 CFR 162.11(a)(3)(ii)(C) additionally provides that a pesticide may become subject of an RPAR action should application of the pesticide "reasonably be anticipated to result in significant local, regional, or national population reductions in non-target organisms, or fatality to members of endangered species."

The Agency has located and reviewed several studies concerning both the acute and chronic toxicity potential of paraquat in relation to terrestrial wildlife. The Agency's review findings are summarized below:

a. Acute toxicity

Beavers (1979) determined an acute oral LD_{50} of 176 (144-213) mg/kg technical paraquat for bobwhite quail. In dietary testing (5 days on feed, 3 days off) the LC_{50} values for paraquat (29.1% a.i.) to ring-necked pheasant, mallard and bobwhite were reported to be 1468, 4048, and 948 ppm, respectively (Hill et al., 1975). These data have been extrapolated to approximate LC_{50} values for 100% active paraquat. The calculated LC_{50}'s, corresponding to the preceeding species, are 427, 1178 and 285 ppm. The extrapolated data indicate that paraquat is highly toxic to birds based upon the LC_{50} for the most sensitive species (Stevens et al., 1980).

In relation to mammals, the acute oral toxicity of paraquat ranges from 35 mg/kg for the Belgian hare (domestic version of the rabbit, Oryctolagus cuniculus) to 150 mg/kg for the rat (Newman, 1971). The application of paraquat 3 lb/gal concentrate to abraded and unabraded skin of male New Zealand white rabbits induced very slight to severe erythema (Bullock, 1977b) One rabbit died (cause unspecified) six days following treatment. The acute dermal toxicity of paraquat 3 lb/gal concentrate to

rabbits has been determined to be 174 (80-376) mg/kg (Bullock, 1977a). Gross pathology included bloody urine, reduced food intake, reduced pulmonary rates, depression, diarrhea, ataxia, convulsions and collapse. Histopathology revealed organ abnormalities including hemorrhagic, edematous lungs, discolored grainy livers, and soft vascularized kidneys.

McElligott (1972) investigated the acute intraperitoneal (IP), subacute dermal and acute dermal toxicity of paraquat (Gramoxone, 24%) to the albino rabbit. The LD_{50} after a single IP injection was calculated to be 18.15 (10.61-31.04) mg/kg. The subacute (20 day) dermal LD_{50} ranged from 4.5 mg cation/kg (6.245 mg dichloride/kg/day) by the occlusive technique to over 24 mg cation/kg when air drying occurred. A single large application of 480 mg cation/kg (with restraining collar) to an uncovered area did not produce mortality and caused only minor reversible systemic symptoms of intoxication. A lesser application of 240 mg cation/kg was, however, fatal within 72 hours when applied beneath an occlusive dressing. When free grooming was allowed, residual skin contamination caused severe tongue ulceration and inability or unwillingness to eat, even after washing the applied site. It has been theorized that the stratum corneum can act as a skin reservoir for applied substances (Stevens et al., 1980).

In relation to other terrestrial organisms, paraquat has been found to be relatively nontoxic to honey bees (Atkins et al., 1975). The Agency has not, however, located any data relative to paraquat's toxicity to other arthropods or lower orders.

b. Accumulation and Chronic Toxicity

The Agency has located and reviewed three studies concerning the chronic toxicity of paraquat to terrestrial wildlife.

The Eley Game Advisory Station's study, although lacking sufficient detail with respect to the experimental design, reported that Gramoxone reduced egg hatch. Pheasant eggs sprayed at the equivalent of 1.0 and 2.0 lb/A yielded hatching rates of 25 percent and 12 percent respectively. The control group was reported to have hatched at a rate of 48 percent.

Lutz-Ostertag and Renou (1974) sprayed paraquat (unknown concentration) on chicken and quail eggs to study the effect on the urogenital tract of developing embryos. The male embryo gonads were reported to appear small and exhibited signs of intersexuality (pseudo-feminisation). The gonads were characterized by having only a small number of gonocytes due to a mitotic disturbance (chromosomes distributed in a confused manner). Male

muellerian tracts were very similar to the female genital system. In female embryos, the size of the ovaries was not affected, but, shape and relief were. Also, very few gonocytes were present in the ovaries.

Hoffman and Eastin (1982) determined that paraquat was the most embryotoxic to mallard eggs of four compounds tested. In one trial, paraquat was examined at rates equivalent to 0.5 and 5 lb a.i./A. In a second trial, three to six geometrically graduated concentrations were used to determine embryo LC_{50} values. Treatments occured on days three and eight and were carried out in aqueous emulsion and oil as a vehicle. Observations were conducted until day eighteen of incubation. The paraquat concentrations remaining on each egg immediately after immersion were within the range of the theoretical residues expected after spraying at the customary rates of 100 gal/A for aqueous suspensions and 11 gal/A for oil formulations.

Paraquat in the aqueous emulsion produced a significant effect on the survival rate for 3-day mallard embryos. Mortality was reported as 23 and 73 percent at 0.5 and 5 lb a.i./A respectively. Mortality ($p < 0.01$) was accompanied by reduced growth, a significant decrease in crown-rump length ($p < 0.05$) and a significantly large incidence of abnormal survivors ($p < 0.01$ only at high rate). When eggs were treated on day 8, 20 percent mortality occured at the lower rate and 47 percent at the higher rate. Again, mortality was accompanied by a significant reduction ($p < 0.01$) in growth and a large incidence of abnormal survivors ($p < 0.05$) at both rates. The LC_{50} values for 3 and 8 day old embryos were 1.5 and 2.5 lb a.i./A respectively.

Paraquat in the oil vehicle had significnat embryotoxic effects at the high rate of application in 3-day embryos ($p < 0.01$, 83% mortality). Mortality at the low rate was 17 percent. There were significant effects on growth and an increased incidence of abnormal survivors ($p < 0.05$). When treatment was on 8-day embryos with oil vehicle, there was a reduced growth ($p < 0.05$) at both treatment levels and 93 percent mortality at the high rate ($p < 0.01$). The LC_{50} values for 3 and 8 day treatment embryos were 0.1 and 0.2 lb a.i./A respectively for the oil formulation.

The Agency believes, based principally upon the results reported by Hoffman and Eastin, that paraquat can, under certain conditions of use, cause significant reductions in certain stages of avian reproduction. The Agency, in cooperation with the Chevron Chemical Company, has evaluated paraquat use and application and has developed methods by which paraquat's impact may be significantly lessened. A discussion of those measures agreed upon by

both the Agency and Chevron Chemical Company is contained within the conclusions section of this document.

c. Field and Incident Data

Newman (1971) reported several instances in which hares were killed following the spraying of paraquat. Two incidents in Britain involved the deaths of 70 to 80 hares following the spraying of paraquat to grassy stubble. In France, a number of hare poisonings have been reported. In some cases, paraquat residues ranging from 1 to 5 ppm have been detected in hares.

To investigate the toxic potential seemingly indicated by these incidents, Newman randomly assigned adult female hares (Belgian Flemish Giant hybrids) to the following treatments: unsprayed grass (3 hares - Group I), Gramoxone (24%) sprayed grass allowed to dry (6 hares - Group II), and Gramoxone sprayed grass available when wet (6 hares - group III). The hares were placed in 30 to 60 M^2 enclosures daily at 9 AM and removed at 4 PM. After a 2 week acclimation period, the grazing areas for the treated groups were sprayed with Gramoxone at 1.12 kg/ha. The hares then grazed daily for 2 weeks.

Following spraying, the grass contained 1370 ppm paraquat ion. At the end of the two-week grazing period, three Group II animals were sacrificed and three were allowed a recovery period of a further week during which they were maintained on rabbit pellets. The sacrificed animals in Group II were examined pathologically, and some effects attributable to the ingestion of paraquat were reported. These effects were lesions of the tongue, pale spleen and pulmonary edema. No significant pathological effects were detected in the other three animals at the end of the recovery period. In Group III, one of the animals died after eight days. Of the five survivors at the end of two weeks, one was sacrificed for pathological examination, while four were allowed a recovery period on rabbit pellets. One of these was examined in detail after the recovery period and showed no abnormal pathology. Some paraquat analyses were performed on organs from the three Group II animals at the end of the two week exposure period, but negligible quantities of paraquat were detected (0.5 ppm or less).

This experiment would tend to indicate that exposure to freshly sprayed grass swards can produce toxic symptoms and even death. The risk to the animal appears to be lessened if the paraquat deposit is dry prior to contact. This difference, however, is impossible to statistically quantify due to the limited number of animals involved in the study (Stevens et al., 1980).

In a comparison study (deLavaur et al., 1973), it was reported that no significant difference in mortality could

be observed between "dried" (1/3 died) and "non-dried" (3/4 died) feeding regimes involving the wild hare (Lepus europaneus). Again, however, the limited number of animals used in the study did not permit the appropriate statistical analysis. Histopathology of three surviving hares, 2 weeks posttreatment, revealed a globular surface of the pulmonary lobes, which were dotted with small blisters. Healthy areas of the pulmonary parenchyma were dotted with atelectasis and emphysema type lesions. Also evident was a wide-spread and deep ulceration of the Malpighian epithelium of the tongue.

Paraquat residues were not detected in lungs, liver or kidneys. In the heart, traces of paraquat (0.8 and 1.1 ppm) were found in two hares. Concentrations of 4.8 and 31 pm paraquat were found in the content of the cecum.

Mean paraquat residues (fresh weight) in plants ranged from 27 to 43 ppm for alfalfa and 50 to 71 ppm for surrounding grasses. Dry weight residues were 150 ppm for alfalfa and 290 ppm for grasses.

The Agency has concluded, on the bases of the preceding two studies, that the hare possesses a pronounced sensitivity to paraquat. Although the numbers of animals involved in the experiments were too small to permit a sound statistical evaluation, the consistent observation of lingual and pulmonary lesions is viewed as presumptive evidence of such sensitivity (Stevens et al., 1980).

Two monitoring studies, conducted by Chevron Chemical Co., (Chevron Chemical Co., 1974 and 1977) did not identify any ill effects to avian or other wildlife species observed. The 1974 study involved the application of paraquat to sunflowers at rates up to 0.5 lb a.i./A. In the 1977 study, a 2% aqueous solution of paraquat was applied during a Paraquat Resin Soaking in the Southern Pines Program. Although of some interest, the results of these studies are of only limited value due to the methods and rates of application (Stevens et al., 1980).

Rivera (1973) reported that 72% of a population of 84 geese died within days after an adjacent field was treated with 20% paraquat. Although the geese were fenced off from the treated field, it is theorized that the heavy rain which fell the same day of application and again the following day ran down slope, forming small puddles which were accessible to the geese. Some of the symptoms observed were: restlessness, ataxia, motionlessness, loss of appetite, salivation, convulsions, and abnormal position of neck and head. Death apparently occurred as a result of contraction of the respiratory muscles. Necropsy showed symptoms of asphyxia, minute hemorrhaging of the epicardium, and pulmonary hyperemia.

IV. Conclusions and Recommendations

With respect to paraquat as an RPAR candidate, the Agency concludes that the presently available data do not support a "Rebuttable Presumption Against Registration" in relation to those criteria cited within 43 FR 30613. Although the Agency believes that 40 CFR 162.11 risk criteria have been exceeded in relation to both avian and mammalian wildlife, certain measures, described below, have been taken which reduce the risks to a degree deemed acceptable.

A. Teratogenicity

While finding the four available open literature studies pertaining to paraquat's potential teratogenicity to be inconclusive, Agency review of two registrant submitted studies found to be valid provided no indication of teratogenicity. The Agency has, therefore, concluded that, in relation to teratogenicity, no scientific basis exists for presuming against paraquat's current registration. The Agency, further, believes that the current data base is adequate and will not require the submission of additional studies.

B. Reproductive Effects

Insufficient data are available with which to assess the potential reproductive effects of paraquat. A No Observed Effect Level (NOEL) could not be established from those three studies located for Agency review. Although insufficient, the Agency has noted that the reveiwed data do not indicate any adverse effect. The Agency has been unable to either establish or disprove the existence of reproductive effects from paraquat exposure. The Agency will, therefore, require that an additional multi-generation reproduction study be submitted for Agency evaluation.

C. Oncogenicity - Chronic Feeding

The Agency has reviewed four studies concerning the potential chronic feeding effects of paraquat. In summary, the Agency found each study to be inadequate. In the absence of acceptable data, the Agency has been unable to arrive at any conclusion concerning paraquat's potential for causing chronic effects or its potential as an oncogen. The Agency, therefore, will require chronic feeding studies utilizing both the rat and the dog and oncogenicity studies involving both rats and mice.

D. Mutagenicity

Incomplete data are available with which to assess the mutagenic potential of paraquat. The available data have provided no evidence that paraquat causes dominant lethal mutations in mice or reverse mutations in the Ames strain of S. typhimurium . Several inadequate studies, however, suggest that paraquat may cause reparable DNA damage in bacteria and in human cells in vitro, induce forward mutations in S. typhimurium and Aspergillus nidulans and induce gene conversion in yeast. Due to study inadequacies, the Agency can not reach a definitive conclusion regarding paraquat's mutagenic

potential. The Agency will, therefore, request submission of additional mutagenic test data. These data requests will include a mammalian *in vitro* point mutation test and a primary DNA damage test.

E. Lack of Emergency Treatment

As discussed earlier in this document, both the oral administration and skin absorption of paraquat have been responsible for poisoning incidents. As little as 1 teaspoon of paraquat can lead to interstitial fibrosis, respiratory failure and death. Following ingestion, several days elapse before dyspnea and several weeks before death. Histopathologic evaluation of the lung in fatal ingestion cases show several states of lung involvement. The primary process appears to consist of hemorrhage, edema, increased macrophages and bronchiolar damage. This is followed by septal thickening, fibrosis, increased fibroblasts and honey combing (Rebello and Mason, 1978). The Agency, however, believes that the therapeutic approach to treatment of acute oral exposure (Cavalli and Fletcher, 1977) has been demonstrated partially effective. The 81% survival rate occurring in those case histories available to the Agency in combination with the rapid availability of treatment information (provided by the placement of a Chevron Chemical Co. 24-hour emergency treatment telephone number on all labeling) suggests an adequate emergency treatment for accidental oral contamination. In addition, the Agency, on April 14, 1982, established an exemption from tolerance for an emetic which is to be incorporated into current paraquat formulations. This emetic is intended to induce rapid vomiting thereby reducing the absorption of paraquat. The Agency, therefore, does not believe that adequate grounds currently exist for the initiation of an RPAR action based upon the lack of emergency treatment for oral exposure.

Currently, no data are available with which to assess the adequacy of emergency treatment for dermal absorption of paraquat. The Agency has noted, however, that relatively few dermal exposure cases have resulted in fatalities. Paraquat products, with the exception of a homeowner use product containing a very low concentration of active ingredient, bear restricted use classification. Applicators of such products are required to undergo training in the safe handling and use of pesticides and receive instruction in product labeling and label interpretation. Current paraquat products bear labeling instructions for mixers and applicators in exposure reduction techniques. Those involved in mixing are instructed to "wear a full face shield, rubber gloves and apron" while applicators facing a risk of exposure are instructed to "wear goggles and approved face mask capable of filtering spray droplets." They are additionally instructed to "wear waterproof footwear and clothing when spraying or when contacting vegetation wet with spray." The Agency believes that the precautionary measures dictated by current labeling are adequate for the prevention of dermal acute toxicity. While reemphasizing that no data are available with respect to emergency treatment for dermal absorption, the Agency has concluded that an RPAR action would not appear warrented.

F. Acute Toxicity

As previously discussed, the acute toxicity of paraquat is high regardless of the route of exposure. The acute oral (rat) and acute dermal (rabbit) toxicity data demonstrate that small increases in dose elicit large changes in response, thus indicating a steep dose-response curve. Death usually occurs within 10 days of exposure as a result of intra-alveolar hemorrhage. Animals which die within 24 hours of dosing show no remarkable pathology. Animals that died within two to five days of dosing, however, demonstrate severe lung congestion, edema and variable inflammatory infiltrate. Animals that died within five to ten days show lungs characterized by hemmorrhage and fibrosis. Although paraquat must be considered highly toxic, neither the acute oral nor dermal toxicity of formulated products exceeds those RPAR levels established under 40 CFR 162.11((a)(3)(i). The Agency, therefore, has concluded that an RPAR action based upon either acute oral or dermal toxicity is not warranted.

Those data relating to acute inhalation toxicity have been reviewed by the Agency and have been judged inadequate. The two studies available for Agency review provided LC_{50} values ranging from 1.0 ug/liter to 6.4 mg/liter. The obvious disparity of these results prevents the Agency from arriving at any conclusion concerning paraquat's inhalation toxicity. The Agency, therefore, will require the submission of a rat acute inhalation study.

G. Subchronic Toxicity

Two studies dealing with the subchronic oral toxicity of paraquat were available for Agency review. Although the 90 day dog study by Sheppard (1981) suggests a dietary No Observed Effect Level of 0.5 mg/kg/day (20 ppm), the absence of a valid second study in another species, prevents the establishment of a NOEL. The available 90-day rat study (Kimbrough and Gaines, 1970) could not be utilized due to the lowest dose tested (9 mg/kg/day) having produced lung fibrosis. While the Agency would, under certain circumstances, require the submission of a valid 90 day rat study, the existing requirement for the submission of chronic rat and dog studies obviates the need for additional subchronic studies.

In evaluating the subchronic dermal toxicity of paraquat, the Agency reviewed the two available studies (McElligott, 1965 and McElligott and Swanston, 1966). These studies, while indicating that paraquat can be absorbed through the skin in sufficient quantities to produce lung effects (congestion and alveolar wall thickening), were determined inadequate for those reasons cited under Section III of this document. The Agency has, therefore, concluded that an additional subchronic dermal study (21-day rabbit) must be submitted for Agency evaluation. This study is to be conducted in concert with a dermal absorption rate asessment.

The available subchronic inhalation studies indicate an extremely low No Observed Effect Level (NOEL). Both Hardy et al. (1979) and Grimshaw et al. (1979) established NOELs of 0.01 ug/liter under the conditions of the experiments. The Agency, utilizing the 0.01

ug/liter NOEL, undertook a non-dietary risk assessment for inhalation exposure. This assessment was conducted as follows:

1. Nondietary Risk Assessment

In the creation of the risk assessment, the Agency established a worst case scenario. It was assumed that applicators would not be wearing protective face masks as called for by product labeling. It was further assumed that 100% of the available paraquat was respirable. Assumptions made in relation to the experimental animals involved in establishing the NOEL were that the rat body weight was 0.250 kg, the minute volume of rat lungs is 0.101 liter minute^{-1}. The experimental exposure period was 6 hours.

Rat exposure 6 hours = 360 min. X 0.101 L min.$^{-1}$ =
36.36 liters of air/day
0.01 ug/L X 36.36 L/day = 0.3636 ug/day
0.3636 ug/day / 0.250 kg = 1.45 ug/kg
1.45 ug/kg = 0.00145 mg/kg (NOEL)

Method of Application	Exposure Estimate (mg/kg/day)	MOS
Aerial Application		
1) Applicator	0.00460 - 0.0091	< 1
2) Drift Exposure	0.00089 - 0.0022	2 - 0.7
3) Flagger	0.00089 - 0.0022	2 - 0.7
Backpack Sprayer	0.00010 - 0.0038	1 - 0.4
Tractor Drawn Boom Sprayer	0.00002[1]	70
Yard/Garden	0.0001	10
Cotton Mill Workers	0.000015	100
Mechanical Harvestors		
1) Cab Door Open	0.000097 - 0.00026	10 - 6
2) Cab Door Closed	0.0000028	500

1/ Wearing face mask

As shown by the preceding table, those populations facing the greatest risk due to inhalation exposure are: aerial exposure (Applicator, Drift and Flagger), Backpack sprayers, Tractor Drawn Boom Spayers, and Yard/Garden Applicators.

2. Agency Conclusions Regarding Subchronic Inhalation Risk

While the Margins of Safety (MOS) would appear exceedingly low for certain applicators, it must be emphasized that the NOEL

utilized in the risk assessment was derived from studies in which the particle sizes all fell within the respirable range. It is unlikely that the simulated rat study situation would occur in actual field situations. The Agency has developed data (Raksphal, 1981) which indicates that in actual field situations only 2 percent of the generated particles are within the respirable range. Further reducing the number of respirable particles would be the use of face masks. It may be seen, therefore, that the actual MOS for any given risk group would probably be significantly greater. With the data at hand, however, the Agency is not in a position to establish Margins of Safety clearly relatable to actual use situations. The Agency, therefore, will require additional testing which will better approximate worker/applicator exposure. Included in this study will be a requirement for an investigation of face mask filtering capabilities.

H. Fish and Wildlife

Mammals, particularly hares, have been demonstrated to be sensitive to paraquat. The best available data indicate that the acute oral toxicity of paraquat ranges from 35 mg/kg for the hare to 150 mg/kg for the rat. Those studies which established the LD_{50} values were undertaken utilizing formulations containing 21 percent paraquat cation. The Agency (Stevens et al., 1980) has extrapolated these values to arrive at theoretical LD_{50} values for technical paraquat. The Agency estimates LD_{50} values ranging from 10.15 mg/kg for the hare to 43.5 mg/kg for the rat. These values are exceeded (approximately 2 to 20x) by expected field exposure levels. Field exposure levels have been calculated to range from 110 ppm for long grasses to 240 ppm for short range grasses (Stevens et al., 1980). For a 2-4 kg hare to consume an amount of paraquat contaminated vegetation equivalent to its' LD_{50}, it would have to consume from 0.07 to 2.8 kg plant material.

Although acute toxicity is of concern, the Agency believes that in many instances mammals would not consume a lethal dose due to either lingual inflammation or the unattractiveness of paraquat dessicated vegetation. The Agency is, potentially, more concerned with the subacute effects. There is evidence that feeding, particularly on freshly sprayed forage, causes severe lingual necroses and a subsequent inability or unwillingness to eat. The stomachs of some dead animals were found to be empty. Several incidents in Britain and France following the spraying of paraquat on a variety of sites (mostly grasses) have been recorded. Paraquat residues were detected in gut and urine samples. The detection of kills may be related to the monitoring effort and the proximity and accessibility of the site to human activity. As a consequence, the reported incidents may be a small sample of a regularly occurring phenomenon. The Agency, however, in evaluating the significance of a pesticide's impact, must take into consideration the sites, rates, timing, etc. of application as they effect exposure potential. Believing that only certain sites of application represent potentially serious exposure opportunities, the Agency has evaluated existing registered sites. The Agency's conclusions are presented below in conjunction with the discussion of avian risk.

With regard to avian species, it has been demonstrated that paraquat is acutely toxic and may, following direct application, cause a reduction in egg hatchability. The acute toxicity to the most sensitive species, while exceeding the 40 CFR 162.11(c)(1)(iii)(B) criterion for restricted use, does not exceed Agency RPAR criteria. The Agency has concluded, therefore, that the available evidence does not support the issuance of an RPAR. The Agency, however, does remain concerned with respect to the paraquat's apparent impact upon egg hatch. Although there is evidence to support the contention that paraquat can adversely affect egg hatch, the Agency must additionally consider the potential for exposure. The Agency, in cooperation with the Chevron Chemical Company, has evaluated the currently registered sites of application. The Agency believes that, in most cases, those crop and pasture sites currently registered would not provide prime wildlife habitat. As a consequence, only limited populations would be at risk. The Agency, however, did conclude that certain noncrop sites, and one pasture application did provide potential for significant wildlife exposure. The Agency and Chevron Chemical Company have agreed to proceed with the voluntary cancellation of those sites which present high exposure potentials. The elimination of these sites (rights-of-way, including highways, parkways, roads, dividers and medians, railroads, electric utility and pipeline and pasture application east of the Cascade and Sierra Nevada Mountains and West of the Rocky Mountains) similarly relieve Agency concerns related to mammalian toxicity. Although paraquat has been found to exceed mammalian risk criteria, the Agency believes that the cancellation of the aforementioned noncrop sites significantly reduces exposure potential and obviates the need for RPAR action.

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