UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: June 26, 2019

SUBJECT: **Paraquat Dichloride:** Draft Human Health Risk Assessment in Support of Registration Review

PC Code: 061601
Decision No.: 512268
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D430827
Regulatory Action: Registration Review
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1.0 Executive Summary

This assessment has been conducted to support the Registration Review of the insecticide paraquat dichloride, herein referred to as paraquat. As part of Registration Review, the PRD of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary and occupational/residential exposure assessments, as needed, to estimate the potential risk to human health that could result from the currently registered uses of paraquat. This memorandum contains HED's human health exposure and risk estimates from paraquat. The current paraquat human health risk assessment contains the following updates from the most recent published risk assessment (D415809, T. Morton, 09/25/2014):

- New points of departure (POD) were selected for all exposure scenarios;
    - The new acute dietary POD (5 mg paraquat ion/kg) is based on clinical signs and mortality in the rat developmental study. The previous acute POD was 1.25 mg paraquat ion/kg.
    - The new chronic dietary POD (0.5 mg paraquat ion/kg/day) is based on respiratory toxicity in two co-critical dog oral toxicity studies. The previous chronic POD was 0.45 mg paraquat ion/kg/day.
    - The new incidental oral POD (0.5 mg paraquat ion/kg/day) is based on the same effects as the chronic dietary POD. An incidental oral POD was not selected in previous risk assessments.
    - The new dermal POD (6 mg paraquat ion/kg/day) is based on the systemic NOAEL from a route specific dermal study. Previously, the dermal POD was based on an oral endpoint and the extrapolated dermal dose would be approximately 25 mg paraquat ion/kg/day.
    - The inhalation POD (0.01 µg paraquat ion/L/day) is based on portal of entry effects in a route specific inhalation study. Previously, the paraquat human health risk assessment selected a respirable (same as new POD) and non-respirable POD (1.25 mg paraquat ion/kg/day) and inhalation risk was assessed using the non-respirable POD based on the assumption that inhalation exposure would only be to particulates in the non-respirable range. The current risk assessment does not make this assumption.
- The conclusions from the epidemiology and Parkinson's disease systematic reviews were incorporated into hazard characterization and accounted for in the POD selection;
- The occupational handler and occupational post-application assessments were updated to incorporate recent updates to the dermal and inhalation PODs, and policy changes for body weight, unit exposure, transfer coefficient, and area/amount treated assumptions;
- A non-occupational spray-drift exposure/risk assessment was completed; and
- The history of human incidents associated with paraquat dichloride use were reviewed in a Tier II human incident report.

Use Pattern

Paraquat dichloride (1,1'-dimethyl-4,4'-bipyridinium dichloride) is a non-selective herbicide currently registered for the control of weeds and grasses in agricultural and non-agricultural areas. It is a contact herbicide that desiccates and destroys plant cell membranes within hours of application. Paraquat is only formulated as a soluble concentrate/liquid (SC/L) formulation. The active ingredient, paraquat dichloride, exists as a mixture of paraquat cations (dications) and chloride anions. Paraquat cation is the toxic moiety and, therefore, the form evaluated for purpose of exposure and risk assessment. Paraquat can be used pre-plant or pre-emergence, at

planting, post-emergence, as a desiccant or harvest aid, as well as a postharvest desiccant. It may be applied to agricultural and non-agricultural areas (e.g., non-crop lands, and pasture lands) with aerial, ground, and handheld spray equipment. Paraquat is a restricted use pesticide (RUP) based on acute toxicity; therefore, there are no paraquat products registered for homeowner use and no products registered for application to residential areas. Tolerances have been established for paraquat under 40CFR§180.205(a) for multiple commodities, and range from 0.01 ppm for egg and milk to 210 ppm for animal feed items. Tolerances with regional registration have been established under 40CFR§180.205(c) at 0.05 ppm for pigeon pea seed and tyfon, and at 0.1 ppm for taro corm.

Exposure Profile

Humans may be exposed to paraquat in food and drinking water since paraquat may be applied directly to growing crops and application may result in it reaching surface and ground water sources of drinking water. Non-occupational exposures may occur as a result of spray drift from off-target applications of paraquat. Occupational handler and post-application exposures are expected from paraquat usage. This risk assessment considers all the aforementioned exposure pathways based on the existing paraquat uses.

All registered labels require occupational handlers (mixers and loaders) to wear "baseline" clothing (i.e., a long-sleeved shirt, long pants, shoes and socks), chemical resistant gloves, a National Institute of Occupational Safety and Health (NIOSH) approved half-mask [assigned protection factor (APF) 10; 90% exposure reduction] respirator, as well as a chemical resistant apron and face shield. Applicators and other handlers (other than mixers and loaders) must wear baseline clothing, chemical resistant gloves, a NIOSH approved half-mask respirator, as well as protective eyewear. Occupational handler exposures are expected to be both short- (1 to 30 days) and intermediate-term (1 to 6 months).

Based on the high number and severity of human health incidents associated with paraquat involving the ingestion of paraquat, both accidental and intentional, the EPA determined that risk mitigation measures were necessary for paraquat pesticide products to meet the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration. This mitigation decision[1] was published in January 2017. The following mitigation measures were implemented in three phases. Submission deadlines and implementation timeframes for these measures are discussed below.

1. Label amendments to emphasize paraquat toxicity and restrict use of all paraquat products to certified applicators only (i.e., prohibiting use by uncertified persons working under the supervision of a certified applicator), and supplemental warning materials
    a. Implementation timing:
        i. Revised labels and supplemental materials were submitted to EPA in March 2017
        ii. Revised labels and supplemental materials were stamped approved by EPA in late Summer/Fall 2018
        iii. New products released into commerce must bear this new labeling by late Summer/Fall 2019

[1] M. Mannix. Amended: Paraquat Dichloride Human Health Mitigation Decision. January 12, 2017. *This document supersedes the December 14, 2016 Paraquat Dichloride Human Health Mitigation Decision.*

2. Targeted training materials for paraquat users
    a. Implementation timing:
        i. Released online in March 8, 2019
        ii. New products released into commerce must bear new labeling specifying the requirement to take the targeted paraquat training by late Summer/Fall 2019

3. Closed-system packaging for all non-bulk (less than 120 gallon) end use product containers of paraquat
    a. Implementation timing:
        i. Revised labels specifying the closed system requirement were due to EPA on March 29, 2019
        ii. The revised labels are currently under review in EPA and should be stamped in Summer/Fall 2019
        iii. All non-bulk products must be in closed systems one year from the date that the labels are stamped by EPA
        iv. EPA's existing stock provision applies

Due to the additional requirement for closed-system packaging for all non-bulk (less than 120 gallons) end use product containers, this occupational handler exposure and risk assessment considers the currently required levels of PPE described above, as well as the closed-system packaging for mixers and loaders.

The likelihood of occupational post-application exposures is dependent on whether paraquat applications are "directed" or "broadcasted." Directed spray applications of paraquat are targeted for control of individual weeds and grasses. Such applications are made with the intent of minimizing the risk of injuring the crop and/or non-target vegetation which are not tolerant of directed paraquat applications. Since applications to the foliage of the crop are not expected to occur, occupational post-application exposures are not likely for directed applications and have not been assessed. Broadcast applications of paraquat are applied directly to the crop for foliage desiccation (to the crop and any weeds in the field) to expedite harvest and reduce seed loss upon harvest. Therefore, occupational post-application exposures are expected for broadcast applications and have been assessed herein. Occupational post-application exposures are expected to be both short- and intermediate-term in duration. Labeled restricted entry intervals (REIs) range from 12 to 24 hours.

Spray drift exposures may also occur following applications of paraquat to agricultural and non-agricultural areas and are expected to be short-term in duration.

Hazard Characterization

Paraquat is poorly absorbed and efficiently eliminated following oral administration. The fraction that is absorbed is excreted primarily as unchanged parent in the urine. The primary target organ of paraquat is the lungs with evidence of lung inflammation, scarring, and compromised lung function observed throughout the toxicity database in different species and across routes of exposure (oral and inhalation). Other target organs identified in the toxicity database include the kidneys (mice and rabbits), and eyes (rats). Paraquat caused minimal to moderate skin irritation in rabbits and rats following acute dermal exposure and was not acutely lethal in rats up to 2000 mg technical concentrate/kg (paraquat ion not calculated). Prolonged dermal exposure, however, is more corrosive to the skin. Repeat dermal exposure in rabbits at

doses ≥2.6 mg paraquat ion/kg/day elicited a varied dermal response (scabbing, epidermal erosion/ulceration, surface exudation, acanthosis, and inflammation) that increased in frequency and severity with duration and dose. These effects are consistent with dermal toxicity described in the human incident report. Skin damage was the most commonly reported symptom for incidents resulting from occupational use and ranged from blisters and dry skin to chemical burns and lesions. Despite evidence of dermal toxicity, no systemic toxicity was observed in rabbits following 21 days of exposure up to 6 mg paraquat ion/kg/day (the highest dermal dose evaluated). Although the skin was an effective barrier within the dose range characterized in the toxicity database, systemic toxicity is anticipated at higher dermal doses that further erode the integrity of the skin and allow unimpeded access to the bloodstream. No evidence of pre- or post-natal sensitivity was observed across the toxicity database. Developmental (reduced body weight/gain and delayed skeletal ossification) and offspring effects (sporadic histopathology lesions) were observed only at parentally toxic doses that were above the selected points of departure (PODs). Limited evidence of age-related sensitivity was observed in the open literature, but only from exposure to a high purity paraquat product (purity >98%), which is not representative of the paraquat products (purity <48%) undergoing Registration Review. The PODs selected for risk assessment account for toxicity from exposure to paraquat sources that are analogous to the technical product (the highest purity products registered) and are thus protective of the developmental and offspring effects resulting from exposure to the registered technical products and lower purity formulations. There was also no evidence of immunotoxicity in response to paraquat.

The relationship between paraquat exposure and Parkinson's disease was assessed based on results reported in guideline and non-guideline studies in the toxicity database and relevant human, animal, and *in vitro* studies identified in two systematic reviews (a focused Parkinson's disease review and a general epidemiology review) of the open literature. The focused Parkinson's disease (PD) systematic review was conducted with support from the National Toxicology Program (NTP). As part of the PD systematic review, NTP and the agency collaborated on a scoping review of the open literature to identify and summarize studies that were relevant to the Agency's evaluation of the paraquat-PD association. In addition to the collaboration, experts from NTP provided technical support on the systematic review process and addressed questions pertaining to neuropathology and PD that aided interpretation of study results. After comprehensive review of the relevant studies, the Agency concluded that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans. Moreover, the few studies from the open literature that report PD-like effects in animal models from exposure routes anticipated for pesticidal uses (e.g. oral, dermal, inhalation) observed them following subchronic exposure to dose levels at least 14 times above the current subchronic and chronic PODs. Thus, the risk assessment accounts for and is protective of the limited evidence of neurotoxic effects reported in the open literature for routes of exposure relevant to the paraquat human health risk assessment.

PODs were selected for dietary (acute and chronic), incidental oral (short-term), dermal (short- and intermediate-term) and inhalation (short- and intermediate-term) exposure scenarios. Uncertainty factors for interspecies extrapolation (UF_A = 10x) and intraspecies variation (UF_H = 10x) were applied to each exposure scenario. The Food Quality Protection Act (FQPA) Safety Factor (SF) was reduced to 1x for all relevant scenarios based on the following: 1) the toxicity database, with contributions from the open literature, is adequate to evaluate the potential for susceptibility in infants and young children resulting from exposure to paraquat, 2) the dietary assessments are based on reliable data and will not underestimate exposure, and 3) the PODs are

protective of all known health effects resulting from paraquat exposure including evidence of susceptibility and neurotoxicity in the open literature.

The acute and chronic dietary, incidental oral, dermal, and inhalation PODs were updated during Registration Review. The acute dietary POD (5 mg paraquat ion/kg) for all populations was based on clinical signs of agonal toxicity and mortality during the first week of exposure in the developmental rat study. Although these effects occurred several days after the initial exposure, they were consistent with a pattern of delayed mortality described in other acute studies in the paraquat toxicity database and human incidents that were attributed to a single dose. The acute reference dose (aRfD) and acute population-adjusted (aPAD) dose are both 0.05 mg paraquat ion/kg. The chronic dietary POD (0.5 mg paraquat ion/kg/day) was based on increased lung weight, incidence of gross lung lesions, and severity of chronic pneumonitis in two co-critical subchronic and chronic dog oral toxicity studies. The chronic reference dose (cRfD) and chronic population-adjusted dose (cPAD) are both 0.005 mg paraquat ion/kg/day. The incidental/adult oral POD (0.5 mg paraquat ion/kg/day) is based on the same endpoints used for the chronic dietary POD.

The dermal POD (6 mg paraquat ion/kg/day) is based on the systemic No Observed Adverse Effect Level (NOAEL) from the route specific 21-day dermal toxicity study in rabbits. Six mg paraquat ion/kg/day was the highest dermal dose tested (HDT) in the subchronic dermal study and there are no additional studies in the toxicity database that investigate systemic or dermal toxicity from repeat exposure at higher dermal doses. Although the toxicity database indicates paraquat is not well absorbed across intact human skin, the corrosive properties of the chemical, detailed in the dermal study and human incident reports, affect the integrity of the skin, particularly after repeat exposure. Further corrosion of the dermal layer is anticipated at doses above the HDT in the subchronic dermal study, which increases the likelihood of systemic toxicity from dermal exposure. Consequently, the HDT from the route specific dermal study was selected to be protective of the potential for systemic toxicity at higher dermal doses.

The inhalation POD (0.01 µg paraquat ion/L/day) is based on evidence of increased incidence of squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx observed when exposed to respirable particles in the route specific subchronic inhalation study in rats. This respirable particle POD was used to assess risk for all inhalation scenarios for Registration Review. Previously, inhalation PODs were selected for both respirable and non-respirable particles and the non-respirable particle POD, based on effects observed in an oral study, was used for purpose of quantifying inhalation exposures and risks. A non-respirable particle POD was not selected for Registration Review because there are no data to confirm that particulates are non-respirable/greater than the respirable particle size range when paraquat is applied in an occupational setting. The level of concern (LOC) for all non-dietary scenarios is 100.

Paraquat is classified Category E – evidence of non-carcinogenicity for humans – and does not require a separate cancer assessment.

Dietary (Food and Water) Exposure and Risk

Acute and chronic dietary exposure assessments were performed for paraquat. The acute assessment is based on tolerance-level residues, 100% crop treated (CT) and uses Dietary Exposure Evaluation Model default processing factors for some commodities. The chronic dietary exposure assessment is a partially refined assessment based on tolerance-level residues and average estimates of percent crop treated. An Estimated Drinking Water Concentration

(EDWC) of 0.15 ppb, as recommended by the Environmental Fate and Effects Division (EFED), was used for both analyses. For the acute assessment, the general U.S. population and all population subgroups have risk estimates that are below HED's level of concern (i.e., 100% of the aPAD). The most highly exposed population subgroup is Children 1-2 years old which utilizes 38% of the aPAD. The general U.S. population utilizes 20% of the aPAD. For the chronic assessment, the general U.S. population and all population subgroups have risk estimates that are below HED's level of concern (i.e., 100% of the cPAD). The most highly exposed population subgroup is Children 1-2 years old which utilizes 25% of the cPAD. The general U.S. population utilizes 6.6% of the cPAD.

Residential Exposures and Risks
Paraquat is a RUP; therefore, there are no paraquat products registered for homeowner use and no products registered for application to residential areas. No residential handler or post-application exposures are expected.

Non-Occupational Spray Drift
A quantitative non-occupational spray drift assessment was conducted for paraquat to assess the potential for exposures from spray drift following agricultural applications. Adult dermal and children 1 to < 2 years old dermal and incidental oral risk estimates from indirect exposure to paraquat result in estimated distances from the field edge to reach the LOC ranging from 0 feet to 150 feet depending on the application rate and equipment type combination assessed and assuming screening level droplet sizes and boom heights. Results indicate that the major spray drift risk concern is from aerial applications.

Aggregate Exposure and Risk
There are no residential uses of paraquat; therefore, the only relevant aggregate risk assessment includes acute and chronic exposures to residues in food and drinking water. Both the acute and chronic food and drinking water analyses are below HED's level of concern. The most highly exposed population subgroup is Children 1-2 yrs old which utilizes 38% of the aPAD, and 25% of the cPAD.

Occupational Handler Exposures and Risks
Occupational handler dermal and inhalation exposure and risk estimates were calculated for the registered uses of paraquat. Dermal and inhalation risks were not combined since the PODs selected are not based on the same toxicological effects. Inhalation exposures are the risk driver for all paraquat occupational handler exposure scenarios assessed except for the mixer/loader/applicator exposure scenarios for which dermal exposures are the highest contributor. Estimated occupational handler risks for paraquat are as follows:

- Mixer/loaders: assuming the currently registered level of respiratory personal protection, (a NIOSH approved half-mask, APF 10 respirator), inhalation risks are of concern [i.e., the margins of exposure (MOEs) are < the LOC of 100] for 13 of 26 exposure scenarios. When considering the risk mitigation decision for these mixer/loader scenarios that require enclosed systems, 21 of 26 remain of concern.
- Loader/applicators: assuming the currently registered level of respiratory personal protection (a NIOSH approved half-mask, APF 10 respirator), the one exposure scenario assessed results in an inhalation risk estimate of concern.
- Applicators and flaggers: assuming the currently registered level of respiratory personal protection (a NIOSH approved half-mask, APF 10 respirator for flaggers, and a closed

system for applicators), inhalation risks are of concern for 19 of 26 exposure scenarios assessed.

- Mixer/loader/applicators: dermal risks are of concern for 6 of the 8 exposure scenarios assessed at the currently required level of personal protection (baseline clothing and chemical resistant gloves). Dermal risks of concern remain for all (6 of the 8) exposure scenarios assessed despite the addition of double layer clothing.

Occupational Post-Application Exposure and Risks
Directed applications of paraquat are made with the intent of minimizing the risk of injuring the crop and/or non-target vegetation which are not tolerant of directed applications. Since applications to the foliage of the crop are not expected to occur, occupational post-application exposures are not likely for directed applications and have not been assessed. Broadcast applications of paraquat are applied directly to the crop for foliage desiccation to expedite harvest and reduce seed loss upon harvest and, therefore, have been assessed. Due to the lack of available dislodgeable foliar residue (DFR) data for paraquat, this assessment uses HED's default assumption that 25% of the application is available for transfer on day 0 following the application and the residues dissipate at a rate of 10% each following day.

Occupational post-application exposure and risks estimated for scouting activities are not of concern (i.e., an MOE $\geq$ 100) on the day of product application for all crops assessed except for alfalfa. For alfalfa, reentry risks are not of concern 4 days following product application. Occupational post-application exposure and risk estimated for cotton mechanical harvesting activities (module builder operator, picker operator, raker, and tramper) range from 11 to 27 days following product application.

Paraquat acute toxicity is low via the dermal route (Category III) and not irritating to the skin (Category III); however, it is severely irritating to mucous membranes (Category I for eye irritation). It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2), active ingredients classified as Acute I for acute dermal, eye irritation and primary skin irritation are assigned a 48-hour REI. Therefore, the currently labeled REIs which range from 12 to 24 hours do not conform with 40 CFR 156.208 (c) (2) requirements. Further, the number of days required for estimated post-application risks associated with paraquat usage estimated for reentry range from 0 to 27 days and may require revision of the labeled REIs to address these concerns.

Occupational Handler Exposure and Risks Using Biomonitoring Data
Occupational handler and post-application biomonitoring studies are available for paraquat. To characterize the occupational handler risk estimates calculated using surrogate, passive dosimetry exposure data, HED has also estimated risks using an available paraquat occupational handler biomonitoring study. The occupational handler biomonitoring study was reviewed, and no human ethics concern was identified. Occupational handler risk estimates were quantified using the absorbed doses measured from the biomonitoring study. The resulting MOEs for mixing/loading and applying paraquat via groundboom range from 13 to 97 (LOC = 100) depending on the combination of application rate and area treated daily.

A paraquat occupational post-application biomonitoring study was also available; however, this study was reviewed and determined to have human ethics concerns, thus no post-application risk estimates were quantified with use of these data.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[1]."

Human Studies Review
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Agricultural Reentry Task Force (ARTF) database; and a chemical-specific biomonitoring study (MRID 43644202) are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board (HSRB). Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[2].

2.0 HED Conclusions

There are no aggregate risks of concern identified for paraquat. However, risks of concern are identified for occupational handlers and workers engaged in post-application activities. Further, there are risks of concern identified from non-occupational spray drift at the field edge.

Please refer to Table 2.2.2 for tolerance recommendations.

2.1 Data Deficiencies

Enforcement Analytical Method: Analytical standards for paraquat dichloride need to be submitted.

In vitro Skin Corrosion: Although not a requirement of registration, *in vitro* data on skin corrosion, such as those reported for Organisation for Economic Co-operation and Development (OECD) Guideline 431, would provide useful information on the interaction between paraquat and skin cells that could be used to refine the assumptions in the dermal toxicity characterization and dermal assessment.

Dislodgeable Foliar Residue (DFR): In accordance with 40CFR158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. Chemical-specific DFR data have not been submitted for paraquat. The highest estimated occupational post-application exposure using default DFR values is not minimal in comparison to the level of concern (i.e., the calculated MOE is not greater than 2 times higher than the level of concern, MOE = 68 compared to the LOC of 100); therefore, HED is recommending that DFR data (Guideline # 875.2100) be required to facilitate

[1] http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf
[2] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

any necessary exposure assessment refinements and to further EPA's general understanding of the availability of dislodgeable foliar pesticide residues.

Further, during cotton harvesting workers are expected to contact residues on cotton bolls directly for which a "dislodgeable boll residue (DBR)" study would be required to refine occupational post-application risks estimated for the crop. These chemical- and crop-specific data are unique; DFR data for other crops cannot be used as a surrogate in the absence of a DBR study. HED is recommending a DBR study be required to further EPA's general understanding of the availability of cotton dislodgeable boll residues. These data should be conducted in accordance with Guideline # 875.2100.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate spectrophotometric method, Method I of the Pesticide Analytical Manual (PAM) Vol. II, is available for enforcing tolerances for residues of paraquat in/on plant commodities. For the method, samples are heated at reflux with 0.5 M sulfuric acid and then applied to a cation exchange column. Paraquat residues are eluted with saturated ammonium chloride solution. Samples are first subjected to Soxhlet extraction in hexane, and the hexane extract is refluxed with sulfuric acid and then applied to the cation exchange column. An aliquot of the column eluate is mixed with 0.2% (w/v) sodium hydrosulfite in 0.3 M sodium hydroxide, which reduces paraquat to a free radical. Residues are determined using a variable wavelength spectrophotometer, measuring the light absorption of the paraquat free radical. The validated limits of quantitation (LOQ) vary from 0.01 ppm up to 0.5 ppm. PAM Vol. II lists a spectrophotometric method, designated as Method Ia (LOD = 0.005 ppm), as available for the enforcement of tolerances for paraquat residues in animal commodities. In addition, an adequate HPLC/UV method is available for the enforcement of tolerances for paraquat residues in livestock tissues and eggs (RAM 004/04, MRID 43226902; this method has not yet been published in PAM Vol. II); the reported LOQ is 0.005 ppm for livestock tissues and eggs.

2.2.2 Recommended Tolerances

In 2009, HED issued guidance on tolerance expressions (S. Knizner, 05/27/2009). HED concludes the tolerance expression for paraquat should be as follows:

> *Tolerances are established for the residues of paraquat, including its metabolites and degradates, in or on the commodities specified in the following table resulting from the application of the dichloride salt of paraquat. Compliance with the following tolerance levels is to be determined by measuring only paraquat (1,1'-dimethyl-4,4'-bipyridinium):*
>
> In addition, there are several tolerance level changes.

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Commodity/**Correct Commodity Definition**	Established Tolerance	Revised Tolerance	Comments
Acerola	0.05	0.05	
Almond, hulls	0.5	0.5	
Animal feed, nongrass, group 18, forage	75.0	75	Corrected value to be consistent with OECD Rounding Class Practice.
Animal feed, nongrass, group 18, hay	210.0	200	Corrected value to be consistent with OECD Rounding Class Practice.
Artichoke, globe	0.05	0.05	
Asparagus	0.5	Remove	Remove; covered by 22A
Atemoya	0.05	0.05	
Avocado	0.05	0.05	
Banana	0.05	0.05	
Barley, grain	0.05	0.05	
Barley, hay	3.5	3.5	
Barley, straw	1.0	1.0	
Beet, sugar, roots	0.5	0.5	
Beet, sugar, tops	0.05	0.05	
Berry and small fruit, group 13-07		0.05	Commodity definition revision
Berry group 13	0.05	remove	
Biriba	0.05	0.05	
Cacao, dried bean			Commodity definition correction
Cacao bean, bean	0.05	0.05	
Canistel	0.05	0.05	
Carrot, roots	0.05	0.05	
Cattle, fat	0.05	0.05	
Cattle, kidney	0.5	0.5	
Cattle, meat	0.05	0.05	
Cattle, meat byproducts, except kidney	0.05	0.05	
Cherimoya	0.05	0.05	
Coffee, green bean			Commodity definition correction
Coffee, bean, green	0.05	0.05	

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Corn, field, forage	3.0	3	
Corn, field, grain	0.1	0.1	
Corn, field, stover	10.0	10	Corrected value to be consistent with OECD Rounding Class
Corn, pop, grain	0.1	0.1	
Corn, pop, stover	10.0	10	Corrected value to be consistent with OECD Rounding Class
Corn, sweet, kernel plus cob with husks	0.05	0.05	
Cotton, gin byproducts	110.0	100	Corrected value to be consistent with OECD Rounding Class
Cotton, undelinted seed	3.5	3.5	
Cowpea, forage	0.1	0.1	
Cowpea, hay	0.4	0.4	
Cranberry	0.05	0.05	
Custard apple	0.05	0.05	
Egg	0.01	0.01	
Endive	0.05	0.07	
Feijoa	0.05	0.05	
Fig	0.05	0.05	
Fruit, citrus, group 10-10		0.05	Commodity definition revision
Fruit, citrus, group 10	0.05	Remove	
Fruit, pome, group 11-10		0.05	Commodity definition revision
Fruit, pome, group 11	0.05	Remove	
Fruit, stone, group 12-12		0.05	Commodity definition revision
Fruit, stone, group 12	0.05	Remove	
Goat, fat	0.05	0.05	
Goat, kidney	0.5	0.5	
Goat, meat	0.05	0.05	
Goat, meat byproducts, except kidney	0.05	0.05	

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Grain, aspirated fractions	65.0	65	Corrected value to be consistent with OECD Rounding Class
Grape	0.05	0.05	
Grass, forage	90.0	90	Corrected value to be consistent with OECD Rounding Class
Grass, hay	40.0	40	Corrected value to be consistent with OECD Rounding Class
Guar, seed	0.5	0.5	
Guava	0.05	0.05	
Hog, fat	0.05	0.05	
Hog, kidney	0.5	0.5	
Hog, meat	0.05	0.05	
Hog, meat byproducts, except kidney	0.05	0.05	
Hop, dried cones	0.5	0.5	
Horse, fat	0.05	0.05	
Horse, kidney	0.5	0.5	
Horse, meat	0.05	0.05	
Horse, meat byproducts, except kidney	0.05	0.05	
Ilama	0.05	0.05	
Jaboticaba	0.05	0.05	
Kiwifruit	0.05	0.05	
Lentil, seed	0.3	0.5	Harmonization with Codex
Lettuce	0.05	0.05	
Longan	0.05	0.05	
Lychee	0.05	0.05	
Mango	0.05	0.05	
Milk	0.01	0.01	
Nut, tree, group 14-12		0.05	Commodity definition revision
Nut, tree, group 14	0.05	Remove	
Okra	0.05	0.05	

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Olive	0.05	0.1	Harmonization with Codex
Onion, bulb, subgroup 3-07A		0.1	Commodity definition revision
Onion, bulb	0.1	Remove	
Onion, green, subgroup 3-07B		0.05	Commodity definition revision
Onion, green	0.05	Remove	
Papaya	0.05	0.05	
Passionfruit	0.2	0.2	
Pawpaw	0.05	0.05	
Pea and bean, dried shelled, except soybean, subgroup 6C, except guar bean	0.3	0.5	Harmonization with Codex
Pea and bean, succulent shelled, subgroup 6B	0.05	0.05	
Pea, field, hay	0.8	0.8	
Pea, field, vines	0.2	0.2	
Peanut	0.05	0.05	
Peanut, hay	0.5	0.5	
Peppermint, fresh leaves			Commodity definition correction
Peppermint, tops	0.5	0.5	
Persimmon	0.05	0.05	
Pineapple	0.05	0.05	
Pineapple, process residue	0.25	0.3	OECD Rounding Class (0.25 to 0.3 ppm)
Pistachio	0.05	Remove	Covered by Nut, tree, group 14-12
Pomegranate	0.05	0.05	
Pulasan	0.05	0.05	
Rambutan	0.05	0.05	
Rhubarb	0.05	0.05	

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Rice, grain	0.05	0.05	
Safflower, seed	0.05	0.05	
Sapodilla	0.05	0.05	
Sapote, black	0.05	0.05	
Sapote, mamey	0.05	0.05	
Sapote, white	0.05	0.05	
Sheep, fat	0.05	0.05	
Sheep, kidney	0.5	0.5	
Sheep, meat	0.05	0.05	
Sheep, meat byproducts, except kidney	0.05	0.05	
Sorghum, forage, forage	0.1	0.1	
Sorghum, grain, forage	0.1	0.1	
Sorghum, grain, grain	0.05	0.05	
Soursop	0.05	0.05	
Soybean, forage	0.4	0.4	
Soybean, hay	10.0	10	Corrected value to be consistent with OECD Rounding Class
Soybean, hulls	4.5	4.5	
Soybean, seed	0.7	0.7	
Spanish lime	0.05		
Spearmint, fresh leaves			Commodity definition correction.
Spearmint, tops	0.5	0.5	
Star apple	0.05	0.05	
Starfruit	0.05	0.05	
Strawberry	0.25	0.3	Corrected values to be consistent with OECD Rounding Class Practice.
Sugar apple	0.05		
Sugarcane, cane	0.5	0.5	
Sugarcane, molasses	3.0	3	Corrected values to be consistent with OECD Rounding Class Practice.

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Sunflower, seed	2.0	2	Corrected values to be consistent with OECD Rounding Class Practice.
Turnip, greens	0.05	Remove	Remove; covered by 4-16B
Turnip, roots	0.05	0.05	
Vegetable, Head and Stem *Brassica,* Group 5-16		0.07	Crop group conversion/revision*
Vegetable, brassica, leafy, group 5	0.05	Remove	
Brassica leafy greens subgroup 4-16B	--	0.07	**Change in crop group 5.** *Brassica leafy greens subgroup 4-16B***
Stalk and Stem Vegetable Subgroup 22A	--	0.05	**Change in crop group 5**. *Stalk and Stem Vegetable Subgroup 22A**
Vegetable, cucurbit, group 9	0.05	0.05	
Vegetable, fruiting, group 8-10			Crop group conversion/revision.
Vegetable, fruiting, group 8	0.05	0.05	
Vegetable, legume, edible podded, subgroup 6A	0.05	0.05	
Vegetable, tuberous and corm, subgroup 1C	0.50	0.5	Corrected values to be consistent with OECD Rounding Class Practice.
Wax jambu	0.05	0.05	
Wheat, forage	0.5	0.5	Corrected value to be consistent with OECD Rounding Class
Wheat, grain	1.1	1.1	
Wheat, hay	3.5	3.5	
Wheat, straw	50.0	50	Corrected value to be consistent with OECD Rounding Class
c) *Tolerances with regional registrations.* Tolerances with regional registration as defined in §180.1(l), are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			

Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review.			
(a) General. (1) Tolerances are established for residues of paraquat, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation in or on the following food commodities:			
Pea, pigeon, seed	0.05	0.05	
Taro, corm	0.1	0.1	
Tyfon	0.05	0.05	

* These recommended conversions of existing tolerances in/on crop subgroup **5A** to crop group **5-16** (*Brassica*, head and stem vegetable) and subgroup 5B to subgroup 4-16B (*Brassica* leafy greens) are consistent with the document entitled "Attachment - Crop Group Conversion Plan for Existing Tolerances as a Result of Creation of New Crop Groups under Phase IV (4-16, 5-16, and 22)," dated 11/3/2015.

2.2.3 International Harmonization

The Codex Alimentarius Commission and Canada have established maximum residue limits (MRLs) of paraquat for many commodities. The International Residue Limit (IRL) status sheet is included as Appendix C. The Agency is currently harmonized with respect to the residue level with Canada where both have established tolerances. The Agency is currently harmonized with respect to the residue level and residue definition with Codex with many commodities. The US tolerance of 0.05 ppm for endive, Vegetable, Head and Stem Brassica, Group 5-16, and Brassica leafy greens subgroup 4-16B is recommended to be increased to 0.07 ppm to harmonize with Codex. The US tolerance of 0.3 ppm for Lentil, seed, and Pea and bean, dried shelled, except soybean, subgroup 6C, except guar bean is recommended to be increased to 0.5 ppm to harmonize with Codex. The US tolerance of 0.05 ppm for olive is recommended to be increased to 0.1 ppm to harmonize with Codex. Numerous U.S. tolerances are based on field trials where detectable residues have been found so harmonization with Codex LOQ MRLs is not possible.

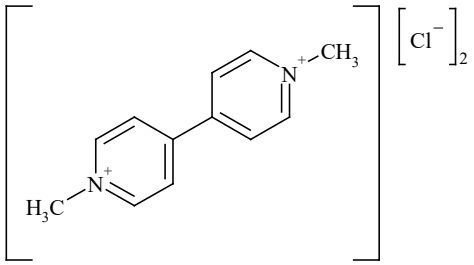
2.3 Label Recommendations

No specific label recommendations are being made; however, there are several risk estimates of concern for occupational handlers. Some of these risk estimates are not of concern with the addition of PPE beyond what is currently on labels. Product label changes regarding PPE and engineering controls for paraquat may be required based on the occupational handler risks of concern identified in this memorandum.

The registered paraquat labels currently specify REIs ranging from 12 to 24 hours which do not conform with 40 CFR 156.208 (c) (2) requirements. Further, the number of days required for estimated post-application risks associated with paraquat usage estimated for reentry range from 0 to 27 days and may require revision of the current REIs to address these concerns.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Nomenclature of Paraquat Dichloride	
Compound	
Common name	Paraquat dichloride
IUPAC name	1,1'-dimethyl-4,4'-bypyridinium dichloride
CAS name	1,1'-dimethyl-4,4'-bypyridinium dichloride
CAS registry number	1910-42-5 (4685-14-7 for the cation)
End-use product (EP)	2.0 lb paraquat cation/gal SC

3.2 Physical/Chemical Characteristics

Physiochemical properties for paraquat are shown in Appendix B.

Paraquat dichloride is freely soluble in water. It has a very low vapor pressure ($<10^{-8}$ kPa) and has a low octanol water partition coefficient of log $K_{OW} = -4.5$ at 20 °C. Paraquat was shown to be very immobile in soil. It does not hydrolyze, does not photodegrade in aqueous solutions, and is resistant to microbial degradation under aerobic and anaerobic conditions. The primary route of environmental dissipation of paraquat is adsorption to biological materials and soil clay particles. Due to the apparent adsorption strength of paraquat for soil clays, these bound residues do not appear to be environmentally available.

3.2 Pesticide Use Pattern

Paraquat dichloride is a non-selective herbicide currently registered for the control of weeds and grasses in agricultural and non-agricultural areas. It is a contact herbicide that desiccates and destroys plant cell membranes within hours of application. Paraquat is only formulated as a soluble concentrate/liquid (SC/L) formulation. It can be applied pre-plant, pre-emergence, at plant, or post-emergence; or as a desiccant/harvest aid or a postharvest desiccant. Paraquat may be applied to agricultural and non-agricultural areas (e.g., conservation reserve program areas, non-crop lands, and pasture lands) with aerial, ground, and handheld spray equipment. It is a RUP; therefore, there are no paraquat products registered for homeowner use and no products registered for application to residential areas.

All registered labels require occupational handlers (mixers and loaders) to wear baseline clothing, chemical resistant gloves, a NIOSH approved half-mask respirator, as well as a chemical resistant apron and face shield. Applicators and other handlers (other than mixers and loaders) must wear baseline clothing, chemical resistant gloves, a NIOSH approved half-mask respirator, as well as protective eyewear.

The registered uses of paraquat are summarized in the Line by Line, and Maximum Use Scenario Pesticide Label Usage Summary (PLUS) Reports as generated by OPP's Biological and Economic Analysis Division (BEAD). Application rates provided by these sources are presented in Appendix D, Table D.1. For purpose of the occupational and non-occupational spray drift risk assessments, HED has used the maximum application rates for all crops and equipment types.

3.3 Anticipated Exposure Pathways

Humans may be exposed to paraquat in food and drinking water since paraquat may be applied directly to growing crops and application may result in it reaching surface and ground water sources of drinking water. Paraquat is a RUP; therefore, there are no paraquat products registered for homeowner use and no products registered for application to residential areas. Non-occupational exposures may occur as a result of spray drift from off-target applications of paraquat. Occupational handler and post-application exposures are expected from paraquat usage. This risk assessment considers all the aforementioned exposure pathways based on the existing paraquat uses.

3.4 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[3]." As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA's NHANES/WWEIA and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures are also evaluated based on home use of pesticide products which includes calculating associated risks for adult applicators and for toddlers, youths, and adults entering or playing in previously treated areas. Spray drift can also potentially result in exposure and it was also considered in this analysis. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicology database for paraquat is complete and adequate for Registration Review. Characterization of paraquat toxicity in mammals was informed both by guideline and non-guideline studies submitted to the Agency and relevant mammalian toxicity studies identified in

[3] Available: http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf

the open literature. The paraquat toxicology database consists of the following guideline and non-guideline studies:

- Acute oral, dermal, inhalation, eye irritation, dermal irritation, and skin sensitization studies
- 90-day oral toxicity study – dog
- 21-day dermal toxicity study – rabbit
- 21-day inhalation study – rat
- Prenatal developmental toxicity study – rat and mouse
- Multi-generation reproduction study – rat
- Combined oral chronic toxicity/carcinogenicity study – rat
- Carcinogenicity study – mouse
- Chronic oral toxicity study – dog
- Acute and subchronic neurotoxicity studies – rat
- Mutagenicity battery
- Immunotoxicity study – mouse
- Non-guideline *in vivo* dermal absorption study – human
- Non-guideline intraperitoneal injection neurotoxicity studies – mouse

A guideline non-rodent developmental study and guideline metabolism and pharmacokinetics study were not available at the time of Registration Review. These are not considered gaps in the toxicity database, as the Hazard and Science Policy Council (HASPOC; TXR 0056294, K. Rury, 04/12/2012) recommended waiving the requirement for a prenatal developmental study in non-rodents, and suitable open literature studies were submitted to fulfil the metabolism and pharmacokinetics requirement. Therefore, there are no outstanding guideline data gaps in the paraquat toxicity database.

As part of Registration Review for paraquat, a broad survey of the literature was conducted to identify studies that report toxicity following exposure to paraquat via exposure routes relevant to human health pesticide risk assessment not accounted for in the Agency's paraquat toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 3971 studies from the literature. During title/abstract and full text screening of these studies, nine were identified as containing potentially relevant information (either quantitative or qualitative) for the paraquat human health risk assessment. An additional 17 relevant studies were identified in the Parkinson's disease (PD) systematic review discussed in the next paragraph. In total, 26 studies from the open literature were evaluated. Full text review of this subset pared down the list to 10 studies that were of sufficient quality and contained either quantitative or qualitative information relevant to the risk assessment. Only one study, Lou *et al.* (2016) [4], reported evidence of adverse health effects in mice at doses that were similar to the current POD. This study was formally reviewed (MRID 50733301; TXR 0057886) and was considered in the selection of the PODs. The data reported in the other nine publications did not have a quantitative impact on the risk assessment; however, the studies did report novel findings, including toxicokinetic and neurotoxicity information, that were incorporated into the hazard characterization of the Registration Review risk assessment. Refer to the paraquat general literature review memo

[4] Lou D, Wang Q, Huang M, and Zhou Z. 2016. Does age matter? Comparison of neurobehavioral effects of paraquat exposure on postnatal and adult C57BL/6 mice. *Toxicol Mech Method.* 26(9): 667-673.

(D449107; TXR 0057887, A. Wray, 06/26/2019) and Appendix A.4 for more details on the search strategy, inclusion/exclusion criteria, literature review criteria, and the conclusions of the general literature review.

In addition to the general literature review, two focused systematic reviews were conducted: 1) a review of the human, animal, and *in vitro* literature evaluating the strength of evidence associating paraquat exposure from pesticidal use to PD (the PD systematic review); and 2) a review of the epidemiology literature evaluating all reported outcomes related to paraquat exposure including PD (the epidemiology review). The PD data gathered for the epidemiology review were also incorporated into the PD systematic review. The results of the systematic reviews and their implications on the Agency's risk assessment for current paraquat registrations are summarized in Sections 4.3.1 and 4.3.2. More details on the PD systematic review and the epidemiology systematic review can be found in the PD systematic review memo (D449106; TXR 0057888, A. Wray, 06/26/2019) and paraquat epidemiology review memo (D449108, A. Niman, 06/26/2019), respectively.

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

A guideline metabolism and pharmacokinetics study is not available for paraquat. Previous risk assessments relied on data from published studies submitted to fulfill the metabolism data requirement [Daniel and Gage 1966[5] (MRID 00055107) Litchfield *et al.* 1973[6] (MRID 00065592)]. Much of the information presented in those studies is consistent with more recent investigations; therefore, those data are discussed below alongside distribution data from the guideline oral toxicity studies (MRID 00132474, 00138637, and 49009501) and new data from more recent publications that address aspects of the ADME not investigated by the older literature or guideline studies.

Paraquat is poorly absorbed and efficiently eliminated by rats following oral administration (Daniel and Gage 1966). Oral absorption (based on urinary data) from a low dose (4-6 mg/kg) gavage exposure was approximately 6% of the administered dose (AD) and increased to 8-14 % when the dose was increased 10-fold (50 mg/kg). No evidence of biliary excretion was observed following an oral dose of 0.5 mg/kg in the same study; however, the study authors did not determine the extent of biliary excretion at higher doses. Hughes *et al*. (1973[7]) reported a similar finding: <1% of the AD in the bile 24 hours after intraperitoneal (IP) injection of 15 mg/kg aqueous paraquat diiodide in rats. Collectively, these data suggest biliary excretion is not a prominent elimination pathway for absorbed paraquat. At low doses, rats primarily excreted ingested paraquat in the feces (93-96% of the AD) with minor contribution from the renal system and a majority of the AD (≥95%) was eliminated within 48 hours. It appears this pattern persists at higher doses based on the urine data, but no fecal data were provided to confirm. Rabbits exhibited a similar pattern of limited oral absorption and efficient elimination at low oral doses (2 mg/kg); however, elimination was impeded by reduced urinary and fecal output at higher doses (30 mg/kg) that was likely related to kidney toxicity that altered renal function (MRID 49009501). The excretion profile of paraquat changed markedly with the route of administration. After subcutaneous injection (12.5-13.2 mg/kg paraquat) in rats, 80-98% of the

[5] Daniel JW and Gage JC. 1966. Absorption and excretion of diquat and paraquat in rats. *Brit J Industr Med.* 23(2): 133
[6] Litchfield MH, Daniel JW, and Longshaw S. 1973. The tissue distribution of the bipyridylium herbicides diquat and paraquat in rats and mice. *Toxicology*. 1: 155-165.
[7] Hughes RD, Millburn P, and Williams RT. 1973. Biliary excretion of some diquaternary ammonium cations in the rat, guinea pig and rabbit. *Biochem. J.* 136: 979-984.

AD was identified in the urine within 24 hours of dosing (Daniel and Gage 1966). Likewise, 84% of the AD was quantified in the urine 24 hours after an IP injection (15 mg/kg paraquat diiodide; Hughes *et al*. 1973).

Orally absorbed paraquat was distributed to the lungs, kidneys, and liver in rats and rabbits (Litchfield *et al.* 1973, MRID 00138637, and MRID 49009501) and to the lungs and kidneys in dogs (MRID 00132474). Paraquat content accumulated in rats from up to 8 weeks of exposure did not persist longer than a week in the lung, kidney, or liver tissue after returning to a normal diet. Persistence following chronic exposure in dogs and rats was not investigated. Brain tissues were not identified as a primary site of distribution in the Litchfield *et al.* (1973) study; however, recent studies from the open literature demonstrate distribution of paraquat to brain tissue in rodents (Widdowson *et al.* 1996[8]; Minnema *et al*. 2014[9]) and specifically to midbrain tissues in mice (Prasad *et al.* 2007[10]) following acute and repeat oral dosing.

The available data suggest that absorbed paraquat is excreted mostly as unchanged parent. Although ~30% of an orally administered dose was identified in the feces as chemically distinct from parent, *in vitro* studies indicate it was likely due to microbial degradation in the gut (MRID 00055107). A small fraction (1.2-2.1% of the AD) of the urinary excreta was also determined to be structurally different from parent. However, this finding more likely represents absorption of the degradates rather than metabolites formed after absorption, which is supported by the lack of metabolites in the urine of rats exposed subcutaneously (same study) or IP (Hughes *et al*. 1973).

4.2.1 Dermal Absorption

Dermal absorption was estimated based on the results of an *in vivo* dermal absorption study conducted in humans (MRIDs 00126097, 00126098, 00126099). These studies were reviewed by an Agency Human Research Ethics reviewer and it was determined that they were ethically acceptable for use in risk assessment[11]. The reviewer also indicated a review by the Human Studies Review Board was not required because the studies did not measure or identify a toxic effect. Human volunteers were administered 8.6 µg paraquat ion/cm^2 on the forearms, back of hands, and back of the lower legs and instructed to refrain from washing the application site for 24 hours. The dermal dose (~ 0.008 mg paraquat ion/kg based on 80 kg human) was well below that which elicited skin irritation in the repeat dose dermal study. Dermal absorption was estimated based on total paraquat content excreted in the urine within a 5-day period (collecting during the exposure and every 24 hours for four days after the wash) and corrected for incomplete urinary excretion based on the excretion patterns observed in Rhesus monkeys (MRID 00126096). The study did not indicate if they looked for dermal lesions on the human volunteers; however, it is assumed that the skin was intact based on the low dermal dose selected. Average dermal absorption estimates ranged from 0.23 to 0.30% of the administered dose indicating it is poorly absorbed across intact skin.

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[8] Widdowson PS, Farnworth MJ, Upton R, and Simpson MG. 1996. No changes in behavior, nigro-striatal system neurochemistry or neuronal cell death following toxic multiple oral paraquat administration to rats. *Hum. Exp. Toxicol.* 15(7): 583-591.

[9] Minnema DJ, Travis KZ, Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck MJ, Mathews JM, Tisdel MO, Cook AR, Botham PA, and Smith LL. 2014. Dietary administration of paraquat for 13 weeks does not result in a loss of dopaminergic neurons in the substantia nigra of C57BL/6J mice. *Regul Toxicol Pharm.* 68(2): 250-258.

[10] Prasad K, Winnik B, Thiruchelvam MJ, Buckley B, Mirochnitchenko O, and Richfield EK. 2007. Prolonged toxicokinetics and toxicodynamics of paraquat in mouse brain. *Environ. Health Persp.* 115(10): 1448-1453.

[11] K. Sherman. Ethics Review of Excretion Study with Human Subjects. 06/11/2012.

The assumption that paraquat does not readily cross the skin may not, however, hold true for higher dermal doses. Repeat dermal dosing is known to elicit dermal toxicity at relatively low topical doses (2.6-6 mg paraquat ion/kg/day) in the laboratory and skin damage is the most common symptom observed in human incidents related to dermal exposure. Observations in the toxicity database and human incident report suggest that, at its most severe, the damage elicited by paraquat could compromise the dermal barrier, allowing greater access to circulation compared to intact skin and increasing the likelihood of systemic toxicity. Understanding the relationship between the corrosive behavior of paraquat and dermal absorption is thus critical to estimating systemic toxicity for paraquat dermal exposures; however, the toxicity database does not explore this relationship at doses > 6 mg paraquat ion/kg/day, in part due to welfare concerns for *in vivo* models. In lieu of data suggesting otherwise, the progressive skin damage observe in the toxicity database is anticipated to progress in severity with increasing dose resulting in higher dermal absorption at dermal doses that exceed the range characterized in the toxicity database.

4.3 Toxicological Effects

The primary target organ of paraquat is the lungs. Evidence of lung inflammation, scarring, and compromised lung function in response to paraquat exposure are observed throughout the toxicity database in different species (rats, mice, and dogs). Effects in the respiratory tract are observed after single and repeat dose exposures regardless of the route of exposure (oral or inhalation); however, inhalation was a more sensitive route of exposure than the oral route in both acute (Category I and II, respectively) and repeat dose studies. Paraquat dichloride is moderately to severely irritating to mucous membranes (Toxicity Category II for eye irritation) leading to portal of entry toxicity in the upper respiratory tract (squamous keratinizing metaplasia and hyperplasia of the larynx epithelium) from repeated inhalation. In dogs, respiratory toxicity was consistently observed following oral exposure regardless of duration and at doses below those observed in the other species tested. The toxicity profile in rodents was more diverse with effects observed in other organ systems following longer duration oral exposure. These effects include inflammation and necrosis of the kidneys in mice and lenticular (eye lens) changes in rats. In mice, the kidney effects were observed in the absence of notable lung toxicity suggesting the mouse renal system was more vulnerable to prolonged repeated exposure. Rodents also exhibited various clinical signs (piloerection, pinched sides, hunched posture, hypoactivity, weight loss/thin appearance and respiratory distress) when exposed via gavage and were considered to represent an agonal response to a bolus dose. Mortality was observed in all species tested and at doses/concentrations as low as 3 mg paraquat ion/kg/day and 1.3 µg paraquat ion/L/day for oral and inhalation exposure, respectively. Death from acute exposure was not always immediate; mortalities after acute oral gavage exposure, for example, were noted up to a week after exposure in rats and were preceded by the clinical signs described above. A similar delay between single dose exposure and death was described in several human ingestion incidents in the incident report.

Renal toxicity was also a hallmark of paraquat toxicity in rabbits. Acute oral exposure elicited loss of appetite, body weight loss, and progressive proximal tubule degeneration, resulting in reduced fecal output and urine flow. Interestingly, none of the characteristic lung effects that define the paraquat toxicity profile in other species were observed in rabbits following acute exposure. Nevertheless, rabbits were more sensitive to acute oral exposure compared to rodents with at least a 2-fold separation in the estimated median lethal dose.

Paraquat causes minimal skin irritation in rabbits following acute dermal exposure (Toxicity Category IV) and elicits a more varied and corrosive dermal response (scabbing, hyperkeratosis, epidermal erosion/ulceration, surface exudation, acanthosis, and inflammation) with prolonged exposure. This response is consistent with dermal toxicity described in the human incident report. Skin damage was the most commonly reported symptom for human incidents resulting from occupational use and ranged from blisters and dry skin to chemical burns and lesions. The first signs of skin irritation and damage in rabbits from repeat dosing occurred at relatively low topical doses (2.6 mg paraquat ion/kg/day) and evolved in diversity and severity with duration and dose. No evidence of systemic toxicity was observed in rabbits following 21 days of dermal exposure up to 6 mg paraquat ion/kg (the highest dermal dose evaluated in the toxicity database) indicating that the skin remained an effective barrier in this dose range despite the structural damage elicited by paraquat. Systemic toxicity is anticipated to result from higher dermal doses that further corrode the skin integrity and allow unimpeded access to the bloodstream. No mortalities were noted following acute dermal exposure in rats up to 2000 mg technical concentrate/kg (paraquat ion was not calculated; Toxicity Category III), though all animals exhibited signs of slight to moderate skin irritation. Paraquat is not a skin sensitizer.

Paraquat did not cause reproductive toxicity. Developmental and offspring toxicity observed in the guideline studies in response to paraquat exposure always occurred in the presence of parental toxicity; therefore, there was no evidence of quantitative susceptibility. Developmental effects included reduced body weight/gain and delayed skeletal ossification and were observed at the same doses that elicited respiratory distress, reduced body weight, lung lesions, and mortality in maternal animals. Offspring effects were limited to sporadic histopathology lesions at parentally toxic doses that were approximately 10X higher than the doses eliciting lung effects in dogs (the most sensitive species). However, a review of the open literature identified age-dependent quantitative sensitivity that was not captured in the guideline studies. Mortality in three-week-old mice was observed at a lower dose level compared to 8-week old mice following acute and subchronic gavage exposure to a high purity paraquat product (>98% a.i.; Lou *et al*. 2016).

The guideline studies did not report evidence of neurotoxicity or immunotoxicity in rodents up to doses that are known to cause respiratory distress. The impact of paraquat exposure on the nervous system and its relationship to PD was further characterized in the PD and epidemiology systematic reviews. The results of the epidemiology review including the evaluation of the body of evidence for PD is presented in Section 4.3.1. The conclusions of the PD systematic review are discussed in Section 4.3.2.

4.3.1 Epidemiology Review Summary

OPP performed a systematic review of the epidemiologic literature on paraquat exposure and identified 74 articles that investigated a range of health outcomes, including PD, lung function and respiratory effects, cancer, and other health outcomes. Further information on OPP's review and evaluation of the available epidemiologic literature is available in the Paraquat Tier II Epidemiology Report (D449108, A. Niman, 06/26/2019).

PD had the most comprehensive body of epidemiologic literature with a total of 13 study populations, including three agricultural cohorts, nine hospital-based populations, and one PD registry in Nebraska (26 articles). Based on the findings from these studies, it was concluded:

- There is *limited, but insufficient epidemiologic evidence* at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and PD. This conclusion is based on mixed findings reported in the Agricultural Health Study (AHS) and Farming and Agricultural Movement Evaluation Study[12,13] – with respect to incident and prevalent cases – and the potential for recall bias. In examination of evidence from other occupational studies, no association was observed in either the French Agriculture and Cancer Cohort[14] or the cohort from Washington State.[15] Similarly, mixed evidence was reported in the remaining three case-control studies, with one study reporting evidence of a positive association in Taiwan,[16] one study reporting a non-significant positive association based on only nine exposed cases,[17] and one study reporting no evidence of an association in the Netherlands.[18] However, these case-control studies contributed less weight in OPP's determination because of their weaker study designs, more limited exposure assessment approach, and potential for recall bias.
- There is *insufficient epidemiologic evidence* at this time to conclude there is a clear associative or causal relationship between non-occupational paraquat exposure and PD. This conclusion was based on the limited number of studies on non-occupational populations, lack of consistent evidence of a positive association, and the potential for bias in the available studies. The California Parkinson's Environment and Genes Study reported evidence of a positive association between paraquat exposure and PD in some publications, for example, but reported no evidence of an association when restricting analysis to paraquat exposure only.[19] A similar case-control study conducted in the Netherlands reported no evidence of a positive association.[20] Both studies relied on geospatial data to estimate exposure which eliminated the potential for recall bias, but may have limited ability to distinguish between proximity to agricultural land, pesticide exposure in general, and specific pesticides as potential PD risk factors with confidence. The results of the ecologic Nebraska Parkinson's Disease Registry Study contributed limited weight to Agency OPP's evaluation because of its more limited study design, but

[12] Kamel F, Tanner CM, Umbach DM, Hoppin JA, Alavanja MCR, Blair A, Comyns K, Goldman SM, Korell M, Langston JW, Ross GW, Sandler DP. Pesticide exposure and self-reported Parkinson's disease in the Agricultural Health Study. *Am J Epidemiol*. 2007, 165(4):364-374.
[13] Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korel M, *et al*. Rotenone, paraquat, and Parkinson's disease. *Environ Health Perspect*. 2011, 119:866–872.
[14] Pouchieu C, Piel C, Carles C, Gruber A, Helmer C, Tual S, Marcotullio E, Lebailly P, Baldi I. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study. *Int J Epidemiol*. 2018, 47(1):299-310.
[15] Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT Jr, Scott KC, Hudnell K, Anger WK, Camicioli R. Parkinsonism and occupational exposure to pesticides. Occup Environ Med. 2001, 58(9):582-9.
[16] Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC. Environmental risk factors and Parkinson's disease: A case-control study in Taiwan. Neurol. 1997, 48:1583-1588.
[17] Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. Occupation and risk of parkinsonism: a multicenter case-control study. Arch Neurol. 2009 Sep; 66(9): 1106-13.
[18] van der Mark M, Vermeulen R, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T, Brouwer M, Huss A, Kromhout H. Occupational exposure to pesticides and endotoxin and Parkinson disease in the Netherlands. *Occup Environ Med*. 2014, 71(11):757-764.
[19] Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am J Epidemiol*. 2009, 169(8):919-926.
[20] Brouwer M, Huss A, van der Mark M, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T, de Snoo GR, Kromhout H, Vermeulen RCH. Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. *Environ Int*. 2017, 107:100-110.

- highlight the need to carefully account for rurality in the design and analysis of studies on paraquat exposure and PD.[21]

In order to strengthen the available evidence, future epidemiologic studies on PD should aim to minimize recall bias and more systematically evaluate paraquat exposure specifically using an approach that addresses co-exposure to other pesticides and evaluates other factors that may be associated with rural living.

Lung function and respiratory effects were examined in nine study populations (17 articles) that included general lung function, wheeze, allergic rhinitis, asthma, and chronic bronchitis. Based on the findings from these studies, it was determined there is *insufficient epidemiologic evidence* at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and the health outcomes investigated, including: general lung function and respiratory symptoms, wheeze, allergic rhinitis, asthma, and chronic bronchitis. While 17 articles were identified, the quality of evidence was determined to be low for all studies because they used a cross-sectional design that could not evaluate the temporal association between paraquat exposure and onset of the health outcomes of interest. Additionally, many studies were conducted outside the United States and may not be generalizable because they focused on regions with different agricultural practices and study populations with different demographic and lifestyle characteristics.

Cancer outcomes were only investigated in four study populations (eight articles) that examined occupational paraquat exposure. Most cancer outcomes investigated in only a single study, typical AHS. Based on the findings from these studies, it was determined that there is *insufficient epidemiological evidence* to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and the health outcomes investigated, including: general lung function and respiratory symptoms, wheeze, allergic rhinitis, asthma, and chronic bronchitis. While 17 articles were identified, all studies were determined to be low quality because they used cross-sectional designs and could not evaluate the temporal association between paraquat exposure and onset of the health outcomes of interest. Additionally, some studies were conducted outside the United States and may not be generalizable because they focused on regions with different agricultural practices and study populations with different demographic and lifestyle characteristics.

Seventeen other health outcomes (25 articles) were investigated in the literature primarily examined occupational paraquat exposure. Most outcomes were only investigated in a single study population. OPP concluded there was *no epidemiological evidence* of an association for the health outcomes general mortality, suicide, and infant birth weight. For health outcomes with a single study with positive findings (OR > 1.0 and significant), it was generally concluded there was insufficient evidence of an association for health outcomes. This included the health outcomes diabetes, myocardial infarction, eye disorders, injury mortality, renal/liver function, oxidative stress, abnormal skin pigmentation, actinic keratosis, depressive symptoms, thyroid disease, and aplastic anemia. OPP concluded there was limited, but insufficient evidence of a clear associative or causal relationship for end-stage renal disease, based on AHS studies on

[21] Wan N and Lin Y. Parkinson's Disease and Pesticides Exposure: New Findings From a Comprehensive Study in Nebraska, USA. *J Rural Health*. 2016; 32(3):303-13.

male farmers that both reported evidence of a positive association.[22,23] While positive associations were reported, there were only a small number of paraquat cases in both studies (21 and 33, respectively), so the ability to assess the exposure-response relationship was limited. As such, while both AHS studies reported positive findings, further investigation is warranted to replicate the results in studies with a larger number of cases and other study populations that may experience chronic paraquat exposure.

4.3.2 Parkinson's Disease Systematic Review

The central nervous system has received considerable attention in the paraquat literature with an emphasis on PD hallmarks including accumulation of α-synuclein in neurons (Lewy bodies), degeneration of vulnerable neuron populations including dopaminergic neurons in the midbrain, depletion of dopamine in the striatum, and impairment of motor and non-motor function. The OPP toxicity database does include several studies that explore general neurotoxicity and PD-specific hallmarks; however, the Agency recognizes that these studies represent a small fraction of the available literature on neurotoxic outcomes related to paraquat exposure and PD.

As part of Registration Review, the Agency conducted a fit-for-purpose systematic review to evaluate the significance and environmental relevance of the postulated association between paraquat exposure and PD. A literature database for the PD systematic review was compiled from three primary sources of data: the OPP paraquat toxicity database for registration, the OPP paraquat epidemiology review (summarized in 4.3.1), and the National Toxicology Program (NTP) scoping review of open literature relevant to evaluating the association between paraquat exposure and PD. Data from the studies were separated into three lines of evidence – human, animal, and *in vitro* – and evaluated for quality, substance, and environmental relevance. Environmental relevance was defined as the likelihood that a given effect would result from an exposure scenario anticipated to occur from typical use of registered paraquat products (e.g. oral including dietary, dermal and inhalation exposure). The Agency integrated environmental relevance considerations into the systematic review in order to contextualize hazard information in terms of risk. Studies that were of sufficient quality and investigated environmentally relevant exposure scenarios were then evaluated in their respective body of evidence and collectively across lines of evidence in the weight of evidence analysis. The conclusions of the PD systematic review are presented here and more information on the methods, review criteria, and study evaluations can be found in the PD systematic review memo (D449106; TXR 0057888, A. Wray, 06/26/2019).

A screen of the open literature and OPP toxicity database returned 28, 217, and 244 human, animal, and *in vitro* studies, respectively, that were relevant to evaluating the association between paraquat exposure and PD. Further review of the relevant animal open literature revealed that many of the studies used injection as the route of administration or were conducted with alternative mammalian models. The Agency acknowledges that a number of injection studies report PD-like effects in rodents following exposure to paraquat; however, injection is not representative of the anticipated exposure scenarios for registered uses of paraquat due to differences in toxicokinetic behavior. These studies were thus excluded from consideration in the PD systematic review due to a lack of environmental relevance. Likewise, studies conducted

[22] Lebov JF, Engel LS, Richardson D, Hogan SL, Hoppin JA, Sandler DP. Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the Agricultural Health Study. Occup Environ Med. 2016, 73:3-12.
[23] Lebov JF, Engel LS, Richardson D, Hogan SL, Sandler DP, Hoppin JA. Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the Agricultural Health Study. Environ Res. 2015, 143(Pt A):168-210.

with alternative mammalian models were excluded because they were determined to be of limited use to evaluating human health risk. Study evaluation of the *in vitro* database focused on the studies that reported the most sensitive response for relevant outcomes within the human and rodent models due to the density of relevant studies available. The *in vitro* studies excluded from study evaluation either presented results that were not meaningfully different from those reported in the evaluated studies, reported outcomes that were not relevant to the weight of evidence analysis, and/or the reported results indicated the *in vitro* model examined was not more sensitive than the relevant models discussed for a particular outcome. Additional studies from all three lines of evidence were excluded based on insufficient quality. In total, data from 26, 11, and 34 studies were considered in the evaluation of the human, animal, and *in vitro* evidence, respectively, and integrated in the weight of evidence analysis. In addition, the 11 acceptable animal studies were considered in the selection of PODs for the Registration Review risk assessment.

Evaluating the link between paraquat exposure and PD is reliant on the strength, consistency, and coherence of PD or PD-like hallmarks within and across the human, animal, and *in vitro* lines of evidence, and concordance with toxicokinetic and mechanistic data. Some evidence connecting environmentally relevant paraquat exposure to motor, neuropathological, and/or neurochemical hallmarks of PD was reported in the acceptable literature compiled for this systematic review; however, confidence in these positive findings was diminished by gaps in the dose and temporal concordance, mixed and conflicting results between and across lines of evidence, and unresolved uncertainties in the studies and overall weight of evidence.

The 26 human studies were the same epidemiology studies identified in the paraquat epidemiology review (discussed in more detail in Section 4.3.1). These studies reported findings on 13 study populations, including three agricultural cohorts, nine hospital-based populations, and one PD registry in Nebraska. These study populations may have been exposed to paraquat through occupational and non-occupational exposure pathways that vary in terms of magnitude, frequency, and duration, with occupational study populations being more likely to experience exposure as a result of direct use of paraquat. With respect to occupational exposure, it was determined that there *is limited, but insufficient epidemiologic evidence of a clear associative or causal relationship.* This conclusion was based on mixed findings in both the AHS cohort and other study populations. These studies may all be subject to uncertainty due to limitations in their design, exposure assessment approach, and potential for bias. With respect to non-occupational study populations, evidence from three study populations was evaluated and it was determined that there is *insufficient epidemiologic evidence of a clear associative or causal relationship.* This conclusion was based on the small number of studies on non-occupational populations, lack of consistent evidence of a positive association, and the potential for bias.

Empirical evidence of motor impairment in laboratory animals was observed in male mice following oral exposure for at least 28 days to doses ≥7.2 mg paraquat ion/kg/day (10 mg

dichloride/kg/day)[24,25,26]. These findings were the strongest evidence of neurotoxicity attributed to paraquat in the animal literature evaluated for this systematic review. The behavioral changes were observed across several studies that used a high purity paraquat product and exhibited a large magnitude of change from controls. Motor impairment was, however, not observed in female mice nor in rats of either sex after oral exposure to paraquat. Only one animal study (Ren *et al.* 2009)[24] presented evidence to suggest the observed motor impairment in male mice was connected to dopaminergic neuron degeneration and neurochemical disruption – two hallmarks integral to the pathology of PD in humans – but there was not enough information in this study nor collectively in the animal literature to evaluate consistency, dose response, or temporal concordance of these findings. Toxicokinetic, *in vitro*, and mechanistic data added credibility to the positive findings in male mice but the lack of supporting empirical evidence for tissue, cellular, and biochemical PD-like hallmarks in the animal studies diminish confidence that the observed motor impairment was a result of a PD-like pathology in mice. Other environmentally relevant routes of exposure were less studied in the literature. No reliable evidence of PD-like hallmarks was observed in mice or rats after repeated intranasal exposure, which was consistent with the toxicokinetic data indicating paraquat did not distribute to the ventral midbrain or striatum after acute exposure. No data were available to evaluate PD-like hallmarks following dermal exposure; however, systemic paraquat concentration is expected to be low following dermal exposure provided the dermal dose does not reach levels that affect the integrity of the skin. Overall, the limited, mixed findings in the animal literature were considered weak evidence of a PD-like response to paraquat exposure.

Qualitative similarities in the positive findings for *in vitro* and behavioral outcomes between rodents and humans indicated some interspecies coherence in the neurological response to paraquat exposure; however, there was a lack of coherence for tissue, cellular, subcellular, and biochemical PD hallmarks, in part because few animal studies and no human studies investigated these hallmarks. The small number of positive findings and the lack of consistency in the findings in the human studies also diminished confidence in the biological plausibility of the animal and *in vitro* findings. Occupational and dietary exposure in humans resulting from pesticidal use of paraquat products currently registered in the United States is not estimated to reach external dose levels that elicited PD-like effects in whole animal studies. These estimates may not apply for uses outside of the United States but do suggest that the PD-like outcomes observed in the laboratory are not likely to occur from label-directed use in the US. Given the weakness within and across lines of evidence and the exposure considerations outlined above, the Agency concluded that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans. The Agency did not evaluate the adverse outcome pathways (AOP) proposed in the open literature nor develop one from the data gathered in the systematic review. Given the lack of sufficient evidence for a causal association, the Agency did not consider an AOP necessary to characterize paraquat toxicity and evaluate risk for registered products.

[24]Ren JP, Zhao YW, and Sun XJ. 2009. Toxic influence of chronic oral administration of paraquat on nigrostriatal dopaminergic neurons in C57BL/6 mice. Chin Med J. 122(19): 2366-2371.

[25]Satpute RM, Pawar PP, Puttewar S, Sawale SD, and Ambhore PD. 2017. Effect of resveratrol and tetracycline on the subacute paraquat toxicity in mice. Hum Exp Toxicol. 36(12): 1303-1314.

[26] Lou D, Wang Q, Huang M, and Zhou Z. 2016. Does age matter? Comparison of neurobehavioral effects of paraquat exposure on postnatal and adult C57BL/6 mice. Toxicol Mech Method. 26(9): 667-673.

The findings of this systematic review were integrated with the rest of the paraquat toxicity profile in the hazard characterization and were considered in the POD selection and uncertainty factor determination for the Registration Review human health risk assessment. In selecting the most sensitive POD to estimate risk, the Registration Review risk assessment accounted for all forms of treatment-related adversity reported for paraquat including the neurotoxic effects discussed in this systematic review. The toxicity profile for paraquat indicates that contact toxicity and effects in the respiratory and renal system occur at lower doses than those eliciting neurotoxicity in animal models. Paraquat is also lethal to pregnant rats at the doses reported to elicit neurotoxicity. Based on these findings, it is expected that a multitude of contact and systemic effects would precede the PD-like neurotoxic effects reported in the literature. Contact, renal, and respiratory toxicity are, therefore, of greater concern to human health and more relevant to assessing risk from paraquat exposure during routine use of pesticidal products with US registration. PODs selected for risk assessment were thus based on the more sensitive respiratory effects and are protective of the neurotoxic effects attributed to paraquat exposure discussed in the PD systematic review.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[27]

The paraquat risk assessment team recommends reducing the FQPA SF to 1X. The dietary assessments are based on reliable data and will not underestimate exposure. The paraquat toxicity database, with contributions from the open literature, is adequate to evaluate the potential for susceptibility in infants and young children resulting from exposure to paraquat. There was no evidence of quantitative developmental or offspring susceptibility in the guideline rodent studies and the HASPOC recommended waiving the non-rodent developmental study requirement because it was not anticipated to provide data or information that would impact risk assessment (TXR 0056294, K. Rury, 04/12/2012). Limited evidence of age-related sensitivity was observed in the open literature, but only from exposure to a high purity paraquat product (>98% purity), which is not representative of the lower purity technical paraquat products and formulations (<48% purity) undergoing Registration Review. The PODs selected for risk assessment account for toxicity from exposure to paraquat sources that are analogous to the technical product and are thus protective of the developmental and offspring effects resulting from exposure to the registered technical products and lower purity formulations. Limited evidence of neurotoxicity including PD-like outcomes was noted in the toxicology database and in the open literature; however, the weight of evidence compiled from relevant human, animal, and *in vitro* studies was considered insufficient to conclude that there is a causal relationship between paraquat exposure from pesticidal use and PD. Lung and respiratory tract toxicity were more sensitive endpoints compared to the neurotoxic and other systemic effects reported in the open literature, thus the PODs selected for risk assessment based on these effects are protective of all known health effects resulting from paraquat exposure.

4.4.1 Completeness of the Toxicology Database

The paraquat toxicology database coupled with the general literature review and the Parkinson's disease systematic review provided adequate information to assess risk for infants and young children. Acceptable guideline developmental, multi-generation reproduction, and acute and subchronic neurotoxicity studies were used to characterize toxicity for these critical life-stages.

[27] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

Although a developmental study in non-rodents is a conventional requirement to register pesticides with food-uses, the HASPOC determined the study was unlikely to have an impact on the risk assessment and thus recommended waiving the requirement for paraquat (TXR 0056294, K. Rury, 04/12/2012). The general literature review and PD systematic review confirmed that the toxicology database reported the most sensitive endpoints for risk assessment. Furthermore, the PD systematic review was used to characterize neurotoxic outcomes resulting from paraquat exposure that were not addressed in the database.

4.4.2 Evidence of Neurotoxicity

Recent studies from the open literature demonstrated accumulation of paraquat in brain tissue following oral exposure, yet guideline, non-guideline, and open literature studies present little evidence to suggest the nervous system is a primary target tissue. Clinical signs of toxicity (hunched posture and piloerection) noted in the guideline acute neurotoxicity study (ACN) and rodent developmental studies were determined to be an agonal response to the bolus dose administered via gavage and were not considered evidence of treatment induced neurotoxicity. This is supported by the lack of neuropathology or motor activity findings following acute exposure. Likewise, no behavioral changes including motor activity or abnormal neuropathology findings were noted during and at the end of a 90-day dietary exposure in the subchronic neurotoxicity study (SCN). In addition to the guideline studies, several non-guideline studies were submitted to the Agency that investigated neurotoxic outcomes specific to Parkinsonism (MRID 49122301-04). Although there is little evidence of PD-like symptoms in the non-guideline studies, deficiencies related to the exposure design limit their usefulness for characterizing paraquat neurotoxicity from pesticidal uses. The connection between paraquat exposure and PD was further explored in the PD and epidemiology systematic reviews. The two systematic reviews concluded that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans.

Across the guideline, non-guideline, and open literature studies, it is apparent that neurotoxicity is not a common response in exposure scenarios that are anticipated to result from pesticidal use of paraquat. The few studies that reported PD-like effects in animal models observed those neurotoxic effects at doses at least 14 times above the current subchronic and chronic PODs, indicating that the respiratory effects are a more sensitive endpoint and the risk assessment accounts for and is protective of the limited evidence of neurotoxicity.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

No evidence of increased quantitative or qualitative susceptibility was seen in rat developmental toxicity and reproduction studies. All fetal and offspring effects were observed in the presence of comparable maternal toxicity. An acceptable rabbit developmental study was not available; however, the HASPOC determined the study was unlikely to have an impact on the risk assessment and thus recommended waiving the requirement for paraquat (TXR 0056294, K. Rury, 04/12/2012). One study in the open literature (Lou *et al*. 2016) reported increased sensitivity to oral exposure to a high purity paraquat product based on age (3 weeks vs. 8 weeks), which is counter to the lack of age and lifestage susceptibility reported in the toxicity database. Although this is a unique finding relative to the rest of the toxicity database, the product used was of higher purity (>98%) than those registered for pesticidal use (<48%), thus the exposure design and results in the Lou *et al*. (2016) study are not considered to be representative of the anticipated exposure scenarios for pesticidal uses of paraquat dichloride. The PODs selected for

risk assessment account for the developmental and offspring effects observed in the database from exposure to risk assessment relevant paraquat products (e.g. technical products and lower purity formulations) and are thus protective.

4.4.4 Residual Uncertainty in the Exposure Database

The dietary risk assessment is conservative and will not underestimate dietary exposure to paraquat. The non-occupational spray drift exposure assessments are based upon the 2012 Residential Standard Operating Procedures (SOPs) and are unlikely to underestimate risks.

4.5 Toxicology Endpoint and Point of Departure Selections

PODs were selected for dietary (acute and chronic), incidental oral (short-term), dermal (short- and intermediate-term) and inhalation (short- and intermediate-term) exposure scenarios. The PODs, uncertainty factors, and calculated reference dose /population adjusted dose or LOCs for each exposure scenario are detailed below. Toxicity studies used to select PODs for each exposure scenario are presented in Table 4.5.4.1 and 4.5.4.2. The toxicology database was re-evaluated during Registration Review to incorporate new toxicity data and to update endpoints selected for PODs to be consistent with current HED practices. HED recognizes that the toxicity database contains studies with established endpoints that are considered conservative in light of current HED practices for determining adversity in toxicity studies (e.g., study endpoints based on decreased bodyweight gain in the absence of decreases in absolute bodyweight). However, it was determined that these studies did not impact endpoints for the risk assessment and, therefore, were not updated for Registration Review.

4.5.1 Dose-Response Assessment

Acute Dietary (All Populations)
The POD for acute dietary exposure for all populations (5 mg paraquat ion/kg) was based on the lowest dose without an acute effect in the developmental rat study (MRID 00113714). At 10 mg paraquat ion/kg, mortality was observed following progressive deterioration of health in three animals. Clinical signs of toxicity (staining of neck and subdued nature) were noted in these animals within 2-3 days of the first dose and evolved to more severe signs of distress (thin, hunched, piloerection, staining around nose, forepaws and eyes) prior to death 5-7 days after the initial exposure. Given evidence in other acute oral studies and human incidents reports of delayed symptoms and lethality from acute exposure, the clinical signs and mortalities observed in these three animals were conservatively assumed to be the result of the initial dose and thus were considered appropriate for assessing acute dietary exposure. Delayed mortalities also considered conservative evidence of an acute effect were noted at a lower dose (3.6 mg paraquat ion/kg) in the Lou *et al.* (2016) study (MRID 50733301) identified in the open literature screen (D449107; TXR 0057887, A. Wray, 06/26/2019); however, the paraquat product used in this study was of much higher purity (> 98%) than the registered products undergoing Registration Review (< 48%) and thus the results were reflective of an exposure scenario that is not relevant to the pesticidal uses of paraquat. The previous acute POD (1.25 mg paraquat ion/kg) was based on alveolar histiocytes noted in the parental population of the multi-generation reproduction study. It was not retained, however, because this lung effect could not be unequivocally attributed to a single dose and thus was considered less robust for an acute POD compared to the clinical signs and mortality in the rat developmental study. Uncertainty factors for interspecies extrapolation (10X) and intraspecies variation (10X) were applied to the NOAEL to calculate the

acute reference dose (aRfD = 0.05 mg paraquat ion/kg). The acute population adjusted dose (aPAD = 0.05 mg paraquat ion/kg/day) is equivalent to the POD divided by all applicable uncertainty factors, including the FQPA SF (1X).

Chronic Dietary (All Populations)
The POD for chronic dietary exposure for all populations was established based on the lung effects observed in the subchronic and chronic dog oral toxicity studies (MRIDs 00072416 and 00132474). These two dog studies were considered compatible because the lung effects were consistent between the two studies and occurred at similar doses despite the difference in duration. The NOAEL (0.5 mg paraquat ion/kg/day) from the subchronic dog study was selected as the chronic dietary POD because it was comparable to the chronic study NOAEL (0.45 mg paraquat ion/kg/day) and was protective of the respiratory effects observed at 0.93-1.5 mg paraquat ion/kg/day in the dog studies including gross lung lesions, increased severity of chronic pneumonitis, and increased lung weights. The critical effects in these studies were appropriate endpoints for the chronic dietary risk assessment because they were consistent with the known targets of paraquat exposure and were the most sensitive endpoints observed in the paraquat toxicity database for repeated oral exposures. The current chronic dietary POD is consistent with the POD previously selected for chronic dietary assessments (0.45 mg paraquat ion/kg/day) that was based on the respiratory effects in the chronic dog oral toxicity study. Uncertainty factors for interspecies extrapolation (10X) and intraspecies variation (10X) were applied to the NOAEL to calculate the chronic reference dose (cRfD = 0.005 mg paraquat ion/kg/day). The chronic population adjusted dose (cPAD = 0.005 mg paraquat ion/kg/day) is equivalent to the POD divided by all applicable uncertainty factors, including the FQPA SF (1X).

Short- and Intermediate-Term Incidental/Adult Oral
The co-critical dog studies were also used to establish the short-term adult/incidental oral POD (0.5 mg paraquat ion/kg/day). The co-critical dog studies are appropriate for assessing short-term oral exposure because the lung effects observed in this study are consistent with the known targets of paraquat toxicity and were observed in a timeframe relevant to the exposure scenario. Furthermore, these were the most sensitive endpoints for oral exposure and are thus protective of all toxicity reported in the paraquat toxicity database. An incidental oral endpoint was not selected prior to this risk assessment. The LOC for oral exposure is 100 based on a combination of uncertainty factors for interspecies extrapolation (10X), intraspecies variation (10X), and FQPA SF (1X).

Short- and Intermediate-Term Dermal
The systemic NOAEL (6 mg paraquat ion/kg/day) from the route specific 21-day dermal study in rabbits (MRID 00156313) was selected to be the POD for the occupational dermal assessment and spray drift assessment. Six mg paraquat ion/kg/day was the highest dose tested (HDT) in the 21-day dermal study and there are no additional studies in the toxicity database that investigate systemic or dermal toxicity from repeat exposure at higher dermal doses. The 21-day study did not test higher due to animal welfare concerns based on the slight to severe skin damage observed at relatively low topical doses (2.6 - 6 mg paraquat ion/kg/day). Reports of skin damage were also noted in human incidents that involved dermal exposure to concentrated or dilute solutions of paraquat. [28] The severity of dermal toxicity in the incident report ranged from

[28] These incidents from 2016 cases show typical paraquat exposures & delayed onset of dermal symptoms:

blisters and dry skin to complete corrosion requiring skin grafts. Although the toxicity database indicates paraquat is not well absorbed across intact human skin, the corrosive properties of the chemical, detailed in the dermal study and human incident reports, affect the integrity of the skin. Further corrosion of the dermal layer is anticipated at doses above the HDT in the subchronic dermal study, which increases the likelihood of systemic toxicity as the barrier separating dermally applied paraquat from the bloodstream erodes. Consequently, the HDT from the route specific dermal study was selected to be protective of the potential for systemic toxicity at higher dermal doses. The rabbit is ostensibly a conservative model for dermal toxicity of paraquat based on evidence of greater sensitivity to acute dermal exposure compared to rats. Nevertheless, regulating based on the systemic NOAEL from the dermal study is appropriate given the lack of data on the mammalian systemic response to repeat dermal dosing above 6 mg paraquat ion/kg/day and the corrosive properties of the chemical that will impact the ability of the skin to restrict paraquat absorption at higher dermal doses. The previous dermal POD (1.25 mg paraquat ion/kg/day) was based on the parental endpoint from the multi-generation reproduction study. Accounting for the low oral absorption (6-14%), the most conservative estimate for a dermal equivalent dose based on this oral POD and the DAF for intact skin (0.23-0.3%) is 25 mg paraquat ion/kg/day[29]. Note that this calculation assumes the skin is intact at the estimated dermal dose level. The LOC for dermal exposure is 100 based on a combination of uncertainty factors for interspecies extrapolation (10X) and intraspecies variation (10X), and, for non-occupational scenarios, the FQPA SF (1X).

Short- and Intermediate-Term Inhalation

The NOAEC (0.01 µg paraquat ion/L/day) from the route specific inhalation study (MRID 00113718) was selected to be the POD for the occupational and residential inhalation assessments. The NOAEC was based on an increased incidence of squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx observed in animals exposed to 0.1 µg paraquat ion/L/day (LOAEC). The route-specific study was appropriate for assessing inhalation risk because the duration and route of administration used in the study were similar to the anticipated inhalation exposure scenarios and life-stage susceptibility was not a concern for inhalation exposure. Previously, the inhalation PODs were selected for respirable and non-respirable particles. The respirable particle POD was the same as the inhalation POD selected currently for Registration Review and the non-respirable particle POD (1.25 mg paraquat ion/kg/day) was based on lung effects observed in the multi-generation reproduction study. For Registration Review, the respirable particle POD was used to assess risk for all inhalation scenarios. A non-respirable particle POD was not selected. Particle size data reported in the study were not sufficient to calculate a human equivalent dose for risk assessment; therefore, an animal equivalent dose (AED) was calculated (see footnote of Table 4.5.4.1 and 4.5.4.2). The

- One case was a certified applicator was loading paraquat into a tank and he accidentally splashed some product which got inside of the chemical resistant gloves he wore. He decontaminated immediately but he developed a burning sensation about 30 minutes later.
- A farmworker sprayed weeds all morning with a backpack sprayer; he wore a waterproof coverall, required mask, gloves and eye protection. He was sweating in the heat and his skin began to burn. The protective overall had broken and paraquat had gotten onto his skin. He went home and decontaminated. His symptoms worsened over time and he went to the emergency room for pain and symptoms several days after the application.
- A 16-year old summer farm employee was told to apply paraquat on his employer's farm when the hose broke and sprayed his pants. He was unaware of danger (under supervision of certified applicator who was not on site that day). The cases continued working and did not become symptomatic with dermal irritation and burning until that evening.

[29] Dermal equivalent dose = (oral POD * oral absorption)/DAF = (1.25 mg paraquat ion/kg/day * 0.06)/0.003 = 25 mg paraquat ion/kg/day

AED for the occupational and non-occupational inhalation scenarios is 0.0026 mg paraquat ion/kg/day. The LOC for inhalation exposure is 100 based on a combination of uncertainty factors for interspecies extrapolation (10X) and intraspecies variation (10X), and, for non-occupational scenarios, the FQPA SF (1X).

4.5.2 Recommendations for Combining Routes of Exposure for Risk Assessment

For all durations, incidental/adult oral and dermal exposures can be combined. Although the dermal assessment is based on the lack of systemic effects from dermal exposure, given the lung is a target organ, it is possible that higher dermal doses would elicit lung toxicity similar to the response observed in the co-critical dog studies that was used to assess incidental/adult oral exposure. The respiratory effects in the route specific inhalation study were observed in a different region of the respiratory tract and thus cannot be combined with the oral and dermal exposures.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Paraquat is currently classified as Category E (evidence of non-carcinogenicity for humans). The carcinogenic potential of paraquat was evaluated by the Toxicology Branch Peer Review Committee (now Carcinogenicity Assessment Review Committee (CARC)) in 1986, 1988, and 1989, and by the Scientific Advisory Panel (SAP) in 1989 (TXR 0007828). In 1986, the Toxicology Branch Peer Review Committee classified paraquat as a Category C carcinogen (limited evidence of carcinogenicity in animals), based on an apparent increase in erroneously combined squamous cell carcinomas in different locations in the head region. In 1988, the Toxicology Branch Peer Review Committee re-evaluated the tumors observed in rats and reclassified paraquat as Category E (evidence of non-carcinogenicity in humans). In February of 1989 the SAP classified paraquat as Category D (equivocal evidence of carcinogenicity) based on squamous cell carcinoma in the nasal cavity of 2 high-dose rats. However, the SAP also commented that endpoints other than carcinogenicity were more relevant for the regulation of paraquat. The following month (March 1989) the Toxicology Branch Peer Review Committee reviewed the carcinogenicity of paraquat, again in light of the SAP conclusions, and determined its previous classification, Category E, was still appropriate based on the available data.

Paraquat was found to induce sister chromatid exchange in Chinese hamster lung fibroblasts and increase the number of aberrant cells at cytotoxic concentrations in human peripheral blood lymphocytes in the presence and absence of metabolic activation. Conversely, paraquat was not mutagenic in the *Salmonella typhimurium* assay, not genotoxic in the unscheduled DNA synthesis assay *in vivo* or *in vitro*, negative for chromosomal aberration in the bone marrow test, and no evidence was found for suppressed fertility or dominant lethal mutagenicity in mice. Based on these considerations there is no concern for mutagenicity.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Paraquat for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	POD	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	Acute NOAEL = 5 mg paraquat ion/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 0.05 mg paraquat ion/kg aPAD = 0.05 mg paraquat ion/kg	Developmental- rat MRID 00113714 Acute LOAEL= 10 mg paraquat ion/kg, based on clinical signs of toxicity and mortality
Chronic Dietary (All Populations)	NOAEL = 0.5 mg paraquat ion/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.005 mg paraquat ion/kg/day cPAD = 0.005 mg paraquat ion/kg/day	Co-critical Dog Oral Studies Subchronic MRID 00072416 LOAEL = 1.5 mg paraquat ion/kg/day based on increased lung weight and incidence of alveolitis in both sexes. Chronic MRID 00132474 LOAEL = 0.93 mg paraquat ion/kg/day, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males
Incidental Oral/Adult Oral Short-Term (1-30 days)	NOAEL = 0.5 mg paraquat ion/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE = 100	Co-critical Dog Oral Studies Subchronic MRID 00072416 LOAEL = 1.5 mg paraquat ion/kg/day based on increased lung weight and incidence of alveolitis in both sexes. Chronic MRID 00132474 LOAEL = 0.93 mg paraquat ion/kg/day, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males
Dermal Short-Term (1-30 days)	NOAEL = 6 mg paraquat ion/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE = 100	21-day Dermal toxicity study - rabbits MRID 00156313 NOAEL = 6 mg paraquat ion/kg/day (HDT)

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Paraquat for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**POD**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Short-Term (1-30 days)	NOAEC = 0.01 µg paraquat ion/L/day AED = 0.0026 mg paraquat ion/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE = 100	21-Day inhalation toxicity study - rat MRID 00113718 LOAEL = 0.10 µg paraquat ion/L/day, based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx
Cancer (oral, dermal, inhalation)	Classification: Category E (evidence of non-carcinogenicity for humans) (TXR 0007828)			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. HDT = Highest dose tested. AED = Animal Equivalent Dose (mg/kg/day) = duration adjusted POD (mg/L) * animal specific conversion factor (44 L/hr-kg BW) * animal daily duration (hr).

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Paraquat for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**POD**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1 day to 6 months)	NOAEL = 6 mg paraquat ion/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	21-day Dermal toxicity study – rabbits MRID 00156313 NOAEL = 6 mg paraquat ion/kg/day (HDT)
Inhalation Short- and Intermediate-Term (1 day to 6 months)	NOAEC = 0.01 µg paraquat ion/L/day AED = 0.0026 mg paraquat ion/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	21-Day inhalation toxicity study in rats MRID 00113718 LOAEL = 0.10 µg paraquat ion/L/day, based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx
Cancer (oral, dermal, inhalation)	Classification: Category E (evidence of non-carcinogenicity for humans) (TXR 0007828)			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. HDT = Highest dose tested. AED = Animal Equivalent Dose (mg/kg/day) = duration adjusted POD (mg/L) * animal specific conversion factor (44 L/hr-kg BW) * animal daily duration (hr).

4.6 Endocrine Disruption

As required by FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for paraquat, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), paraquat is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[30] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[31]

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The qualitative nature of residues in plant commodities is understood based upon studies depicting the metabolism of paraquat in carrots and lettuce following preemergence treatment and in potatoes and soybeans following desiccant treatment. The residue of concern in plants is

[30] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[31] https://www.epa.gov/endocrine-disruption

the parent paraquat. The qualitative nature of residues in livestock is adequately understood based on the combined results of studies conducted with ruminants (goats and cows), swine, and poultry. The residue of concern in eggs, milk, and poultry and livestock tissues is also parent paraquat.

Table 5.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent Paraquat	Parent Paraquat
	Rotational Crop	Parent Paraquat	Parent Paraquat
Livestock	Ruminant	Parent Paraquat	Parent Paraquat
	Poultry	Parent Paraquat	Parent Paraquat
Drinking Water		Parent Paraquat	N/A

5.2 Summary of Plant and Animal Metabolism Studies

In plant metabolism studies reflecting preemergence treatment, the total radioactive residues were 0.0048 ppm in carrot root and 0.0034 ppm in lettuce leaf samples following a single preemergence application of [^{14}C] paraquat at rates of 13.1 lb ai/A for carrots and 12.8 lb ai/A for lettuce (~13x the maximum rate of 1 lb ai/A for each crop). These data suggest that radioactive residues of paraquat are not readily taken up from the soil in significant quantities by these crop commodities following this mode of treatment. No further residue characterization and identification was conducted on these samples because of the low magnitude of radioactivity obtained. In *plant metabolism studies reflecting desiccant treatment*, the total radioactive residues were 0.075 and 0.087 ppm in potatoes, 0.652 and 0.841 ppm in soybeans, and 506.3 and 768.5 ppm in soybean foliage following a single foliar desiccant application of uniformly ring-labeled [^{14}C] paraquat at 7.8 or 7.9 lb ai/A for potatoes and 7.3 lb ai/A for soybeans (~6x the maximum seasonal rate of 1.25 lb ai/A for potatoes and 29x the maximum single application rate of 0.25 lb ai/A for soybeans). Paraquat cation was the major ^{14}C-residue identified and accounted for ~91% of the total radioactivity in potatoes, ~84% of the total radioactivity in soybeans, and virtually all of the total radioactivity in soybean foliage. Other minor metabolites found in soybean foliage were QINA (quaternary iso-nicotinic acid, a photodegradant) and monoquat (1-methyl-4,4'-bipyridinium ion), each at 0.3% of TRR.

In a ruminant metabolism study, a lactating goat was dosed with ring-labeled [^{14}C] paraquat at 103 ppm in the diet for seven days. The total radioactive residue, expressed as ppm paraquat, was 0.02-0.03 ppm in fat (peritoneal and subcutaneous), 0.08-0.12 ppm in muscles (fore- and hind-quarter), 0.56 ppm in liver, and 0.74 ppm in kidney. The maximum total radioactivity in milk increased daily to a maximum of 0.0092 ppm paraquat ion equivalents four hours before slaughter; 75.7% of the TRR of this sample was found to be paraquat. In edible tissues, paraquat accounted for the majority of the identified residues including ~49-120% of TRR in fat, ~90-100% of TRR in muscles, ~48% of TRR in liver, and ~95% of TRR in kidney. Other metabolites that were identified in tissues were the monopyridone of paraquat (1,2-dihydro-1,1'-dimethyl-4,4'-bipyridinium ion) which accounted for 3.2% of TRR in liver and monoquat which

accounted for 3.4% of TRR in liver and 6.5% of TRR in peritoneal fat. A pig metabolism study reflecting use of ring-labeled [^{14}C] paraquat and a feeding level of 2.44 ppm is also available. Total radioactive residues were 0.20 ppm paraquat equivalents in liver, 0.38 ppm in kidney, 0.05 ppm in muscle, and 0.01 ppm in fat. Paraquat was found to comprise ~70% of TRR in liver, 101% of TRR in kidney, 95% of TRR in muscle, and 106% of TRR in fat. Liver tissue, the only tissue analyzed for residues other than paraquat, was found to contain monoquat at ~4% of TRR. In a poultry metabolism study, laying hens were dosed with ring-labeled [^{14}C] paraquat at 30 ppm in the diet for ten consecutive days. Radioactive residues were found in all examined tissues (including liver, abdominal and subcutaneous fat, and leg and breast muscle). Paraquat was the major residue (~80-98% of TRR) identified in all poultry tissues; monoquat was a minor metabolite (~4% of TRR each) in liver and kidney. The total radioactive residues in the yolks and albumen of the eggs increased irregularly from nondetectable (<0.01 ppm paraquat ion equivalents) on the first two days of the study to a maximum of 0.1812 ppm in the yolk and 0.0014 ppm in the albumen on the eighth day. Virtually all the radioactivity in the yolk was identified as paraquat; no analysis of albumen was reported.

5.3 Summary of Environmental Degradation

Paraquat undergoes minimal degradation in the environment, and thus is very persistent (as parent). However, it's very high propensity to bind to solids, particularly clay, makes it very immobile. In addition, paraquat does not readily appear to desorb from clay. The greatest cause for concern is likely to be erosion of contaminated sediments off-site and subsequent re-deposition onto non-target areas (especially surface water bodies). There is an additional (minor) concern for the one use (wheat) that includes aerial spray; however, this use entails very small amounts (relative to all other uses), so spray drift onto nearby surface water drinking water sources should be fairly limited. Because of its very low mobility and strong tendency to bind tightly to soils, paraquat contamination of drinking water supplies derived from groundwater is expected to be highly unlikely. In addition, the strong binding characteristics of paraquat are likely to render most residues in raw drinking water sources removable through sedimentation processes, which are typically included as part of standard drinking water treatments.

5.4 Comparison of Metabolic Pathways

Paraquat is very stable. In both primary crops and rotational crops, parent paraquat was the only major residue. In goats, pigs, and poultry, paraquat was again the only residue of concern. Paraquat was not metabolized by rats. It was poorly absorbed after oral administration to rats, dogs and mice. Once absorbed, paraquat was rapidly distributed to most tissues but especially to lungs and kidneys. Tissues other than lungs did not retain paraquat. In the environment, paraquat is very persistent and undergoes minimal degradation. As a result of the findings of the plant and animal metabolism studies as well as the environmental degradation studies, parent paraquat is the only residue of concern considered in this human health risk assessment.

5.5 Food Residue Profile

Adequate field trial data, following treatments according to the maximum registered use patterns, have been submitted for all registered crops, and adequate feeding studies have been submitted to support tolerances for residues in livestock commodities. No additional data are required. Residues in plants are generally low. For example, many crops show residues which were below the limit of quantification (LOQ; 0.05 ppm). Processing studies indicate that paraquat residues

do not concentrate except in sugar cane molasses and pineapple processed residue. Feeding studies with cattle and hens indicate that livestock commodity residues resulting from consumption of potentially treated feed items will be generally <LOQ in livestock commodities. Under the current plant-back restrictions, residues of paraquat are not expected in rotational crops.

5.6 Water Residue Profile

J. Lin, Review of Jar Test Results for Drinking Water Assessment Purpose. D396402. 01/10/2012.

The EDWCs used in the dietary risk assessment were provided by EFED in the reference provided immediately above. This drinking water concentration was verified by EFED on 6/12/2017 by J. Lin. EFED reviewed a non-guideline supplemental mobility study (MRID 48659501). The submitted study was conducted to evaluate the effects of traditional water treatment processes on paraquat and to determine the mobility of paraquat through soil filtration column. This memorandum only addresses the first aspect on the effects of using jar tests as a mean to mimic traditional water treatment processes to determine whether the results of jar tests are sufficient to provide the justification to refine the previous drinking water assessment (D381972, J. Lin, 05/11/2011).

^{14}C-paraquat, spiked at ~30 ppb into the raw surface water samples from five representative US CWS (community water supply) facilities, was effectively removed by a combination of typical water treatment processes conducted on a laboratory-scale: the "laboratory jar test" (coagulation using alum with either lime or soda ash, flocculation and sedimentation), followed by duel media filtration (anthracite atop of filtering sand). The combination process was able to reduce the level of ^{14}C-paraquat to approximate or below the limit of detection of about 0.15µg/L (ppb). The jar test results allow EFED to better characterize potential levels in finished water for drinking water assessment purpose. The level of paraquat in the finished water of 0.15 µg/L should be used for the acute and chronic drinking water assessment.

5.7 Dietary Risk Assessment

T. Morton. Paraquat Dichloride: Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Registration Review of Paraquat Dichloride. D447108. 06/13/2019.

Unrefined acute and partially refined chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the PAD. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.7.1 Overview of Residue Data Used

Tolerance level residues were used in both the acute and chronic dietary exposure analyses.

5.7.2 Percent Crop Treated Used in Dietary Assessment

BEAD's Usage and Label Use Team (ULUT) provided a screening-level usage analysis (SLUA) for paraquat (9/19/2016). The acute assessment assumed 100 % crop treated. For the chronic analysis, the following average percent crop treated values were used: almond (25%), apple (25%), apricot (10%), artichoke (25%), asparagus (10%), avocado (1%), barley (2.5%), green beans (2.5%), blueberries (15%), broccoli (2.5%), cabbage (2.5%), caneberries (50%), cantaloupe (5%), carrots (2.5%), cauliflower (1%), celery (2.5%), cherry (20%), corn (2.5%), cotton (20%), cucumber (5%), dry beans/peas (5%), figs (20%), garlic (1%), grapefruit (5%), grapes (20%), hazelnut (50%), kiwifruit (25%), lemon (2.5%), lettuce (2.5%), nectarine (15%), olive (5%), onion (5%), orange (10%), peach (25%), peanut (30%), pear (10%), green peas (1%), pecan (5%), peppers (5%), pistachio (25%), plum/prune (10%), pomegranate (15%), potato (5%), pumpkin (5%), rice (1%), soybean (2.5%), spinach (2.5%), squash (5%), strawberry (5%), sugar beet (1%), sugarcane (5%), sunflower (2.5%), sweet corn (1%), tangelo (10%), tangerine (5%), tomato (10%), walnut (15%), watermelon (5%), and wheat (1%).

5.7.3 Acute Dietary Risk Assessment

The general U.S. population and all population subgroups have risk estimates that are below HED's level of concern (i.e., 100% of the aPAD). The most highly exposed population subgroup is Children 1-2 yrs old which utilizes 38% of the aPAD. The general U.S. population utilizes 20% of the aPAD.

Table 5.7.3. Results of Acute Dietary Exposure Analysis for Paraquat (Food and Drinking Water)

Population Subgroup	aPAD (mkd)*	95th Percentile	
		Exposure (mkd)	% aPAD
General U.S. Population	0.05	0.009760	20
All Infants (< 1 year old)		0.013165	26
Children 1-2 years old		**0.019239**	**38**
Children 3-5 years old		0.017447	35
Children 6-12 years old		0.012849	26
Youth 13-19 years old		0.007915	16
Adults 20-49 years old		0.006213	12
Adults 50+ years old		0.005243	10
Females 13-49 years old		0.006024	12

*mkd: milligram per kilogram per day

5.7.4 Chronic Dietary Risk Assessment

The general U.S. population and all population subgroups have risk estimates that are below HED's level of concern (i.e., 100% of the cPAD). The most highly exposed population subgroup is Children 1-2 yrs old which utilizes 25% of the cPAD. The general U.S. population utilizes 6.6% of the cPAD.

Table 5.7.4. Results of Chronic Dietary Exposure Analysis for Paraquat (Food and Drinking Water)			
Population Subgroup	**cPAD (mkd)***	**Exposure (mkd)**	**% cPAD**
General U.S. Population	0.005	0.000329	6.6
All Infants (< 1 year old)		0.000850	17
Children 1-2 years old		**0.001250**	**25**
Children 3-5 years old		0.000841	17
Children 6-12 years old		0.000494	9.9
Youth 13-19 years old		0.000264	5.3
Adults 20-49 years old		0.000244	4.9
Adults 50+ years old		0.000236	4.7
Females 13-49 years old		0.000229	4.6

*mkd: milligram per kilogram per day

5.7.5 Cancer Dietary Risk Assessment

An assessment of cancer risk was not performed because paraquat was classified as being a Category E chemical (evidence of non-carcinogenicity in humans).

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Paraquat is a restricted use pesticide (RUP); therefore, there are no paraquat products registered for homeowner use and no products registered for application to residential areas.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

There are no residential uses of paraquat; therefore, the only relevant aggregate risk assessments include acute and chronic exposure to residues in food and drinking water. The aggregate risk estimates are equivalent to the acute and chronic dietary (food and water) exposure assessments.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

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Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[32] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to < 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

To evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was used. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of paraquat. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

In accordance with 40CFR158, TTR data are required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses that could result in post-application exposure to turf. For paraquat, chemical-specific TTR data are not available, therefore, the estimated TTR value is based on a default assumption from the 2012 Residential SOPs that the transferable residue available for exposure is 1% of the total deposited residue, which is assumed to be equivalent to the maximum application rate. TTR data are not required since paraquat is not registered for use on residential turf; however, if submitted, these data could potentially refine the spray drift risks.

A screening approach was developed based on the use of the AgDrift® model in situations where specific label guidance that defines application parameters is not available.[33] AgDrift® is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, or groundboom sprayers. When AgDrift® was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for

[32] This approach is consistent with the requirements of the EPA's Worker Protection Standard.
[33] http://www.agdrift.com/

common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

The spray drift risk estimates are based on an estimated deposited residue concentration resulting from screening level agricultural application scenarios. Paraquat is used on various agricultural and non-agricultural crops and can be applied via groundboom and aerial application equipment. Paraquat is not applied by airblast equipment and, therefore, has not been assessed for this equipment type. The recommended drift scenario screening level options are listed below:

- Groundboom applications are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.
- Aerial applications are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[34]

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options. Different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height, use of a helicopter instead of fixed wing aircraft, crop canopy conditions). Further, if chemical-specific TTR data were submitted, these data could be used for refinement of spray drift risk estimates.

Dermal and incidental oral risk estimates are combined for children 1 to < 2 years. Although the dermal assessment is based on the lack of systemic effects from dermal exposure, given the lung is a target organ, it is possible that higher dermal doses would elicit lung toxicity similar to the response observed in the co-critical dog studies that was used to assess incidental oral exposure.

Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates
Results of the adult and children 1 to < 2 years old non-occupational spray drift risk assessment for paraquat are presented in Table 8.1.1 and 8.1.2, respectively.

Adult dermal and children 1 to < 2 years old combined dermal and incidental oral risk estimates from indirect exposure to paraquat result in estimated distances from the field edge ranging from the field edge (0 feet) to 150 feet to reach the LOC (i.e., an MOE ≥ 100) depending on the application rate and equipment type combination assessed and assuming screening level droplet sizes and boom heights. Results indicate that the major spray drift risk concern is from aerial applications.

[34] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture.

Appropriate drift reduction technologies such as changing the spray type/nozzle configuration to coarser spray applications may result in less drift and reduced risk concerns (i.e., higher MOEs) from aerial applications. Similarly, using coarser sprays and lowering boom height for groundboom sprayers reduces risk concerns.

Table 8.1.1 Adult Spray Drift Assessment for Paraquat

Exposure Scenarios	Application Type	Spray Type/Nozzle Configuration	Application Rate (lb ai/A)	Distance to Dermal MOE ≥ 100
Adult Dermal Exposure to Turf Following Spray Drift	Aerial	Fine to Medium	1.5	75 feet
	Groundboom	High Boom Very Fine to Fine		10 feet
	Aerial	Fine to Medium	1.0	50 feet
	Groundboom	High Boom Very Fine to Fine		10 feet
	Groundboom	High Boom Very Fine to Fine	0.94	10 feet
	Aerial	Fine to Medium	0.80	Field Edge
	Groundboom	High Boom Very Fine to Fine		
	Aerial	Fine to Medium	0.60	
	Groundboom	High Boom Very Fine to Fine		
	Aerial	Fine to Medium	0.50	
	Groundboom	High Boom Very Fine to Fine		
	Aerial	Fine to Medium	0.30	
	Groundboom	High Boom Very Fine to Fine		

Table 8.1.2 Children 1 to < 2 Years Old Spray Drift Assessment for Paraquat

Exposure Scenarios	Application Type	Spray Type/Nozzle Configuration	Application Rate (lb ai/A)	Distance to Dermal MOE ≥ 100	Distance to Oral HtM MOE ≥ 100
Children 1 to <2 Years Old Exposures to Turf Following Spray Drift	Aerial	Fine to Medium	1.5	150 feet	10 feet
	Groundboom	High Boom Very Fine to Fine		50 feet	Field Edge
	Aerial	Fine to Medium	1.0	100 feet	
	Groundboom	High Boom Very Fine to Fine		25 feet	
	Groundboom	High Boom Very Fine to Fine	0.94	25 feet	
	Aerial	Fine to Medium	0.80	75 feet	
	Groundboom	High Boom Very Fine to Fine		10 feet	
	Aerial	Fine to Medium	0.60	50 feet	
	Groundboom	High Boom Very Fine to Fine		10 feet	
	Aerial	Fine to Medium	0.50	50 feet	
	Groundboom	High Boom Very Fine to Fine		10 feet	
	Aerial	Fine to Medium	0.30	Field Edge	
	Groundboom	High Boom Very Fine to Fine			

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2014-0219).

HED used this screening analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis were required for paraquat. Air monitoring data are available from California Air Resources Board (CARB) for paraquat, although the study dates to 1987 and all samples collected were below the minimum detection limit (MDL) of 0.022 µg/m^3. The following is a summary from the CARB website[35] regarding the air monitoring study and results:

Paraquat (Gramoxone®) is a non-selective herbicide used to control broadleaf weeds and grasses. It is also used as a pre-harvest defoliant for cotton and hops. The greatest use in California in 2000 was on cotton (268,477 pounds). Paraquat is regulated as a restricted material.

Ambient air monitoring was conducted from August 31 to November 5, 1987, at four sites in Fresno County. The background sites were located at the ARB air monitoring stations in Fresno and Bakersfield. Monitoring was scheduled to coincide with expected applications to cotton. All of the 318 samples analyzed (field blanks included) were below the MDL (0.022 µg/m^3 for a 24-hour sample).

Based on the results of the study which were all below the MDL, no bystander post-application inhalation exposures would be expected from volatilization following applications of paraquat to cotton in CA.

It should be noted these ambient air monitoring data have several uncertainties; the older study may not be reflective of current agricultural practices and is limited to a single geographic area and crop. Additional air monitoring studies would be necessary to make a more definitive risk finding relating to paraquat volatilization exposures. HED will continue to monitor for data to determine if further analysis is required for paraquat during Registration Review.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to paraquat and any other substances and paraquat does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that paraquat has a common mechanism of toxicity with other substances. In 2016, EPA's Office

[35] https://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/EH0201.pdf

of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[36] and conducting cumulative risk assessments (CRA)[37]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for paraquat suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

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11.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses of paraquat. The quantitative exposure/risk assessment developed for occupational handlers is based on the exposure scenarios presented in Appendix D, Table D.1.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: A summary of the maximum application rates used for the occupational handler risk assessment are presented in the Line by Line, and Maximum Use Scenario PLUS Reports as generated by BEAD. Also, the maximum application rates are presented in the summary of occupational handler exposures and risks provided in Appendix D, Table D.1.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the ORETF database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and

[36] *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

[37] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[38]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[39].

Area Treated or Amount Handled: The area treated/amounts handled are presented in Appendix D, Table D.1. The assumptions are based on guidance in the Science Advisory Council for Exposure (ExpoSAC) Policy 9.1.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). Based on the registered uses of paraquat, short- and intermediate-term exposures are expected. However, the dermal and inhalation PODs are the same for both durations; therefore, the assessment is applicable to both short- and intermediate-term exposures.

Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Results are presented starting at the lowest level of PPE consistently required on all registered labels. Paraquat product labels direct mixers, loaders, and applicators and other handlers to wear baseline clothing, chemical resistant gloves, and a NIOSH approved half-mask, PF10 respirator.

Estimates of inhalation exposure and risk for occupational handler exposure assessments consider the reduction in exposure afforded by respirators. Typically, results are presented for "baseline," defined as no respirator, and then, because they are the occupational standard in the pesticide industry, for half-face filtering facepiece or elastomeric respirators, quantified via application of their corresponding APF of 10 (90% exposure reduction). This format, in some cases along with risk estimates for engineering controls, provides a variety of options for risk management decisions.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in the supporting paraquat occupational and residential risk assessment.

Combining Exposures/Risk Estimates

Dermal and inhalation exposures have not been combined for paraquat since the effects selected for these routes of exposure are not the same.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

[38] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[39] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Inhalation exposures are the risk driver for all paraquat occupational handler exposure scenarios assessed with the exception of the mixer/loader/applicator exposure scenarios for which dermal risks are the driver. The summary of occupational handler risks is presented in Appendix D, Table D.1. Estimated occupational handler risks for paraquat are as follows:

- Mixer/loaders: assuming the currently registered level of respiratory personal protection, a NIOSH approved half-mask, APF 10 respirator, inhalation risks are of concern [i.e., the margins of exposure (MOEs) are < the LOC of 100] for 13 of 26 exposure scenarios. When considering the risk mitigation decision for these mixer/loader scenarios that requires enclosed systems, 21 of 26 remain of concern.
- Loader/applicators: assuming the currently registered level of respiratory personal protection (a NIOSH approved half-mask, APF 10 respirator), the one exposure scenario assessed results in an inhalation risk estimate of concern.
- Applicators and flaggers: assuming the currently registered level of respiratory personal protection (a NIOSH approved half-mask, APF 10 respirator for flaggers, and a closed system for applicators), inhalation risks are of concern for 19 of 26 exposure scenarios assessed.
- Mixer/loader/applicators: dermal risks are of concern for 6 of the 8 exposure scenarios assessed at the currently required level of personal protection (baseline clothing and chemical resistant gloves). Dermal risks of concern remain for all exposure scenarios (6 of the 8) assessed despite the addition of double layer clothing.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application.

11.2 Occupational Handler Biomonitoring Data Evaluation

An occupational handler biomonitoring study is available for paraquat. The study, as summarized below, was previously reviewed by HED[40] and risk estimates were previously presented using these data. In March 2000, the HED Exposure Science Advisory Committee (ExpoSAC) reviewed the study and determined it to be acceptable for use in risk assessment.

[40] T. Brennan. Review of *Paraquat: Worker Exposure During Mixing, Loading, and Application of GRAMOXONE® EXTRA to Pecans Using Vehicle-Mounted Ground Boom Equipment. MRID 43644202. D278099. 09/26/2001.*

For the purposes of characterizing the risks based on surrogate, passive dosimetry occupational handler exposure data (AHETF and PHED), the chemical-specific biomonitoring study data have been used to quantify occupational handler risks estimates from the absorbed doses measured. An ethics review of the occupational handler biomonitoring study was conducted[41], and it was concluded that, "there is no barrier in law or regulation to EPA relying on the study in its actions under FIFRA or §408 of FFDCA."

The following summarizes the occupational handler biomonitoring study, *MRID 43644202: Paraquat: Worker Exposure During Mixing, Loading, and Application of GRAMOXONE® EXTRA to Pecans Using Vehicle-Mounted Ground Boom Equipment.*

The biomonitoring study was submitted by the registrant, Zeneca Inc., to support label revisions related to personal protective equipment requirements for mixers, loaders and applicators. Paraquat formulated as GRAMOXONE® EXTRA herbicide in water was applied at a maximum application rate of 0.94 lb ai/A by groundboom spray to pecan orchards in southwestern Georgia and southeastern Alabama in September 1994. Depending on worker preference, PPE worn in the study was varied and consisted of gloves, respirator, face shield, goggles, apron, and/or Tyvek suits.

Urinary excretion of paraquat was measured as the indicator of exposure to workers who mixed, loaded, and applied the herbicide. A total of 17-combined mixer/loader/applicator monitoring units were monitored. The following samples were taken for each subject: a complete 24-hour pre-exposure urine sample, a 24-hour exposure day (Day 0) urine sample, and 24-hour urine samples on days 3 through 5. Field fortified urine samples and controls were prepared and were stored with the experimental samples. Storage stability tests showed that paraquat was stable in urine over the storage period.

Air monitoring was also conducted during mixing and loading and application of paraquat. Each subject wore two personal air sampling pumps, one for each activity. Per the study report, the raw data from air monitoring were never analyzed by the authors since the concentrations of paraquat in urine were so low.

Urinary paraquat was measured by radioimmunoassay procedure described and validated in volume one of the study (MRID 43644201). It is not clear whether laboratory fortification and control samples were run concurrently with each set of field samples. The limit of quantitation (LOQ) was 1.0 ng/ml for a 1 ml sample. The level of detection was 5 ng/ml. Urinary creatinine was measured by the Jaffe reaction and a Kone Specific Analyzer.

Application of paraquat was conducted on fifteen separate pecan farms using groundboom spray equipment mounted on open-cab tractors. GRAMOXONE® EXTRA herbicide was mixed with surfactant and water to produce 13 to 42 gallons/acre spray mixture. Workers either poured the formulated product directly into the spray tank or measured it into an open calibrated container before transferring it to the spray tank.

Although the study sponsor requested that the workers comply with label requirements for PPE, they did not interfere with the individual subject's typical practices. As a result, a wide variety

[41] M. Arling. Ethics Review of Paraquat Biomonitoring Study of Handlers Mixing, Loading, and Applying Gramoxone to Pecans via Groundboom Equipment. 10/29/2018.

of PPE was employed. For mixing and loading activities, this ranged from 9 workers wearing only baseline clothing, 4 wearing baseline clothing plus chemical resistant gloves, 3 wearing baseline clothing plus gloves and face/eye protection, and 1 worker wearing apron in addition to baseline clothing plus gloves, face/eye protection, and a half face respirator. All 17 applicators wore baseline attire, and two workers also wore Tyvek suits during application. The time spent mixing and loading ranged from 14 to 104 minutes, and the total time of exposure from 230 to 660 minutes. All activities relevant to worker exposure were reported and all workers conducted both mixing/loading and applying activities. The total amount of formulated product handled ranged from 2.9 to 27.6 gallons dependent on the type of application and field acreage. Applications were made with typical commercial application equipment, which varied from site to site.

Absorbed paraquat was estimated from the results of the biomonitoring study using a urine excretion rate of 59% (over a 7-day period) derived from a paraquat pharmacokinetics study in monkeys (MRID 00126096). The pharmacokinetics study measured urinary excretion of paraquat dichloride for 7 days following a single dose injected intramuscularly into the thighs of adult Rhesus monkeys.

The biomonitoring study results showed that 6 of the 17 urine samples collected contained detectable paraquat. All 6 samples were taken from Day 0 (day of product application) samples. Of the 6 workers with detectable paraquat exposure, none wore protective equipment while handling the formulation. There was no discernable trend between the amount of pesticide handled and the exposure incurred.

The mean unit dose calculated from the biomonitoring study was 3.6×10^{-6} mg/kg/lb ai. This value was calculated using the actual body weights of the test subjects.

Estimated Biomonitoring Risks and Characterization

The occupational handler biomonitoring data were used to estimate an internal dose reflective of exposures associated with mixing/loading and applying paraquat via groundboom spray equipment. All registered maximum groundboom application rates (0.30 – 1.5 lb ai/A) for paraquat were used to estimate a range of potential risks. The resulting MOEs for mixing/loading and applying paraquat via groundboom range from 13 to 97 where the level of concern is 100 **(**Table 11.2).

While the biomonitoring data do not result in estimated risks of concern for paraquat, there are several uncertainties related to its interpretation: 1) The study participants wore a variety of attire and personal protective clothing not reflective of currently registered labels. 2) The same participants that conducted mixing/loading activities also performed the product application, while in the deterministic assessment these activities are assessed separately. 3) The relative contribution for dermal and inhalation exposures and their relative impact to the measured urinary outputs is unclear; however, comparison of the estimated biomonitoring risks to deterministic estimates assuming the highest contribution from dermal exposures is consistent with monitoring data in available occupational handler exposure databases (i.e., PHED and AHETF). 4) The selected inhalation endpoint for paraquat is based on portal of entry effects. These uncertainties are explained in detail below.

All current registered labels require occupational handlers (mixers and loaders) to wear baseline clothing, chemical resistant gloves, a NIOSH approved half-mask respirator, as well as a

chemical resistant apron and face shield. Applicators and other handlers (other than mixers and loaders) must wear baseline clothing, chemical resistant gloves, a NIOSH approved half-mask respirator, as well as protective eyewear. Sixteen of the 17 biomonitoring study workers conducting mixing/loading activities wore less PPE than is required by current labeling (all wore baseline attire at a minimum). For the applicator activities, all 17 workers wore attire and PPE less than that currently required (12 of the 17 wore less than baseline attire). Therefore, the resulting biomonitoring data are not reflective of current practice which would likely offer greater personal protection if worn as directed by product labeling. Interpretation of the biomonitoring results cannot be attributed to any specific level of attire or PPE; rather, the data can be interpreted only as less than currently required by product labeling. Protection factors that allow for scaling exposures to increased levels of personal protection are utilized where empirical monitoring data are not available. However, given the wide variety of attire and PPE donned by study participants, scaling the resulting doses to be reflective of additional PPE would be inappropriate. Further complicating the interpretation of the biomonitoring outcomes as they relate to the occupational handler deterministic estimates, all 17 occupational handlers monitored conducted both mixing/loading and application activities. Typical deterministic risk assessments conducted for occupational handlers, including that completed for paraquat, estimate these activities individually which limits direct comparison of the findings to the deterministic risk assessment outputs. Further, the current mitigation measures being enacted for the mixers and loaders require closed-system packaging for all non-bulk (less than 120 gallons) end use product containers. Thus, the comparison of the biomonitoring risk estimates to the deterministic occupational handler estimates must also consider the deterministic risk estimates generated to reflect the mixing and loading non-bulk engineering control requirement.

The relative contribution of dermal vs inhalation exposures to the biomonitoring workers cannot be determined. Passive dosimetry monitoring for dermal exposures was not conducted. Further, while inhalation monitoring was conducted analysis of these samples was not performed since "exposures to paraquat were so low." Per the study report, "The data (urinary measures) confirm that the inhalation exposure to paraquat during both mixing, loading and application was negligible despite the fact that only one worker wore a respirator during mixing and loading and none during application." The surrogate unit exposure data recommended for use in deterministic assessment of occupational handler exposures from mixing/loading for and application activities via groundboom equipment, along with the inhalation monitoring issues above, support that the dermal route is anticipated to be the major contributor to overall exposure. Therefore, for purpose of estimating occupational handler risks from the biomonitoring data, it was assumed that dermal exposures lead to all of the measured exposures. Evaluation of the biomonitoring data was conducted based on comparison of the measured urinary excretion of paraquat (corrected using a 59% excretion rate from the above referenced study in monkeys), to the equivalent internal dose of 0.014 mg/kg/day as the dermal point of departure after adjusting for absorption (i.e., 6 mg/kg/day dermal point of departure x 0.23% dermal absorption). This approach allows for dermal risks to be calculated, though the biomonitoring study did not measure for the portal of entry effects which is the basis of the inhalation POD selected for paraquat. Occupational handler dermal and inhalation deterministic risk estimates were presented separately since the endpoints are not the same. Thus, the biomonitoring estimated risks should be compared to the dermal risks estimated for mixing/loading activities for liquid formulated products and for groundboom activities.

There is uncertainty associated with the equivalent internal dose approach in that the data sources being relied upon are from different species. That is, the dermal POD is derived from a 21-day

dermal toxicity study in rabbits; the DAF is derived from an *in vivo* study conducted in humans; and the metabolic study used to back calculate internal dose in the biomonitoring study was conducted in monkeys. Despite these species differences and the associated uncertainties across species, these are the best available data.

There is also uncertainty associated with the reverse dosimetry approach to derive an internal POD to compare the bio-monitored doses for quantification of risk. The use of the DAF applied to an external dose to estimate the equivalent internal dose may over or under estimate potential worker exposures but is consistent with the assumption that dermal exposures are the drivers. Additionally, the use of the chronic dietary POD was also considered for quantitation of risk estimates with use of the biomonitoring data. However, this approach may underestimate risks. The chronic dietary POD is based on an external dose administered via gavage. Oral absorption of paraquat is estimated to be low in mammals thus the external dose and internal dose cannot be assumed equivalent. It would, therefore, not be appropriate to compare the external dose used to derive the chronic dietary POD to the unit dose calculated using the urinary measures from the biomonitoring study because the urinary data reflect the internal, systemic paraquat concentration in the workers.

Table 11.2. Estimated Occupational Handler Risks with Use of Biomonitoring Data

Exposure Scenario	Unit Dose (mg/kg/lb cation)	Equipment Used / No. Of Observations	Clothing Scenario Monitored	Application Rate (lb ai/acre)	Area Treated Daily (acres)	Total Daily Dose [a] (mg/kg/day)	MOE [b]
Ground Application	3.60E-06	Open Cab Tractor / 17	9 reps no PPE worn; 4 reps gloves worn only when mixing; 2 reps gloves, face shield, and apron, 1 rep respirator, face shield, goggles, apron, gloves, and Tyvek for applying; 1 rep face shield, goggles, apron, gloves, and Tyvek for applying	1.5	200	0.0011	13
				1.0	200	0.00072	20
					80	0.00029	48
				0.94	80	0.00027	52
				0.80	200	0.00058	24
					80	0.00023	61
				0.60	80	0.00017	81
				0.50	200	0.00036	39
					80	0.00014	97
				0.30	200	0.00022	65

a. Total Daily Dose (mg/kg/day) = Unit Dose (mg/kg/lb ai) x appl rate (lb ai/A) x acres per day.
b. MOE = Equivalent Internal Dose (mg/kg/day) / Total Daily Dose (mg/kg/day). Where: Equivalent Internal Dose = 0.0014 mg/kg/day. LOC is an MOE = 100.

11.3 Occupational Post-Application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.3.1 Occupational Post-Application Dermal Exposure/Risk Estimates

HED collaborated with BEAD for the evaluation of the potential for, and types of, occupational post-application exposures from paraquat usage.[42] Based on input from BEAD it was determined that the likelihood of paraquat occupational post-applications exposures is dependent on whether applications are "broadcasted" or "directed". Broadcast applications of paraquat are applied directly to the crop for foliage desiccation (to the crop and any weeds in the field) to expedite harvest and reduce seed loss upon harvest. Therefore, occupational post-application exposures are expected for broadcast applications and have been assessed. Per BEAD, at this late stage of the crops, scouting to make sure the application was effective would be the only activity conducted since all crops assessed are generally mechanically harvested. Additionally, HED expects cotton mechanical harvest activities to result in the potential for post-application worker exposures.

Directed spray applications of paraquat are targeted for control of individual weeds and grasses. Such applications are made with the intent of minimizing the risk of injuring the crop and/or non-target vegetation which are not tolerant of directed applications. Since these applications are not expected to result in foliar residues on the crop and/or non-target vegetation, occupational post-application exposures are not likely for directed applications and have not been assessed.

Occupational Post-Application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed below on an individual basis.

Exposure Duration : HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. For paraquat, based on the registered uses, short- and intermediate-term exposures are expected. However, the POD for dermal exposures is the same for both durations; therefore, the assessment is applicable to both short- and intermediate-term exposures.

Transfer Coefficients : It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[43]" which, along with additional information about the ARTF data, can be found at the Agency website[44].

Scouting Transfer Coefficient: On November 1, 2018, the HED ExpoSAC discussed occupational post-application exposures to desiccated crops and whether the associated post-application activities and exposures would be significant. A proposal to reduce the scouting activity transfer coefficient (TC) for reentry into fields with desiccated commodities was discussed. Several factors were considered in the discussion, including: the likelihood of

[42] William Chism (BEAD). Personal email communication, 07/5/2018. Subject: Re: Paraquat Post-Application Crops/Activities Input Needed.
[43] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[44] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

scouting exposures for paraquat; exposures expected for defoliants vs desiccants; residue availability following paraquat application and commodity desiccation; and the surrogate TCs associated with scouting activities.

Likelihood of Scouting Exposures for Paraquat
A chemical-specific occupational post-application biomonitoring study in cotton was previously reviewed by HED.[45] The study, which monitored workers conducting scouting activities, was conducted by the registrant as a worst-case representation of worker activities following paraquat application: "This exposure study was representative of the normal work pattern of the crop consultant during inspection of cotton following paraquat application as a harvest aid and ensured that the timing of dermal exposure and absorption was as representative as possible."[46] Study scouting activities consisted of walking 100 feet into the field, handling and attempting to crack a few bolls, bending foliage and stems, and then crossing three or four rows and exiting the field. The subjects spent 15 minutes in the field and 15 minutes out and then proceeded in another untouched area of the field for a total of 10 trips into the field or 2.5 hours of field exposure and 2.5 hours of between field activities. The selection of scouting activities by the registrant is consistent with preliminary information provided by BEAD relating to the use pattern and is thought to represent typical scouting activities following paraquat application. However, it is unclear whether scouting practices have changed significantly from the time of the biomonitoring study, 1994, to present.

As described above, BEAD indicated that scouting activities for all applicable crops and mechanical harvesting for cotton would likely occur following broadcast application of paraquat as a harvest aid/desiccant to make sure the application was effective. BEAD provided additional information[47] that these scouting activities could be conducted without spending a lot of time in the field and scouting for cotton boll opening could occur either in the field or from a vehicle if the leaf desiccation had occurred quickly. Further, BEAD provided a reference[3] that described that crops treated with paraquat could experience leaf desiccation in the range of 5 to 7 days; thus, reducing the potential for exposures to foliage treated with paraquat.

Exposures Expected for Defoliants vs. Desiccants
A previous meeting of the ExpoSAC resulted in the determination that post-application assessment of scouting was not required for commodities treated with a defoliant. The July 1, 2004 ExpoSAC Meeting Minutes state, "The scouting that follows defoliant application would consist only of looking at the plants from a distance to see if the leaves are falling off and does not involve a typical scouting exposure. REI calculations are not needed for these exposures." This determination was discussed in the November 1, 2018 ExpoSAC meeting; specifically, how it should be interpreted for the assessment for paraquat which is a desiccant. A defoliant is a chemical which causes leaves to drop from plants by resulting in more rapid development of abscission layers. In contrast, desiccants are chemicals used to hasten harvest by accelerating the drying of plant tissues. With desiccants, leaves are often cleaned from the seeds or plants following harvest since these have not been abscised from the plant. Further, a link provided in a BEAD email communication (http://ipm.ucanr.edu/PMG/r114800111.html) provided the

45 T. Manville. Review of Paraquat Worker Reentry Biomonitoring Study. D215539. 02/05/1996.
46 T. Iwata. Worker Exposure During Re-Entry into Paraquat-Treated Cotton Fields; Biological Monitoring in Georgia in 1994. MRID 436182-02. 3/29/95.
47 Caleb Hawkins. Personal email communication, 11/16/2018. Subject: RE: HED Paraquat Post-Application Activity Inquiry, Cont'd.

following information relating to paraquat usage in cotton: "PARAQUAT COMMENTS: Considered a desiccant because at label rates it rapidly desiccates leaves and can cause them to stick to the plants rather than to abscise. Used to help open mature bolls by causing direct injury but is not generally applied as a desiccant until after 80% or more of bolls are open because it can prevent further boll development and opening if applied too early." Since paraquat is not particularly effective at leaf abscission, it is likely that the desiccated leaves can remain on the plant; thus, resulting in the potential for paraquat exposures from scouting activities.

Residue Availability Following Paraquat Application

Typically, HED determines measures of available residue on treated commodities through evaluation of submitted chemical-specific dislodgeable foliar residue (DFR) data. Chemical-specific dislodgeable foliar residue data have not been submitted for paraquat. Therefore, the potential for paraquat residues on treated commodities remains an uncertainty. However, since it is likely that the desiccated leaves remain on the plant, there is the potential for paraquat residues to remain on foliar surfaces. In the absence of DFR data, and the potential for residues to remain, HED evaluated available field trial data for paraquat residues on desiccated commodities and determined residues are present up to 3-4 weeks following application. Residues were detectable in the following commodities/PHIs: undelinted cotton seed up to 14 day PHI; cotton gin byproducts at 3 day PHI; wheat grain up to a 10 day PHI; wheat hay up to a 43 day PHI; heat forage up to a 41 day PHI; soybean seed up to a 17 day PHI; soybean hay up to a 43 day PHI; and soybean forage up to a 53 day PHI. Field trial data are not typically used for quantitative assessment of occupational post-application exposures and risks since these data represent residues available in/on the plant and, therefore, potentially overestimate the foliar residues to which a worker would be exposed. However, these data confirm the presence of paraquat residues in desiccated commodities and were considered relevant for qualitative characterization of potential occupational post-application exposures.

TCs Associated with Scouting Activities

The TCs recommended for occupational post-application scouting activity assessments are 210 and 1,100 and are based on exposure studies conducted in non-desiccated fields and represent significant foliar contact to the treated foliage. For the 1,100 TC, study participants walked through high density, 3-6 foot crops of beans, corn, and peas touching and pulling leaves. The 210 TC is based on scouting activities in less dense crops of cotton and tomatoes. Since the leaves of commodities treated with paraquat desiccate, but don't abscise from the plant, post-application foliar exposures are expected. However, the levels of potential paraquat exposure derived from using TCs generated from exposure studies conducted in higher density crops are conservative, particularly for the highest of the TCs, 1,100.

Conclusion

The ExpoSAC evaluated all lines of evidence presented and determined 1) scouting activities are likely following paraquat usage 2) as a desiccant, there is the potential for foliar contact following application 3) paraquat residues are likely present on previously treated commodities and 4) the higher surrogate scouting TC of 1,100, which represents activities in high density crops, likely overestimates the exposures from scouting activities in desiccated commodities. Ultimately, the ExpoSAC recommended that the lower scouting TC, 210, be used exclusively since it allows for a more reasonable, albeit health protective, estimate of the anticipated post-application exposures following paraquat application.

Sunflower Scouting Transfer Coefficient: A default TC of 90 is recommended for sunflowers. This TC is considered unique since it is applicable only to sunflowers and is the only hairy leaf crop to which paraquat is applied. Therefore, HED recommends the default TC of 90 be used for assessment of scouting exposures in sunflowers following paraquat usage.

Mechanical Cotton Harvest Transfer Coefficients: The recommended mechanical cotton harvest TCs were recently reviewed due to the submission of summary information from a 2016 survey by the National Cotton Council[48] and an October 18, 2018 meeting with OPP and the National Cotton Council. The summary of the survey was submitted as a response to public comments for Registration Review of the active ingredient, cypermethrin, to make the case that the use of trailers for harvesting cotton had become obsolete, indicating that tramping cotton should no longer be included as a worker activity in cotton harvest post-application assessments. Due to the timing of the submission and the potential implications for cotton harvest post-application assessment for other active ingredients, this issue was also considered for paraquat. The submitted summary information presents the results from a national survey of cotton mechanical harvest practice, specifically the transition from conventional harvest activities for cotton (mechanically or manually packed trailers), to the newer round mini module harvesters. The survey results as presented in the submitted comment are as follows including a summary graph:

"A survey was sent to 436 cotton ginning operations inquiring how cotton was delivered to the gin from fields. A total of 152 responses were received and were summarized by region of operation. The survey shows high adoption of new harvest technology utilizing round bale or mini module cotton harvesters (% Rd/Mini Mod). Many still utilize the conventional module builders that are mechanically packed (% Conv. Mod). For the U.S. cotton crop, the wagon or trailer transport method (% Trailers) is only used for a very small percentage of cotton and most cotton transported in trailers is not packed. The manual packing method is used by a few producers on a very small number of bales.

According to survey respondents (n=152):

- 0.17% of the harvested cotton is transported in trailers in the Southeast
- 0.29% of the harvested cotton is transported in trailers in the Midsouth
- 0.01% of the harvested cotton is transported in trailers in the Southwest
- 0.16% of the harvested cotton is transported in trailers in the West.

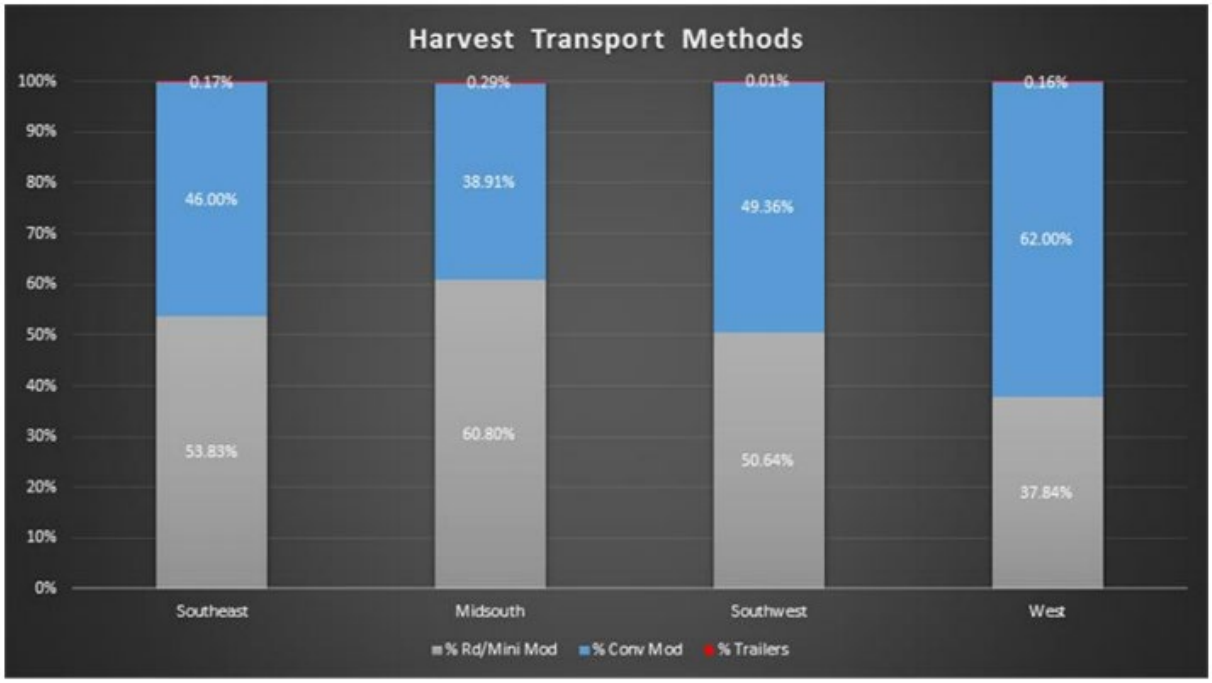
Of the 0.17% of cotton transported in trailers in the Southeast, 18.57% is manually packed and 81.43% is not packed. Of the 0.29% of cotton transported in trailers in the Midsouth, 20% is mechanically packed and 80% is not packed. In the Southwest and West regions, no cotton transported in trailers is packed. The Southeast was the only region reporting the use of trailers combined with manual packing of harvested cotton.

Applying the survey results from 2016 production to determine an estimate of manually packed seed cotton at harvest yields: 3,891,000 total bales produced in the Southeast in 2016 with 0.17% transported in trailers = 6,615 bales originally transported in trailers. 18.57% of those 6,615 bales manually packed = 1,228 bales manually packed (which would likely be lower if weighting was applied). Therefore 1,228/16,524,000 (total U.S. production in bales of ginned lint) =

[48] Steve Hensley. Response: Docket ID Number EPA-HQ-OPP-2012-0167. 4/30/2018.

0.00743% of total U.S. cotton production was transported in trailers to the gin that were manually packed."

National Cotton Council
December 2016 Gin Survey of Harvest Transport Practices.



Similar to HED's policy relating to the assessment of occupational handler exposures and risks for human flaggers, which has also become an outdated practice, HED matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED will continue to present quantitative risk estimates for tramping cotton, we acknowledge that cotton harvest practice is moving increasingly toward the newer round mini module harvesters and use of trailers is becoming obsolete. Further, while HED expects that the round mini module harvesters will potentially result in a reduced potential for post-application exposures: 1) the TCs derived from the conventional harvest methods are the only exposure data available for assessment of these activities and HED will continue to rely on these data; 2) although < 1% of all cotton harvested nationally is manually packed, the potential remains for manual tramping of cotton; and 3) although the mini module harvesting technique is becoming more regularly used, the 2016 survey results suggest that the number of national respondents using the mini module vs conventional harvest techniques is approximately equivalent (i.e., 40 - 60% reporting use of either dependent upon the area of the country surveyed). Following the October 18, 2018 meeting with the National Cotton Council, HED provided information relating to cotton harvest post-application risk assessment and identified the need for exposure data specific to harvest activities with the round mini module and requested the raw survey data to be formally submitted in order to confirm the summary information provided. The Agency will continue to engage the National Cotton Council and monitor all available information sources, including any new exposure or survey data, to best assess and characterize the cotton harvest post-application harvest exposure potential.

Application Rate: The application rates used in the assessment are presented in the Line by Line, and Maximum Use Scenario Pesticide Label Usage Summary (PLUS) Reports as generated by BEAD.

Exposure Time: The average occupational workday is assumed to be 8 hours.

Dislodgeable Foliar Residues: Chemical-specific dislodgeable foliar residue data have not been submitted for paraquat. Therefore, this assessment uses HED's default assumption that 25% of the application is available for transfer on day 0 following the application and the residues dissipate at a rate of 10% each following day.

In the absence of chemical-specific DFR data, EPA uses default values. The *2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* includes an analysis of a number of DFR studies, which resulted in the selection of a revised default values for the fraction of the application rate available for transfer after a foliar application (F_{AR}). These values are based on an analysis of 19 DFR studies. Since that time, the Agricultural Re-entry Task Force has submitted information (MRID 49299201) that corrects an application rate error made in the original submission of "ARF039 – Determination of Dermal and Inhalation Exposure to Reentry Workers During Chrysanthemum Pinching in a Greenhouse" (EPA MRID 45344501). As a result, the range of F_{AR} values was revised from 2% - 89% to 2% - 47%. In the data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient; formulation; field conditions in the studies; weather conditions (e.g., humidity); or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in F_{AR} values is not expected when considering DFR data for a single chemical. At this time, the ARTF submission did not alter the selection of 25% as the reasonable, high-end default value. Because DFR data are not available for paraquat, EPA is using the default value of 25%. Although there may be a small degree of uncertainty in the use of the default DFR value (i.e., there is a small chance that the F_{AR} value may exceed the applicable default value), it is likely that the health-protective aspects of EPA's occupational post-application assessment methodology will more than compensate for this potential uncertainty. For example, when assessing residential and occupational post-application exposure to gardens and ornamentals, EPA assumes the following: exposures occur to zero-day (i.e., day of application) residues every day of the assessed exposure duration (i.e., EPA assumes that no dissipation or degradation occurs, it doesn't rain, etc.); individuals perform the same post-application activities performed in the transfer coefficient study day after day (e.g., weeding, harvesting, pruning, etc.); and individuals engage in these post-application activities for a high-end amount of time every day (represented by data reflecting time spent gardening based on survey data). Given these conservatisms and their potential compounding nature, EPA can rely upon the calculated exposure estimates with confidence that exposure is not being underestimated.

The highest estimated occupational post-application exposure using default DFR values is not minimal in comparison to the level of concern (i.e., the calculated MOE is not greater than 2 times higher than the level of concern, MOE = 68 compared to the LOC of 100); therefore, HED is recommending that DFR data (Guideline # 875.2100) be required to facilitate any necessary exposure assessment refinements and to further EPA's general understanding of the availability of dislodgeable foliar pesticide residues.

During cotton harvesting and scouting activities workers are expected to contact residues on cotton bolls directly for which a "dislodgeable boll residue (DBR)" study would be required to refine occupational post-application risks estimated for the crop. These chemical- and crop-specific data are unique; DFR data for other crops cannot be used as a surrogate in the absence of a DBR study. A DBR study should be conducted in accordance with Guideline # 875.2100.

Biomonitoring Exposure Data

An occupational post-application biomonitoring study available for paraquat was previously reviewed by HED.[49] These data are not used for occupational post-application risk quantitation due to human ethics concerns relating to a 17-year-old study participant.[50] "Under §26.1703, EPA is prohibited from relying on research involving intentional exposure to human subjects who are pregnant women (and therefore, their fetuses), nursing women, or children. Children are persons under 18 years old. This study falls within that category." Therefore, HED does not rely on this biomonitoring study as a part of the paraquat occupational post-application quantitative exposure and risk assessment.

Occupational Post-Application Non-Cancer Dermal Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in the occupational and residential exposure assessment that supports this document.

Occupational Post-Application Non-Cancer Dermal Risk Estimates

Occupational post-application exposure and risks estimated for scouting activities are not of concern (i.e., an MOE ≥ 100) on the day of product application for all crops assessed except for alfalfa. For alfalfa, reentry risks are not of concern 4 days following product application. Cotton post-application risks are not of concern 11 days following application for the mechanical harvesting activity, module builder; not of concern 20 days following application for the mechanical harvesting activities, picker operator and raker; and not of concern 27 days following application for the mechanical harvesting activity, tramper. The summary of the anticipated post-application activities and associated transfer coefficients for the registered crops/use sites is presented in Table 11.3.1.

Table 11.3.1. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for Paraquat

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	Application Rate	DFR/DBR[1]	Dermal Dose (mg/kg/day)[2]	MOE on Day 0[3]	DAT[4]
Alfalfa	Scouting	210	1.5	4.2	0.088	**68**	4
Guar, Lentils			1.0	2.8	0.059	100	0
Corn, field			1.0	2.8	0.059	100	0
Corn, pop			1.0	2.8	0.059	100	0
Cotton			1.0	2.8	0.059	100	0
	Harvesting, Mechanical, Module Builder Operator	900		2.0	0.18	**33**	11

[49] T. Manville. Review of Paraquat Worker Reentry Biomonitoring Study. D215539. 02/05/1996.
[50] M. Arling. Ethics Review of Paraquat Biomonitoring Study (MRID 43618202). 12/11/2018.

Table 11.3.1. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for Paraquat							
Crop/Site	**Activities**	**Transfer Coefficient (cm^2/hr)**	**Application Rate**	**DFR/DBR[1]**	**Dermal Dose (mg/kg/day)[2]**	**MOE on Day 0[3]**	**DAT[4]**
	Harvesting, Mechanical, Picker Operator	2,400			0.48	**13**	20
	Harvesting, Mechanical, Raker	2,400			0.48	**13**	20
	Harvesting, Mechanical, Tramper	5,050			1.0	**5.9**	27
Grasses Grown for Seed	Scouting	210	1.0	2.8	0.059	100	0
Forage Crop			1.0	2.8	0.059	100	0
Clary, Sage			0.80	2.2	0.047	130	0
Peanut			1.0	2.8	0.059	100	0
Potato			1.0	2.8	0.059	100	0
Soybean			1.0	2.8	0.059	100	0
Sugarcane			1.0	2.8	0.059	100	0
Sunflower		90	1.0	2.8	0.025	240	0

1 DFR = Application Rate (lb ai/A) × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.25 and D = 0.10 per day
DBR = Application Rate (lb ai/A) × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 2 and D = 0.10 per day
2 Daily Dermal Dose = [DFR/DBR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (80 kg).
3 MOE = POD (6 mg/kg/day) ÷ Daily Dermal Dose.
4 DAT = Day after treatment/application for MOE to be greater than the LOC (100).

Restricted Entry Interval

Paraquat acute toxicity is low via the dermal route (Toxicity Category III) and not irritating to the skin (Toxicity Category IV); however, it is severely irritating to mucous membranes (Toxicity Category I for eye irritation). It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2), active ingredients classified as Acute I for acute dermal, eye irritation and primary skin irritation are assigned a 48-hour REI. Therefore, the currently labeled REIs which range from 12 to 24 hours do not comport with 40 CFR 156.208 (c) (2) requirements. Further, the number of days required for estimated post-application risks associated with paraquat usage estimated for reentry range from 0 to 27 days and may require revision of the labeled REIs to address these concerns.

11.3.2 Occupational Post-Application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e.,

flux studies, route-specific inhalation toxicological studies) or further analysis is required for paraquat.

12.0 Public Health Incident Data Review

E. Evans and S. Recore. Paraquat: Tier II Human Incidents Report. D446902. 07/25/2018.

HED performed an updated Tier II review of human incidents for paraquat using the following sources: OPP Incident Data System (IDS); and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR); the Agency-sponsored National Pesticide Information Center (NPIC); and California's Pesticide Incident Surveillance Program (PISP) databases.

Paraquat is highly acutely toxic when inhaled or ingested. HED found that the acute health effects reported to the incident databases queried are consistent across the databases. These health effects primarily include dermal, ocular, and neurological effects. HED did not identify any aberrant effects outside of those anticipated.

Most incidents were classified as low to moderate severity. The effects reported were generally mild/minor to moderate and resolved rapidly. However, high severity incidents and deaths did occur due to accidental ingestion, exposure, and misuse.

Across the databases reviewed, the majority of paraquat incidents were occupational exposure accidents which occurred during application or handling - primarily from leaks/spills/splashes or equipment malfunctions. Dermal symptoms were the most frequently reported symptoms among cases including: welts, hives, peeling skin, chemical burns, swelling, blisters, lesions; followed by ocular symptoms, including: blurred vision, ocular pain, chemical conjunctivitis, corneal abrasion, vision problems

Main IDS 2012-2018 identified 63 paraquat incidents. 81% were moderate severity (systemic health effects). Also, five were bystander exposures (drift). Four paraquat deaths & four high severity incidents were also identified: two severe applicator/handler accidents, two fatal accidental ingestions, and four intentional harm cases (2 suicides, one attempted suicide, and one malicious poisoning attempt)

SENSOR-Pesticides (aggregate data through 2014) found 140 paraquat case reports; most cases were occupational and involved applying, mixing/loading or repairing equipment when exposed. Many cases involved PPE issues, including spray/splash getting into eyes although wearing safety glasses. Many cases involved application equipment failures, including backpack leaks. Many cases were not adequately trained when applying under supervision, but these cases are not a violation of federal requirements as the new safety requirements are not yet in effect.

Finally, a review of paraquat incidents for trend over time in IDS was conducted. The number of paraquat incidents reported to IDS from 2008 to 2017 has remained relatively constant. There has been an average of 22 paraquat incidents (ranging from a low of 15 incidents to a high of 32 incidents) reported to IDS per year over the last 10 years.

13.0 References

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J. Lin. Review of Jar Test Results for Drinking Water Assessment Purpose. D396402. 01/10/2012;

E. Evans and S. Recore. Paraquat: Tier II Human Incidents Report. D446902. 07/25/2018.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food uses for paraquat are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Toxicology Data Requirements for Paraquat Food Use Registrations

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	no[1]	--
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	CR	--
870.3465	90-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	waived[2]	yes[2]
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes[3]
870.4100b	Chronic Toxicity (nonrodent)	no	--
870.4200a	Oncogenicity (rat)	yes	yes[3]
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes[3]
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	--
870.6100b	90-Day Neurotoxicity (hen)	no	--
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Develop. Neurotoxicity	no	--
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes

[1]Subchronic oral exposure in rodents was evaluated in the developmental, reproduction, and chronic/oncogenicity rodent guideline studies. Consequently, a separate oral subchronic study is not required.
[2]Recommended for a waiver by HASPOC (TXR 0056294, K. Rury, 04/12/2012).
[3]Chronic toxicity (rat) and Oncogenicity (rat) study requirements were satisfied by the combined Chronic/ Oncogenicity study in rats.
CR = conditionally required

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Paraquat Dichloride			
Guideline No./Study/Species/Strain	**MRID/TXR #/Purity/Classification**	**Results**	**Toxicity Category**
870.1100 Acute oral (rat) Alpk:APfSD SPF Wistar rats	43685001 (1994) TXR 0011944 33.0% paraquat **Acceptable**	**Male LD_{50}** = 344 mg/kg[1] **Female LD_{50}** = 283 mg/kg[1]	II
870.1200 Acute dermal (rat) Alpk:APfSD SPF Wistar rats	43685002 (1994) TXR 0011944 33% paraquat dichloride **Acceptable**	**Male/Female LD_{50}** > 2000 mg/kg	III
870.1300 Acute inhalation (rat) Alderley Park SPF rats	00046105 (1968) TXR 0000248 Crystalline Paraquat Cl_2	**Male/Female LC_{50}** = 1 µg paraquat ion/L[2]	I[3]
870.2400 Eye irritation (rabbit) NZ White rabbits	43685004 (1994) TXR 0011944 33.0% paraquat ion **Acceptable**	Moderate to severe irritation	II
870.2500 Dermal irritation (rabbit) NZ White rabbits	43685004 (1994) TXR 0011944 33.0% paraquat ion **Acceptable**	Minimal irritation	IV
870.2600 Skin sensitization	43685005 (1994) TXR 0011944 **Acceptable**	Negative	N/A

[1] LD50 values are reported based on mg paraquat dichloride technical product. Assuming the purity is referring to paraquat cation, the male and female LD_{50} values are 114 and 93 mg paraquat ion/kg, respectively.
[2] Estimated by the study authors. Results are supported by 2005 study conducted with technical paraquat dichloride (0.36 µg paraquat ion/L< **Female LC_{50}** <2.49 µg paraquat ion/L; MRID 48877203)
[3] Reviewer for this study did not determine a Toxicity Category or provide a classification; however, the estimated LC_{50} falls into Toxicity Category I. This is supported by the conclusions of MRID 48877203 that paraquat dichloride technical is Toxicity Category I for acute inhalation.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.3150 90-Day oral toxicity (dog) Beagle dogs	00072416 (1981) TXR 0053747 **Acceptable/ Guideline** 32.2% w/w paraquat ion 0, 0.2, 0.5, 1.5, 3 mg paraquat ion/kg/day via diet for 13 weeks	NOAEL = 0.5 mg paraquat ion/kg/day LOAEL = 1.5 mg paraquat ion/kg/day based on increased lung weight and incidence of alveolitis in both sexes. *Maximum tolerated dose was exceeded at 3 mg/kg/day
870.3200 21-Day dermal toxicity (rabbit) NZ White rabbits	00156313 (1986) TXR 0057886 **Acceptable/ Guideline** 43.5% w/w paraquat ion 0, 0.5, 1.15, 2.6, 6 mg paraquat ion/kg/day applied 6 hrs/day, 7 days/week over a 21-day period	Systemic NOAEL = 6 mg paraquat ion/kg/day (HDT) Systemic LOAEL = not established Dermal NOAEL = 1.15 mg paraquat ion/kg/day Dermal LOAEL = 2.6 mg paraquat ion/kg/day based on small scabs at the treatment site in both sexes, and epidermal erosion/ulceration, surface exudation, acanthosis, and inflammation in males
870.3465 21-Day inhalation toxicity SD rats	00113718 (1979) TXR 0053747 **Acceptable/Guideline** 40% w/v paraquat ion 0, 0.01, 0.1, 0.5, 1.3 µg paraquat ion/L, whole body for 6 hrs/day, 5 days/week for 3 weeks	NOAEC = 0.01 µg paraquat ion/L LOAEC = 0.1 µg paraquat ion/L based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx *Mortality at 1.3 µg paraquat ion/L
870.3700a Prenatal developmental (rat) Alderly Park Wistar-derived (Alpk:SPF SD) rats	00113714 (1978) TXR 0057886 **Acceptable/ Guideline** 38% w/v paraquat ion 0, 1, 5, 10 mg paraquat ion/kg/day via gavage on gestation day 6 through 15, inclusive	Maternal NOAEL = 1 mg paraquat ion/kg/day Maternal LOAEL = 5 mg paraquat ion/kg/day based on mortality, clinical signs of toxicity (piloerection, thin and hunched appearance, croaking), and decreased body weight gains. Developmental NOAEL = 1 mg paraquat ion/kg/day Developmental LOAEL = 5 mg paraquat ion/kg/day based on slightly decreased fetal body weights and on delayed ossification.
870.3700a Prenatal developmental (rat) Alderly Park Wistar-derived (Alpk:SPF SD) rats	43964701 (1992) TXR 0053747 **Acceptable/ Guideline** 38.2% w/v paraquat ion 0, 1, 3, 8 mg paraquat ion/kg/day via gavage on gestation day 7 through 16, inclusive	Maternal NOAEL = 8 mg paraquat ion/kg/day Maternal LOAEL = not established Developmental NOAEL =8 mg paraquat ion/kg/day Developmental LOAEL = not established

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.3700a Prenatal developmental (mouse) SPF Alderley Park mice	00096338 (1978) TXR 0053747 **Acceptable/ Guideline** 38% w/v paraquat ion (100% paraquat dichloride) 0, 1, 5, 10 mg paraquat ion/kg/day via gavage on gestation days 6-15, inclusive	Maternal NOAEL = 1 mg paraquat ion/kg/day Maternal LOAEL = 5 mg paraquat ion/kg/day based decreased maternal body weight gain. Developmental NOAEL = 10 mg paraquat ion/kg/day Developmental LOAEL = not established
870.3700a Prenatal developmental (mouse) Crl:CD-1 (ICR) BR mice	43949902 (1992) TXR 0053747 **Acceptable/ Guideline** 38.2% w/v paraquat ion 0, 7.5, 15, 25 mg paraquat ion/kg/day via gavage on gestation days 6-15, inclusive	Maternal NOAEL = 15 mg paraquat ion/kg/day Maternal LOAEL = 25 mg paraquat ion/kg/day based on mortality, clinical signs of toxicity, decreased body weights, and body weight gains, increased lung weights, and gross lesions in the lung Developmental NOAEL = 15 mg paraquat ion/kg/day Developmental LOAEL = 25 mg paraquat ion/kg/day based on retardation of the skeleton and decreased fetal body weights
870.3700b Prenatal developmental (rabbits) NZ White rabbits	49009505 (1991) TXR 0056764 **Unacceptable** 33.6% w/w paraquat ion 0, 1, 1.5, 2 mg paraquat ion/kg/day via gavage on gestation days 7 through 19, inclusive	Study was not conducted in compliance with GLP, no Quality Assurance statement was provided, and no individual data were provided.
870.3700b Prenatal developmental (rabbits)	Recommended to be waived by HASPOC (TXR 0056294)	
870.3800 Reproduction and fertility effects (rats) Wistar-derived Alderley Park rats	00126783 (1982), 00149749, 00149748 (1985) TXR 0053747 **Acceptable/ Guideline** 32.7% w/w paraquat ion 0, 1.25, 3.75, 7.5 mg paraquat ion/kg/day administered via diet	Parental NOAEL = 1.25 mg paraquat ion/kg/day Parental LOAEL = 3.75 mg paraquat ion/kg/day based on increased incidences of alveolar histiocytes in both sexes. Offspring NOAEL = 7.5 mg paraquat ion/kg/day Offspring LOAEL = not established *sporadic evidence of histopathology lesions in offspring were observed at 7.5 mg paraquat ion/kg/day, but due to the sample analysis methods it could not be determined if they were treatment related. These lesions were not observed at dose levels that impact the paraquat risk assessment; therefore, the DER for this study was not updated. Reproduction NOAEL = 7.5 mg paraquat ion/kg/day Reproduction LOAEL = not established

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.4100a Chronic toxicity (rat)	See 870.4300	
870.4100b Chronic toxicity (dog) Beagle dogs	00132474 (1983) TXR 0053747 **Acceptable/ Guideline** 32.2% w/w paraquat ion M: 0, 0.45, 0.93, 1.51 mg paraquat ion/kg/day F: 0, 0.48, 1, 1.58 mg paraquat ion/kg/day via diet for 52 week	NOAEL = 0.45 mg/kg/day in males and 0.48 mg/kg/day in females LOAEL = 0.93 mg/kg/day in males and 1 mg/kg/day in females based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males
870.4200 Carcinogenicity (mouse) Swiss-derived mice	00059727, 00087924 (1981) TXR 0053747 **Acceptable/ Guideline** 32.7% w/w paraquat ion (44.6% w/w paraquat dichloride) 0, 0 (2nd control), 1.9, 5.6, 15.0/18.8 mg paraquat ion/kg/day administered via diet for 99 weeks *Doses estimated by reviewers	NOAEL = 1.9 mg paraquat ion/kg/day LOAEL = 5.6 mg paraquat ion/kg/day based on decreased body weights and food consumption in females, and increased incidences of renal tubular necrosis, tubular dilation, and interstitial nephritis in males *No evidence of increased tumor incidence when compared to controls
870.4200 Carcinogenicity (mouse) JCL:ICR mice	40202403 (1982) TXR 0053747 **Acceptable/ Guideline** 98% paraquat dichloride (% paraquat ion not reported) 0, 0.3, 1.5, 4.5, 15 mg /kg/day administered via diet for 104 weeks *Doses estimated by reviewers	NOAEL = 4.5 mg/kg/day LOAEL = 15 mg/kg/day based on reduced survival (females) *No evidence of increased tumor incidence when compared to controls

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.4300 Combined chronic toxicity/carcinogenicity (rats) Fischer 344 rats	00138637 (1983), 00153223 (1985), 40202401, 40202402 (1987), 41317401 (1989) TXR 0053747 **Acceptable/ Guideline** 32.7% w/w paraquat ion (96.1% paraquat dichloride) 0, 0 (2nd control), 1.25, 3.75, 7.5 mg paraquat ion/kg/day administered via diet for 117 weeks in males and 124 weeks in females *Doses estimated by reviewers	NOAEL = 1.25 mg paraquat ion/kg/day LOAEL = 3.75 mg paraquat ion/kg/day based on ocular opacity in females corroborated by microscopic lenticular changes.
870.4300 Combined chronic toxicity/carcinogenicity (rats) Wistar rats	40218001 (1982) TXR 0053747 **Acceptable/ Guideline** 98% paraquat dichloride (% paraquat ion not reported) M: 0, 0.25, 1.26, 4.15, 12.25 mg/kg/day F: 0, 0.3, 1.5, 5.12, 15.29 mg/kg/day administered via diet for 104 weeks	NOAEL = 4.15 mg/kg/ day in males and 5.12 mg/kg/day in females LOAEL = 12.25 mg/kg/day in males and 15.29 mg/kg/day in females based on mortality
870.5100 *Gene Mutation* Bacterial reverse mutation *Salmonella typhimurium* TA98, 100, 1535, 1537, 1538	00100440 (1977) TXR 0053747 **Acceptable/ Guideline** 99.9 % paraquat dichloride 0-1000 µl/plate - /+ S9	**No evidence of induced mutant colonies over background** up to cytotoxic concentrations (≥100 µl/plate - /+ S9)
870.5100 *Gene Mutation* Bacterial reverse mutation *Salmonella typhimurium* TA98, 100, 1535, 1538	00100441 (1977) TXR 0053747 **Acceptable/ Guideline** 99 % paraquat dichloride 0-5000 µl/plate - /+ S9	**No evidence of induced mutant colonies over background** up to cytotoxic concentrations (≥500 ug/plate).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.5375 *Cytogenetics* *In vitro* mammalian cell chromosomal aberration assay Human peripheral blood lymphocytes	00152692 (1985) TXR 0053747 **Acceptable/ Guideline** 99.6% paraquat dichloride 0.75 - 3500 µg/mL -/+ S9 for 3 hours with a 25 hour recovery period	Increases in aberrant cells only observed at cytotoxic concentrations in presence and absence of S9-activation
870.5385 *Cytogenetics* Mammalian bone marrow chromosomal aberration test (rat) Wistar rats	40202405 (1987) TXR 0053747 **Acceptable/ Guideline** 33.0% w/w paraquat ion 0, 15, 75, 150 mg paraquat ion/kg via oral gavage	**No evidence of chromosome aberration induced over background**
870.5450 *Other Geneotoxicity* Dominant lethal assay (mouse) Male CD-1 mice	00100442 (unknown) TXR 0053747 **Acceptable/ Guideline** 23.8% w/v paraquat ion 0, 0.04, 0.4, 4 mg/kg/day via gavage for 5 days	No time-related positive response of increased pre- or post-implantation loss compared to controls.
870.5900 *Other Geneotoxicity* *In vitro* sister chromatid exchange assay Chinese hamster lung fibroblasts	00152695 (1985) TXR 0053747 **Acceptable/ Guideline** 99.4% paraquat dichloride 0 - 2470 ug/mL +/- S9	Positive response of SCE induced over background with clear dose response in presence of S9-activation; Positive response of SCE induced over background w/o clear dose-response in absence of S9-activation.
870.5550 *Other Geneotoxicity* Unscheduled DNA synthesis in primary rat hepatocytes Primary rat hepatocytes	00152693 (1985) TXR 0053747 **Acceptable/ Guideline** 99.6% paraquat dichloride 0 – 10^{-9} M	No evidence of unscheduled DNA synthesis

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.5550 *Other Geneotoxicity* Unscheduled DNA synthesis in primary rat hepatocytes Male Alderly Park albino rats	40202404 (1987) TXR 0053747 **Acceptable/ Guideline** 33.0% w/v paraquat ion 0, 45, 78, 120 mg/kg administered via drinking water	No evidence of unscheduled DNA synthesis
870.6200a Acute neurotoxicity screening battery Alpk:Ap$_f$SD rats	47994201 (2006) TXR 0057886 **Acceptable/ Guideline** 33.4% w/w paraquat ion (46.1% w/w paraquat dichloride) 0, 8.4, 25.1, 84 mg paraquat ion/kg administered via gavage in deionized water	Neurotoxicity NOAEL = 84 mg paraquat ion/kg Neurotoxicity LOAEL = not established Systemic NOAEL = 25.1 mg paraquat ion/kg Systemic LOAEL = 84 mg paraquat ion/kg based on clinical signs of toxicity (piloerection, irregular breathing, flaccidity, pinched sides, upward spinal curvature, ocular discharge) and mortality
870.6200b Subchronic neurotoxicity screening battery Alpk:Ap$_f$SD rats	47994202 (2006) TXR 0055342 **Acceptable/ Guideline** 33.4% w/w paraquat ion (46.1% w/w paraquat dichloride) M: 0, 1, 3.4, 10.2 mg paraquat ion/kg/day F: 0, 1.1, 3.9, 11.9 mg paraquat ion/kg/day administered via diet for 13 weeks	NOAEL = 10.2-11.9 mg paraquat ion/kg/day LOAEL = not established
870.6300 Developmental neurotoxicity	Study not submitted	
870.7485 Metabolism and pharmacokinetics (rat)	Guideline study not submitted, see non-guideline study	

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Paraquat Dichloride		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR #/ Classification /Doses**	**Results**
870.7800 Immunotoxicity (mouse) Female B6C3F1 mice	48667301 (2011) TXR 0056276 **Acceptable/ Guideline** 99.9% w/w paraquat dichloride (% paraquat ion not reported) 0, 6.9, 19.9, 27.3 mg/kg bw/day administered via diet for 28 days	Immunotox/Systemic NOAEL = 27.3 mg/kg/day Immunotox/Systemic LOAEL = not established No suppression of the humoral or innate components of the immune system.

Table A.2.3 Special (Non-guideline) Study Toxicity Profile - Paraquat		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/ Classification /Doses**	**Results**
Non-guideline Sub-chronic neurotoxicity C57BL/6J mice	49122304 (2013) TXR 0056764 **Unacceptable** 99.9% a.i. M: 0, 1.7, 10.2 mg paraquat ion/kg/day F: 0, 2.7, 15.6 mg paraquat ion/kg/day Administered via diet for 13 weeks *Positive Control:* MPTP 10 mg/kg injected 4 times every 2 hours on a single day	The study presented null results for the paraquat exposed animals; however, homogeneity and stability data for the paraquat-treated diet were inadequate and created uncertainty in the exposure analysis and reported dose levels. *Positive Control Results:* Reversible clinical signs including hunched posture, piloerection, hypoactivity, and/or tremors, and weight loss after dosing in both sexes, significant decrease in TH+ neurons and total contour volume in SNpc, decreases in DA, DOPAC, and HVA concentration, and increase in DA turnover in striatal tissues in males only. No effect on brain weight.
Non-guideline Sequential neuropathology C57BL/6J male mice	49122301 (2013) TXR 0057437 **Acceptable/Non-guideline** 99.9% a.i. 0, 10, or 15 mg/kg/week Administered via IP injection once per week for up to 3 weeks *Positive Control:* MPTP 10 mg/kg injected 4 times every 2 hours on a single day	No treatment related clinical signs observed and no difference in brain appearance. Paraquat concentration increased with cumulative dose. No evidence of neuropathology anomalies in the SNpc; however, stereology of immunostained sections demonstrated a decrease in TH+ and total neurons in the SNpc in animals treated with 3 x 15 mg/kg paraquat. Total neuron counts with CVO stained did not corroborate finding of decreased total neuron count. *Positive Control Results:* Evidence of neuron damage and neuron death in SNpc based on staining and stereology. As with the paraquat treated animals, total neuron count of CVO stained samples did not demonstrate significant decrease in total neuron count.

Table A.2.3 Special (Non-guideline) Study Toxicity Profile - Paraquat		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/ Classification /Doses**	**Results**
Non-guideline Neurotoxicity range-finding C57BL/6J male mice	49122302 (2012) TXR 0057437 **Acceptable/Non-guideline** 99.9% a.i. 0, 10, 15, or 25 mg/kg/week Administered via IP injection once per week for 3 weeks *Positive Control:* MPTP 10 mg/kg injected 4 times every 2 hours on a single day	Mortality at 25 mg/kg/week. No treatment-related effects on dopamine, dopamine metabolites, or dopamine turnover. Non-significant decrease in TH+ neurons in the SNpc and significant decrease in mean total contour volume in brain sections at 15 and 25 mg/kg/week. Total neuron count was not statistically different from controls in any treatment group. *Positive Control Results:* Decrease in total contour volume and TH+ neurons with variable statistical significance based on the staining procedure, non-significant decrease in total neurons, decrease in dopamine and dopamine metabolite concentrations and increase in dopamine turnover in striatal samples
Non-guideline Multi-time and multi-dose neuropathology C57BL/6J male mice	49122303 (2013) TXR 0057437 **Acceptable/Non-guideline** 99.9% a.i. 0, 10, 15, or 25 mg/kg/week Administered via IP injection once per week for up to 3 weeks *Positive Control:* MPTP 10 mg/kg injected 4 times every 2 hours	No neuropathology effects observed in the striatal and substantia nigra brain tissues, transient decrease in body weight, two 25 mg/kg animals euthanized in extremis *Positive Control Results:* Evidence of neuron damage and neuron death in the SNpc
Non-guideline Sub-chronic study 3 and 8-week-old C57BL/6J male mice	50733301 (Lou *et al*. 2016) TXR 0057886 **Acceptable** >98% a.i. 0, 3.6, or 7.2 mg paraquat ion/kg/day via gavage for 28 consecutive days	NOAEL = not established LOAEL = 3.6 mg paraquat ion/kg/day based on mortality in the 3-week-old mice *mortality in 8-week-old mice only observed at 7.2 mg paraquat ion/kg/day **mortalities observed on days 2, 3, 5, and 6 in the 3-week-old mice are considered to conservatively represent an acute response to exposure

Table A.2.3 Special (Non-guideline) Study Toxicity Profile - Paraquat		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/ Classification /Doses**	**Results**
Non-guideline Sub-chronic study 8-week-old Wistar male rats	Chen *et al*. 2017 **Acceptable** Not reported (assumed high purity based on source) 0, 0.5, 2, or 8 mg paraquat /kg/day via gavage for 8 weeks	Sperm, tissue weight, and testis tissue effects were observed in all dose groups, though the magnitude of change in these effects were small in the 0.5 mg/kg/day treatment group. Absolute testis and epididymis weight in the 0.5 mg/kg/day group were <13% different from controls and the changes in weight were not significant after normalizing for body weight. Sperm number in the 0.5 mg/kg/day treatment group decreased by <10% relative to controls, the increase in total percentage of abnormal sperm was marginal, and no significant impact on sperm motility or viability was observed. Testis tissue from rats in this treatment group also did not exhibit evidence of oxidative stress or apoptosis. Given the low magnitude of the change from controls, none of the reproductive effects observed in rats from the 0.5 mg/kg/day treatment group were indicative of an adverse response to treatment. Rats from the 2 and 8 mg/kg/day treatment groups exhibited a wider array of changes in the male reproductive tissues (decreased testis weight, decreased sperm number concurrent with decrease in sperm viability and increase in percent of head, tail and multiple sperm abnormalities, and evidence of oxidative stress and apoptosis in testis tissue) that were significantly different from the controls and generally of higher magnitude relative to the 0.5 mg/kg/day group.
Non-guideline Urinary excretion in monkeys	00126096 (1982) TXR 0053747 **Acceptable/Non-guideline** 99.8% radiochemical purity Single intramuscular injection of 607 ug paraquat dichloride	*Monkeys eliminated 43.5-51.5% of the administered radioactivity in the urine within 24 hours post-dose and 52.3-72.3% (average 58.6%) within 7 days post-dose.

Table A.2.3 Special (Non-guideline) Study Toxicity Profile - Paraquat		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/ Classification /Doses**	**Results**
Non-guideline Metabolism	00055107 Daniel and Gage 1966 TXR 0005824 **Acceptable** 0.5, 0.7, 4 ,6, 50 mg/kg via oral gavage	Oral absorption from a low dose (4-6 mg/kg) gavage exposure was estimated to be approximated 6% of the administered dose (AD) based on the amount excreted in the urine up to 96 hours after exposure (no biliary data for these dose groups were available). Absorption from a 50 mg/kg oral dose was estimated to be 8-14% of the AD based on the urinary content alone. The study authors did not provide information on radioactivity content in fecal or biliary excretion nor calculate a percent recovery in rats exposed to the higher dose. Regardless of dose, paraquat dichloride was primarily excreted in the feces with minor contribution from the renal system. A majority (95-101%) of the dose was eliminated within 48 hours in animals exposed to 4 or 6 mg/kg. Despite a marginal difference in dose, there was a notable difference in the elimination efficiency, particularly in the fecal elimination. Eighty percent of the 4 mg/kg dose (5% in urine, 75% in feces) was present in excreta at 24 hours compared to 43% of the 6 mg/kg dose (5% in urine, 38% in the feces). There was no evidence of biliary excretion in rats receiving an oral dose of 0.5 mg/kg suggesting it is not a prominent elimination pathway; however, the study does not provide enough information to determine if this behavior persists at higher doses. The excretion profile of paraquat dichloride changed markedly with the route of administration. After subcutaneous injection (12.5-13.2 mg/kg), 80-98% of the AD was identified in the urine within 24 hours of dosing. Paraquat dichloride appears to undergo a form of metabolism after ingestion. Thirty to forty percent of the dose eliminated in the feces of a rat orally exposed to 0.7 mg/kg was not parent. Likewise, 1.2-2.1% of the urine content eliminated from a rat orally exposed to 50 mg/kg was structurally different from paraquat dichloride. The identify of these metabolites or degradates was not elucidated nor the metabolic pathways involved; however, an *in vitro* study suggested microbial degradation contributed to the formation of compounds in the fecal excreta that were not identical to parent.
Non-guideline Metabolism Male mice and M/F Wistar albino rats	00065592 Litchfield *et al.* 1973 TXR 0005824 **Acceptable** 50, 120, and 250 ppm paraquat ion in the diet for 8 weeks	Audioradiography analysis indicated that paraquat dichloride was rapidly distributed throughout most tissues (brain and spinal cord excluded) following intravenous administration in male mice. At 24 hours post dose, paraquat was still observed in the lungs and in the brain and spinal cord despite not being part of the initial distribution. Following dietary administration, the kidneys, liver, and lungs of male rats contained quantifiable amounts of paraquat dichloride. Content in the brain was near or below the detection limit regardless of dose or exposure duration. Paraquat was not detected in any tissue after returning to normal diet for 7 days indicating it does not accumulate in these tissues. Data for female rats was not shown.

Table A.2.3 Special (Non-guideline) Study Toxicity Profile - Paraquat		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/ Classification /Doses**	**Results**
Non-guideline Metabolism Rats	Hughes *et al*. 1973 **Acceptable** Single 15 mg/kg paraquat diiodide dose via IP injection	<1% of the AD in the bile 24 hours. No urinary metabolites identified suggesting lack of paraquat metabolism.
Non-guideline Dermal absorption (human)	00126097, 00126098, 00126099 (1982) TXR 0053747 **Acceptable/Non-guideline** 99.8% radiochemical purity Single dose of 11.8 ug paraquat dichloride/cm^2 to 6 community volunteers	In dermal absorption study with healthy adult male volunteers, 0.23-0.3% of the applied paraquat dichloride was absorbed through the intact skin (dosing sites were the forearms, back of the hands, and lower legs) during the 24 hr exposure period. Differences in absorption due to application site were noted.
Non-guideline Acute Oral Toxicity and Metabolism New Zealand rabbits	49009501 (1993) TXR 0056764 Acceptable/Non-guideline 33% paraquat ion Acute Oral Study: Single dose of 2, 4, 8, 12, 16, 20, 24, 30, 40, or 50 mg paraquat ion/kg via gavage Metabolism Study: Single dose of 0, 2, or 30 mg paraquat ion/kg	NOAEL = not established. LOAEL = 30 mg paraquat ion/kg bw based on renal damage revealed by azotemia and by microscopic pathology findings of multifocal hydropic change in the S2 segment of the proximal tubules and additional renal damage. *No NOAEL is indicated because of the limited testing of only 2 animals at all but one of the lower doses tested. Metabolism Study: The peak concentration in blood plasma was reached within one hour after treatment and the concentration rapidly returned to near zero following treatment. At the lower dose (2 mg paraquat ion/kg), 94% of the total dose was excreted over 7 days, of which about 7% was eliminated in the urine, with 6% of the total dose being eliminated by that route in the first 24 hours. The remainder of the dose was excreted in the feces, with about 60% of the total dose being eliminated by that route in the first 24 hours. While the lower dose of paraquat had no effect on urinary output, the higher dose (30 mg paraquat ion/kg) reduced the urine flow by about 50% over the duration of the experiment and also produced a marked reduction in fecal output. As a result of the reduced urine and fecal outputs, only a small proportion of the administered dose was eliminated by these routes during the 72 hours studied. Urine and feces only accounted for elimination of 8% and 3% of the dose, respectively.

A.3 Executive Summaries

A.3.1 Studies Used for Points of Departure (POD)

Acute Dietary POD

Rat Developmental Study (MRID 0011374)

In a developmental toxicity study (MRID 00113714), paraquat dichloride (100% technical grade; Batch # ADYM76/C; 38% w/v paraquat ion) in 0.5% aqueous Tween 80 was administered daily via oral gavage to 29-30 presumed pregnant Alderly Park Wistar-derived (Alpk:SPF SD) rats/group at a dose volume of 10 mL/kg at dose levels of 0, 1, 5, or 10 mg/kg/day of paraquat ion from gestation day (GD) 6 through 15. All surviving dams were killed on GD 21. The lungs and kidneys from at least 11 surviving dams/group were examined microscopically. The fetuses were removed by cesarean section and examined.

At ≥ 5 mg paraquat ion/kg/day, dams exhibited clinical signs of toxicity including subdued nature, staining, piloerection, weight loss, hunched appearance, and respiratory distress. Clinical signs were first observed on GD 7 and increased in prevalence (both in number of animals affected and frequency of observation) and severity with dose and exposure duration. Body weight gains at doses ≥ 5 mg paraquat ion/kg/day were decreased by 37-74% during the treatment (GD 6-16) interval (calculated by the reviewers; statistics not performed) and by 24-29% for the overall (GD 0-21) study ($p \leq 0.001$).

A total of 13 dams across the three dose groups and the controls died or were sacrificed moribund prior to scheduled termination. The study authors attributed the lone mortality in the control and the two mortalities in the 1 mg paraquat ion/kg/day dose group to intubation error. One 5 mg paraquat ion/kg/day dam had excessive blood loss from the vagina that was considered to be treatment related and was euthanized on GD 18. The other mortality in the 5 mg paraquat ion/kg/day dose group was attributed to intubation error. At 10 mg paraquat ion/kg/day, eight dams died or were sacrificed moribund and an additional dam delivered prematurely on GD 21, but was not sacrificed. Of these eight mortalities, six were attributed to the test substance and two were attributed to intubation error.

Three dams that died or were killed in extremis in the 10 mg paraquat ion/kg/day group exhibited clinical signs of toxicity related to treatment within one to three days of the first dose (GD 7-9) that progressed in severity until death or sacrifice between five and seven days after the first dose (GD11-13). Although these mortalities did not appear to be the result of a single dose given the length of time between the initial dose and death, acute studies in the paraquat toxicity database and human incidents indicate that death can be delayed up to a week after exposure to a single oral dose of paraquat dichloride and are often preceded by clinical signs of deteriorating health. The similarities between the three treatment-related mortalities in the 10 mg paraquat ion/kg/day group that occurred during the first week of exposure and the pattern of delayed mortality observed in the acute studies suggest these mortalities may have been a result of the initial dose rather than a compounding effect from the repeated dosing. Consequently, the three mortalities observed in 10 mg paraquat ion/kg/day group during the first week were conservatively attributed to the initial dose and identified as an acute response to treatment. The treatment-related mortality in 5 mg paraquat ion/kg/day and the other three treatment-related mortalities in the 10 mg paraquat ion/kg/day group occurred more than a week after the start of the exposure

and thus were considered to reflect toxicity from repeat dosing rather than an acute effect. Gross necropsy of the six dams that died or were sacrificed moribund in the 10 mg paraquat ion/kg/day dose group indicated that the lungs were red and patchy, and microscopic examination revealed large amount of edema fluid and polymorph infiltration in the alveoli, while the kidneys showed widespread degenerative change in the proximal tubules.

The maternal LOAEL is 5 mg paraquat ion/kg/day based on mortality (GD18), clinical signs of toxicity, and decreased body weight gains. The maternal NOAEL is 1 mg paraquat ion/kg/day.

There was no effect on the proportion of dams having one or more resorptions, and there were no treatment-related effects on sex ratio or embryonic or fetal survival. There were no increases in fetal external visceral, or skeletal malformations or variations at any dose tested, indicating that paraquat dichloride is not teratogenic in rats at the dose levels tested.

At ≥ 5 mg paraquat ion/kg/day, fetal body weights were reduced by 3-6%. Skeletal ossification was slightly retarded in these groups, as indicated by decreased ossification of the caudal vertebrae and decreased degree of ossification in the digits in the fore- and hind-limbs. The percent of fetuses with 7 or 8 caudal vertebrae ossified was decreased ($p \leq 0.05$) at this dose (8% treated vs 26% controls). The percent of fetuses with "good" (Grade 2) ossification in the digits in the fore-limbs was dose-dependently decreased at 5 (29%) and 10 (23%) mg paraquat ion/kg/day compared to controls (42%). The percent of fetuses with Grade 2 or 3 ossification in the digits in the hind-limbs was dose-dependently decreased at ≥5 mg paraquat ion/kg/day (20% each treated) compared to controls (42%). Likewise, the percent of fetuses with "poor" (Grade 5) ossification in the digits of the hindlimbs was increased at ≥5 mg paraquat ion/kg/day (23-32%) compared to controls (13%). These decreases in growth and development are probably associated with the maternal toxicity observed at this dose.

The developmental LOAEL is 5 mg paraquat ion/kg/day based on slightly decreased fetal body weights and on delayed ossification. The developmental NOAEL is 1 mg paraquat ion/kg/day.

This study is classified **Acceptable/Guideline** and satisfies the guideline requirements (OCSPP 870.3700a; OECD 414) for a developmental study in the rat.

Chronic Dietary and Incidental Oral PODs

Subchronic Dog Oral Toxicity Study (MRID 00072416)

In a subchronic toxicity study (MRID 00072416), technical grade paraquat dichloride (32.2% w/w paraquat cation, Mond Reference No.: Y00061/009/004) was administered in the diet to 3 beagle dogs/sex/dose at nominal concentrations of 0, 7, 20, 60, or 120 ppm paraquat cation for up to 13 weeks. Actual intakes are estimated to be 0, 0.2, 0.5, 1.5, and 3 mg/kg/day based on Subdivision F conversion factor of 1 ppm = 0.025 mg/kg/day.

No treatment-related adverse effects were observed on ophthalmoscopic examination, hematology, clinical chemistry, or urinalysis parameters findings, or during auscultation.

At 60 ppm, absolute and relative to body lung weights were increased by 39-56% in 1 dog/sex. Alveolitis, characterized by a mixture of exudative and proliferative reactions resulting in alveolar collapse, distortion, and interstitial hypercellularity, was observed in 5/6 dogs (vs 0 controls).
The maximum tolerated dose was exceeded at 120 ppm. Two dogs/sex were sacrificed *in extremis* during the first month, suffering from marked dyspnea, harsh rales, slow and/or irregular heartbeat, and weight loss. These two dogs lost 0.90-1.20 kg. Only 1 dog/sex survived until terminal sacrifice. Decreased food consumption was noted in the female survivor. Absolute and relative to body lung weights were increased, and alveolitis was observed in all 6 dogs.

The LOAEL is 60 ppm (approximately equivalent to 1.5 mg/kg/day) based on increased lung weight and incidence of alveolitis in both sexes. The NOAEL is 20 ppm (approximately equivalent to 0.5 mg/kg/day).

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement (OCSPP 870.4100b; OECD 452) for a subchronic oral toxicity study in dogs.

Chronic Dog Oral Toxicity Study (MRID 00132474)

In a chronic toxicity study (MRID 00132474), technical grade paraquat dichloride (32.3% w/w paraquat cation, Mond Reference No.: S358/2) was administered in the diet to 6 beagle dogs/sex/dose at nominal concentrations of 0, 15, 30, or 50 ppm (equivalent to 0/0, 0.45/0.48, 0.93/1.00, and 1.51/1.58 mg/kg/day paraquat cation in males/females) for up to 52 weeks.

No treatment-related adverse effects were observed on mortality, body weights, body weight gains, or on ophthalmoscopic examination, hematology, clinical chemistry or urinalysis parameters.
Increased incidences of the following clinical signs were observed at 50 ppm in both sexes: hypernea (4/6 vs 1/6, each sex), increased vesicular sound (3-4/6 vs 0/6), and reddening of tongues (6/6 vs 4/6, each sex). The frequency of these observations was also increased at 50 ppm. These signs were first observed at Week 13 (hypernea and increased vesicular sound) and week 9 (tongue reddening). Food consumption was decreased in one 50 ppm dog/sex. The hypernea was corroborated by further findings of pulmonary toxicity. The other findings are considered equivocal.

Lungs were the target organ. Absolute and relative to body lung weight were each increased by 36% in males and 61% in females at 50 ppm. Chronic pneumonitis was observed in 44 of the 48 dogs that were evaluated; therefore, an increased incidence was not observed. However, an increase in severity was observed in the 30 and 50 ppm groups; the incidence (# affected/6, treated vs controls) of slight to marked chronic pneumonitis was 5-6 treated males vs 2 controls and 3-6 treated females vs 1 control. This lesion correlated to yellow discoloration and consolidation of areas of the lungs observed grossly. Additionally, the incidence and severity of minimal to moderate focal granuloma was increased in the 30 and 50 ppm males (5/6 each treated vs 4/6 controls). Focal pleural fibrosis was observed in 3/6 males at 50 ppm vs 2/6 controls and may have been treatment-related.

Small amounts of the paraquat cation were detected in the lungs of all treated groups (0.13-1.04 μg/g) and in the kidney of the 30 and 50 ppm groups (0.12-0.19 μg/g).

The LOAEL is 30 ppm (equivalent to 0.93/1.00 mg/kg/day in males/females) based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males. The NOAEL is 15 ppm (equivalent to 0.45/0.48 mg/kg/day in males/females).

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on an increase in pulmonary toxicity.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement (OCSPP 870.4100b; OECD 452) for a chronic oral toxicity study in dogs.

Dermal POD

21-Day Rabbit Dermal Toxicity Study (MRID 00156313)

In a 21-day dermal toxicity study (MRID 00156313 [Accession # 260635]), paraquat dichloride (43.5% w/w paraquat cation; Lot/Batch # SX-1465) in distilled water was applied directly to the hair-clipped intact skin of 6 New Zealand white rabbits/sex/dose at dose levels of 0, 0.50, 1.15, 2.60, or 6.00 mg/kg/day paraquat cation for 6 hours/day, 7 days/week during a 21-day period.

No treatment-related effects were observed on clinical signs, body weight, body weight gain, food consumption, on hematology or clinical chemistry parameters, or organ weights. All animals survived until scheduled sacrifice. No evidence of systemic toxicity was noted.

At 2.60 mg paraquat ion/kg/day, small scabs were noted at the treatment site in 2 males (Days 18 and 21) and 1 female (Days 15, 18, and 21). Microscopically evidence of dermal irritation was found in 3 males and included: epidermal erosion/ulceration, surface exudation, acanthosis, and/or inflammation.

At 6.00 mg paraquat ion/kg/day, very slight to well-defined erythema was noted in 4-6 rabbits/sex at Days 11, 15, 18, and 21. Small scabs were found at the treated site in 1-2 rabbits/sex on Day 11 and 12/12 rabbits at Days 15, 18, and 21. Large scabs were noted in 2-3 rabbits/sex. Grossly, crusty scabs, redness, thickened appearance, and/or prominent subcutaneous vessels were noted. Microscopically, the same lesions were observed as in the 7.8 mg/kg/day group.

The dermal LOAEL is 2.60 mg paraquat ion/kg/day, based on small scabs at the treatment site in both sexes and epidermal erosion/ulceration, surface exudation, acanthosis, and/or inflammation in males. The dermal NOAEL is 1.15 mg paraquat ion/kg/day.

The systemic LOAEL was not established. The systemic NOAEL is 6 mg paraquat ion/kg/day.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OCSPP 870.3200; OECD 410) for a 21-day dermal toxicity study.

Inhalation POD

21-Day Rat Inhalation Toxicity Study (MRID 00113718)

In a subchronic inhalation toxicity study (MRID 00113718), Sprague-Dawley rats were exposed by whole body inhalation to paraquat dichloride (approximately 40% paraquat ion) administered as a respirable (particle size < 2 µm) aerosol at nominal concentrations of 0, 0.01, 0.1, 0.5, or 1.0 µg/L paraquat ion (equivalent to analytical concentrations of 0, 0.012, 0.112, 0.487, and 1.280 µg/L, respectively) for 6 hours/day, 5 days/week for 3 weeks. The numbers of rats of each sex assigned to these groups were as follows: 32 (control group); 16 (0.5 µg/L); and 36 (remaining groups). Parameters examined included clinical observations, body weights, food consumption, and water consumption. At the end of the three-week treatment period (15 total exposures), 16 rats/sex from the control group and 8 rats/sex/group from the remaining groups were terminated and examined; 8 rats/sex/group were euthanized and examined after a two-week recovery period. Gross and microscopic examinations were restricted to the respiratory tract (nasal passages, pharynx, tongue, larynx, trachea, and lungs). The remaining rats (4/sex/dose) in the control, 0.01, and 0.1 µg/L groups were euthanized after the 5th exposure, the 15th exposure, and 1, 2, and 3 days after the 15th exposure for paraquat estimations

There were no treatment-related effects on body weights, food consumption, water consumption, or gross pathology at any concentration.

The 1.0 µg/L group was not exposed after Day 1 because 28/36 males (78%) and 29/36 females (80%) died from respiratory failure in the subsequent 14 days.

All rats in the 0.1 µg/L group exhibited nasal discharge and squamous keratinizing metaplasia, and/or hyperplasia of the epithelium of the larynx. The changes in the epithelium were still observed in 11/16 (69%) of the rats euthanized at the end of the recovery period.

Additionally, in the 0.5 µg/L group, the following findings were observed after 3 weeks: (i) extensive ulceration, necrosis, inflammation and squamous keratinizing metaplasia, and marked/moderate hyperplasia of adjacent epithelia in larynx of all rats; and (ii) aggregations of foamy macrophages in the bronchioles or alveoli, hypertrophy of the epithelium and thickened alveolar walls in the lungs of most or all rats. After the 2-week recovery period, no ulceration or necrosis was observed in the larynx, but changes in the lungs were still seen. In addition, disruption of bronchiolar epithelium, adjacent to the macrophage aggregation, was noted.

At 0.01 µg/L, there were no treatment-related effects on any parameter.

The LOAEL is 0.10 µg/L based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx. The NOAEL is 0.01 µg/L.

At the request of the Agency, this study was conducted for a duration of three weeks, instead of the 90 days required by Guideline OPPTS 870.3465. Aside from the different study duration, this study was conducted in accordance with Guideline OPPTS 870.3465.

This 21-day inhalation toxicity study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3465; OECD 413) for a subchronic inhalation study in the rat.

A.3.2 Other Studies Updated for Registration Review

Acute Neurotoxicity Study (MRID 47994201)

In an acute neurotoxicity study (MRID 47994201), groups of fasted 42 day-old Alpk:ApfSD rats 10/sex/dose were given a single oral dose of paraquat technical (33.4% w/w paraquat ion, 46.1% w/w paraquat dichloride, preparation P47) in deionized water orally (by gavage) at 10 mL/kg at doses of 0, 25, 75, or 250 mg/kg paraquat technical/kg body weight. This corresponded to doses of 0, 8.4, 25.1, and 84 mg paraquat ion/kg. Animals were observed for 14 days after dosing. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10/sex/group one week prior to dose administration, at approximately 2 hours after dose administration on Day 1, and at one week (Day 8) and two weeks (Day 15). At study termination, 5/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, 5/sex/group of control and 84 mg paraquat ion/kg animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No effects of the test chemical were observed in the functional observational battery (FOB), or on motor activity and nervous system histopathology.

One 84 mg paraquat ion/kg male dosed with paraquat technical was found dead on Day 5. This male had shown a slightly reduced foot splay reflex on Days 1-4 with piloerection and "sides pinched in" on Day 4. One 84 mg paraquat ion/kg female was killed on Day 4, due to adverse clinical signs of irregular breathing (indicative of respiratory distress), flaccidity, "sides pinched in", and upward spinal curvature from Days 2-4, and piloerection and ocular discharge on Days 3-4. The clinical signs preceding death in these two animals were consistent with an agonal response to treatment and were not considered evidence of neurotoxicity. The lack of significant findings in the FOB, motor activity, and neuropathology assessments further supports this conclusion. Similar clinical signs were not observed in the other animals from this treatment group nor the other treatment or control groups. All other animals survived to scheduled sacrifice.

The LOAEL for neurotoxicity was not observed. The NOAEL is 84 mg paraquat ion/kg (250 mg/kg paraquat technical).

The systemic LOAEL is 84 mg paraquat ion/kg (250 mg/kg paraquat technical) based on clinical signs and mortality in males and females. The NOAEL is 25.1 mg paraquat ion/kg (75 mg/kg paraquat technical).

This neurotoxicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (OCSPP 870.6200a; OECD 424).

A.4 Paraquat General Literature Review Results

Paraquat Search
Date and Time of Search: 01/29/2018; 8:00 am
Search Details:

((Paraquat) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal))

Studies Identified in PubMed*: 3974
SWIFT-Review** Tags:
2517 for Animal
2343 for Human (1454 studies tagged as "Human" were not included in the "Animal" tag)
0 for NO TAG

Paraquat Dichloride Search
Date and Time of Search: 01/29/2018; 8:00 am
Search Details:

((Paraquat dichloride)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal))

Studies Identified in PubMed*: 132
SWIFT-Review** Tags:
99 for Animal
67 for Human (33 studies tagged as "Human" were not included in the "Animal" tag)
0 for NO TAG

All studies identified in the PubMed search were screened when the citation list was ≤100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag.

After screening both citation lists, it was determined that all 132 publications identified in the paraquat dichloride search were captured in the paraquat search. An additional 17 relevant animal studies were identified in a separate systematic review that focused on Parkinson's disease (D449106; TXR 0057888 A. Wray, 06/26/2019) and were included in the general literature review.

Number of Articles Identified as Relevant for Risk Assessment: 26
Citations of Articles Identified as Relevant for Risk Assessment:

1. Anderson D, McGregor DB, and Purchase IFH. 1976. Dominant lethal studies with paraquat and diquat in male CD-1 mice. *Mutat Res*. 40: 349-358.
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5. Chen Q, Niu Y, Zhang R, Guo H, Gao Y, Li Y, and Liu R. 2010. The toxic influence of paraquat on hippocampus of mice: Involvement of oxidative stress. *Neurotoxicology*. 31(3): 310-316.

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9. Fredriksson A, Fredriksson M, and Eriksson P. 1993. Neonatal exposure to paraquat or MPTP induces permanent changes in striatum dopamine and behavior in adult mice. *Toxicol Appl Pharmacol*. 122(2): 258-264.

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12. Li HF, Zhao SX, Xing BP, and Sun ML. 2015. Ulinastatin suppresses endoplasmic reticulum stress and apoptosis in the hippocampus of rats with acute paraquat poisoning. *Neural Regen Res*. 10:467-472.

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14. Luty S, Latuszyńska J, Halliop J, Tochman A, Obuchowska D, Korczak B, Przylepa E, and Bychawski E. 1997. Dermal toxicity of paraquat. *Ann Agric Envron Med*. 4(2): 217-227.

15. McElligott TF. 1972. The dermal toxicity of paraquat: Differences due to techniques of application. *Toxicol Appl Pharmacol*. 21: 361-368.

16. Minnema DJ, Travis KZ, Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck MJ, Mathews JM, Tisdel MO, Cook AR, Botham PA, and Smith LL. 2014. Dietary administration of paraquat for 13 weeks does not result in a loss of dopaminergic neurons in the substantia nigra of C57BL/6J mice. *Regul Toxicol Pharm*. 68(2): 250-258.

17. Naudet N, Antier E, Gaillard D, Morignat E, Lakhdar L, Baron T, and Bencsik A. 2017. Oral exposure to paraquat triggers earlier expression of phosphorylated α-synuclein in the

enteric nervous system of A53T mutant human α-synuclein transgenic mice. *J Neuropathol Exp Neurol*. 76(12): 1046-1057.

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23. Rojo AI, Cavada C, de Sagarra MR, and Cuadrado A. 2007. Chronic inhalation of rotenone or paraquat does not induce Parkinson's disease symptoms in mice or rats. *Exp Neurol*. 208(1): 120-126.
24. Salovsky P and Shopova V. 1993. Synergic lung changes in rats receiving combined exposure to paraquat and ionizing radiation. *Environ Res*. 60:44-54.
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Conclusion of Literature Search: Full text review of the 26 relevant studies pared down the list to 10 studies (Widdowson *et al.* 1996; Rojo *et al.* 2007; Ren *et al.* 2009; Satpute *et al.* 2017; Naudet *et al.* 2017; Endo *et al.* 1988; Minnema *et al.* 2014; Prasad *et al.* 2007; Lou *et al.* 2016; Chen *et al.* 2017) that were of sufficient quality and contained either quantitative or qualitative information relevant to the risk assessment. Only one study, Lou *et al.* 2016, reported evidence of adverse health effects in mice at doses that were similar to the current PODs. This study was formally reviewed (MRID 50733301; TXR 0057886) and was considered in POD selection. The data reported in the other nine publications did not have a quantitative impact on the risk assessment; however, the studies did report novel findings, including toxicokinetic and neurotoxicity information, that were incorporated into the hazard characterization of the Registration Review risk assessment.

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.

**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize citations lists that were larger than 100. Studies identified in the PubMed search were tagged and grouped based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).

Appendix B: Physicochemical Properties of Paraquat Dichloride

Table B.1. Physicochemical Properties of Technical Grade Paraquat Dichloride		
Parameter	**Value**	**Reference**
Melting point/range	decomposes at ca. 340 °C	Product Chemistry Chapter of the Paraquat Dichloride Update, 10/10/1991
pH	6.4 at 20 °C	
Density	1.5 g/cm^3 at 25 °C	
Water solubility (20 °C)	freely soluble in water: 618-620 g/L at pH 5.2, 7.2, and 9.2	
Solvent solubility (20 °C)	<0.1 g/L in acetone, dichloromethane, toluene, ethyl acetate, and hexane; 143 g/L in methanol	
Vapor pressure	<<10^{-8} kPa at 25 °C	
Octanol/water partition coefficient, Log(K_{OW})	log K_{OW} = -4.5 at 20 °C	
UV/visible absorption spectrum	Not available	

Appendix C: International Residue Limit Status Sheet

Paraquat Dichloride (061601; 06/13/2018)

Table C.1. Summary of US and International Tolerances and Maximum Residue Limits			
***Residue Definition*:**			
US		Canada	Codex[3]
40 CFR 180.205: Tolerances are established for residues of paraquat, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation		Paraquat: 1,1'-dimethyl-4,4'-bipyridinium	Paraquat cation
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*		
	US	Canada	Codex
Acerola	0.05	--	--
Almond, hulls	0.50		0.01
Animal feed, nongrass, group 18, forage	75	--	--
Animal feed, nongrass, group 18, hay	200	--	--
Artichoke, globe	0.05		0.05
Atemoya	0.05	--	0.01
Avocado	0.05	--	0.01
Banana	0.05	--	0.01
Barley, grain	0.05	0.05	--
Barley, hay	3.5	--	--
Barley, straw	1.0	--	--
Beet, sugar, roots	0.50	--	0.05
Beet, sugar, tops	0.05	--	--
Berry and small fruit, group 13-07	0.05	0.05 individual	0.01
Biribi	0.05		--
Cacao, dried bean	0.05		--
Canistel	0.05		0.01
Carrot, roots	0.05	0.05	0.05
Cattle, fat	0.05		0.05
Cattle, kidney	0.50		--
Cattle, meat	0.05		0.005
Cattle, meat byproducts, except kidney	0.05		--
Cherimoya	0.05		0.01
Coffee, green bean	0.05		--
Corn, field, forage	3.0		--
Corn, field, grain	0.10	0.1	0.03 maize 0.05 flour
Corn, field, stover	10		10
Corn, pop, grain	0.10	0.1	0.03
Corn, pop, stover	10		--
Corn, sweet, kernel plus cob with husks removed	0.05	0.05	0.03
Cotton, gin byproducts	100		--
Cotton, undelinted seed	3.5		2
Cowpea, forage	0.10		--
Cowpea, hay	0.40		--
Cranberry	0.05		0.01
Custard apple	0.05		0.01
Egg	0.01		0.005
Endive	0.07		0.07
Feijoa	0.05		0.01
Fig	0.05		0.01

Table C.1. Summary of US and International Tolerances and Maximum Residue Limits			
***Residue Definition*:**			
US		Canada	Codex[3]
Fruit, citrus, group 10-10	0.05		0.02
Fruit, pome, group 11-10	0.05	0.05 individual	0.01
Fruit, stone, group 12-12	0.05	0.05 individual	0.01
Goat, fat	0.05		0.05
Goat, kidney	0.50		--
Goat, meat	0.05		0.005
Goat, meat byproducts, except kidney	0.05		--
Grain, aspirated fractions	70		--
Grape	0.05		0.01
Grass, forage	90		--
Grass, hay	40		--
Guar, seed	0.50		0.5
Guava	0.05		0.01
Hog, fat	0.05		0.05
Hog, kidney	0.50		--
Hog, meat	0.05		0.005
Hog, meat byproducts, except kidney	0.05		--
Hop, dried cones	0.50		0.10
Horse, fat	0.05		0.05
Horse, kidney	0.50		--
Horse, meat	0.05		0.005
Horse, meat byproducts, except kidney	0.05		--
Ilama	0.05		0.01
Jaboticaba	0.05		--
Kiwifruit	0.05		0.01
Lentil, seed	0.50		0.5
Lettuce	0.05		0.07
Longan	0.05		0.01
Lychee	0.05		--
Mango	0.05		0.01
Milk	0.01		0.005
Nut, tree, group 14-12	0.05		0.05
Okra	0.05		0.05
Olive	0.10		0.10
Onion, bulb, subgroup 3-07A	0.10	0.1	--
Onion, green, subgroup 3-07B	0.05	0.05	--
Papaya	0.05		0.01
Passionfruit	0.20		0.01
Pawpaw	0.05		0.01
Vegetable, legume, edible podded, subgroup 6A	0.05	0.05 individual	0.5
Pea and bean, succulent shelled, subgroup 6B	0.05	0.05 individual	0.5
Pea and bean, dried shelled, except soybean, subgroup 6C	0.50		0.5
Pea, field, hay	0.80		--
Pea, field, vines	0.20		--
Peanut	0.05		--
Peanut, hay	0.50		--
Peppermint, fresh leaves	0.50		--
Persimmon	0.05		0.01
Pineapple	0.05		0.01
Pineapple, process residue	0.30		--
Pistachio	0.05		0.05

Table C.1. Summary of US and International Tolerances and Maximum Residue Limits			
***Residue Definition*:**			
US		Canada	Codex[3]
Pomegranate	0.05		0.01
Pulasan	0.05		0.01
Rambutan	0.05		0.01
Rhubarb	0.05		--
Rice, grain	0.05		0.05
Safflower, seed	0.05		--
Sapodilla	0.05		0.01
Sapote, black	0.05		0.01
Sapote, mamey	0.05		0.01
Sapote, white	0.05		0.01
Sheep, fat	0.05		0.05
Sheep, kidney	0.50		--
Sheep, meat	0.05		0.005
Sheep, meat byproducts, except kidney	0.05		--
Sorghum, forage, forage	0.10		--
Sorghum, grain, forage	0.10		--
Sorghum, grain, grain	0.05		0.03
Soursop	0.05		0.01
Soybean, forage	0.40		--
Soybean, hay	10		--
Soybean, hulls	4.5		--
Soybean, seed	0.70		0.5
Spanish lime	0.05		0.01
Spearmint, fresh leaves	0.50		--
Star apple	0.05		0.01
Starfruit	0.05		--
Strawberry	0.30		0.01
Sugar apple	0.05		0.01
Sugarcane, cane	0.50		--
Sugarcane, molasses	3.0		--
Sunflower, seed	2.0		2
Turnip, roots	0.05		0.05
Vegetable, Head and Stem Brassica, Group 5-16	0.07		0.07
Brassica leafy greens subgroup 4-16B	0.07		0.07
Stalk and Stem Vegetable Subgroup 22A	0.05		
Vegetable, cucurbit, group 9	0.05		0.02
Vegetable, fruiting, group 8-10	0.05		0.05
Vegetable, tuberous and corm, subgroup 1C	0.50		0.05
Wax jambu	0.05		--
Wheat, forage	0.50		--
Wheat, grain	1.1		--
Wheat, hay	3.5		--
Wheat, straw	50		--
Completed: T. Morton; 05/30/2018			

[1] Includes only commodities of interest for this action.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix D. Summary of Paraquat Occupational Handler Exposure and Risk Estimates

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat

Exposure Scenario	Crop or Target	Dermal Unit Exposure[1] (µg/lb ai)	Level of PPE or Engineering control[2]	Inhalation Unit Exposure[1] (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate[3]	Area Treated or Amount Handled Daily[4]	Dermal LOC = 100		Inhalation LOC = 100	
								Dose[5] (mg/kg/day)	MOE[6]	Dose[7] (mg/kg/day)	MOE[8]
Mixer/Loader											
Liquid, Backpack, Broadcast	All Use Sites	37.6	SL/G	0.0219	APF10 R	0.015 lb ai/gallon	40 gallons	0.000283	21000	0.000000164	16000
		29.1	DL/G					0.000219	27000		
		8.6	EC	0.083	EC			0.0000645	93000	0.000000623	4200
	Pastureland	37.6	SL/G	0.0219	APF10 R	0.019 lb ai/gallon		0.000358	17000	0.000000208	13000
		29.1	DL/G					0.000276	22000		
		8.6	EC	0.083	EC			0.0000818	73000	0.000000789	3300
Liquid, Mechanically-pressurized Handgun, Broadcast	All Use Sites	37.6	SL/G	0.0219	APF10 R	0.015 lb ai/gallon	1000 gallons	0.00705	850	0.00000411	630
		29.1	DL/G					0.00546	1100		
		8.6	EC	0.083	EC			0.00161	3700	0.0000156	170
	Pastureland	37.6	SL/G	0.0219	APF10 R	0.019 lb ai/gallon		0.00893	670	0.0000052	500
		29.1	DL/G					0.00691	870		
		8.6	EC	0.083	EC			0.00204	2900	0.0000198	130
Liquid, Aerial	Nursery (ornamentals, vegetables, trees, container stock)	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	60 A	0.0283	210	0.0000164	160
		29.1	DL/G					0.0219	270		
		8.6	EC	0.083	EC			0.00645	930	0.0000623	**42**
	Field crop, typical: Asparagus; Brassica (head and stem) Vegetables; Carrots (Including	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	350 A	0.165	**36**	0.0000959	**27**

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Tops); Corn, Sweet; Cucurbit; Vegetables; Eggplant; Fruiting Vegetables; Leafy Vegetables; Lettuce; Melons; Peas (Unspecified); Pepper; Sugar Beet; Tomato; Turnip Greens Orchard/Vineyard; Almond	29.1	DL/G					0.128	**47**		
		8.6	EC	0.083	EC			0.0376	160	0.000364	**7.1**
	Field crop, typical: Legume Vegetables; Sage, Clary	37.6	SL/G	0.0219	APF10 R	0.80 lb ai/A	350 A	0.131	**46**	0.0000766	**34**
		29.1	DL/G					0.102	**59**		
		8.6	EC	0.083	EC			0.0301	200	0.00029	**9**
	Field crop, typical: Lentils; Peas, Dried Type; Tuberous and Corm Vegetables; Orchard/Vineyard; Grapes	37.6	SL/G	0.0219	APF10 R	0.50 lb ai/A	350 A	0.0823	**73**	0.0000479	**54**
		29.1	DL/G					0.0636	**94**		
		8.6	EC	0.083	EC			0.0189	320	0.000181	**14**
	Field crop, typical: Root and Tuber Vegetables	37.6	SL/G	0.0219	APF10 R	0.30 lb ai/A	350 A	0.0494	120	0.0000288	**90**
		29.1	DL/G					0.0383	160		
		8.6	EC	0.083	EC			0.0113	530	0.000109	**24**
	Field crop, high acreage: Alfalfa; Clover	37.6	SL/G	0.0219	APF10 R	1.5 lb ai/A	1200 A	0.846	**7.1**	0.000493	**5.3**
		29.1	DL/G					0.655	**9.2**		
		8.6	EC	0.083	EC			0.194	**31**	0.00186	**1.4**
	Field crop, high-acreage; Barley; Beans, Dried-Type; Corn, Field; Corn, Pop; Cotton; Deciduous/Broadleaf/Hardwood; Fallowland; Forestry; Grasses Grown for Seed; Mint; Nonagricultural Areas; Pastureland/Rangeland; Peas (Unspecified); Potato, White/Irish (or Unspecified);	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	1200 A	0.564	**11**	0.000329	**7.9**
		29.1	DL/G					0.436	**14**		

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Rice; Root and Tuber Vegetables; Safflower; Sorghum; Soybeans; Sugarcane; Sunflower; Tuberous and Corm Vegetables; Wheat	8.6	EC	0.083	EC			0.129	**47**	0.00125	**2.1**
	Field crop, high acreage: Legume Vegetables	37.6	SL/G	0.0219	APF10 R	0.80 lb ai/A	1200 A	0.451	**13**	0.000263	**9.9**
		29.1	DL/G					0.349	**17**		
		8.6	EC	0.083	EC			0.103	**58**	0.000996	**2.6**
	Field crop, high acreage: Peas, Dried-Type	37.6	SL/G	0.0219	APF10 R	0.50 lb ai/A	1200 A	0.283	**21**	0.000164	**16**
		29.1	DL/G					0.219	**27**		
		8.6	EC	0.083	EC			0.0645	**93**	0.000623	**4.2**
Liquid, Groundboom	Nursery (ornamentals, vegetables, trees, container stock)	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	60 A	0.0283	210	0.0000164	160
		29.1	DL/G					0.0219	270		
		8.6	EC	0.083	EC			0.00645	930	0.0000623	**42**
	Orchard/Vineyard: Arecola (West Indies Cherry); Apple; Apricot: Avocado; Banana; Bushberries; Caneberries; Citrus; Cocoa; Coffee; Fig; Grapes; Guava; Kiwi; Nectarine; Olive; Papaya; Passion Fruit (Granadilla); Peach; Pear; Persimmon; Pistachio; Plum; Prune; Subtropical/Tropical Fruit; Tree Nuts	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	40 A	0.0188	320	0.000011	240
		29.1	DL/G					0.0145	410		
		8.6	EC	0.083	EC			0.0043	1400	0.0000415	**63**
	Orchard/Vineyard: Macadamia Nut (Bushnut)	37.6	SL/G	0.0219	APF10 R	0.50 lb ai/A	40 A	0.0094	640	0.00000548	470
		29.1	DL/G					0.00728	820		
		8.6	EC	0.083	EC			0.00215	2800	0.0000208	130

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Field crop, typical: Artichoke; Asparagus; Brassica (head and stem) Vegetables; Carrots (Including Tops); Corn, Sweet; Cucurbit Vegetables; Eggplant; Flowering Plants; Fruiting Vegetables; Garlic; Ginger; Leafy Vegetables; Lettuce; Manioc (Cassava); Melons; Okra; Onions; Peas (Unspecified); Pepper; Pineapple; Root and Tuber Vegetables; Rhubarb; Sugar Beet; Tomato; Turnip Greens; Yam	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	80 A	0.0376	160	0.0000219	120
		29.1	DL/G					0.0291	210		
		8.6	EC	0.083	EC			0.0086	700	0.000083	**31**
	Field crop, typical: Tobacco	37.6	SL/G	0.0219	APF10 R	0.94 lb ai/A	80 A	0.0354	170	0.0000206	130
		29.1	DL/G					0.0274	220		
		8.6	EC	0.083	EC			0.00809	740	0.000078	**33**
	Field crop, typical: Legume Vegetables; Sage, Clary; Taro; Vegetables (Unspecified)	37.6	SL/G	0.0219	APF10 R	0.80 lb ai/A	80 A	0.0301	200	0.0000175	150
		29.1	DL/G					0.0233	260		
		8.6	EC	0.083	EC			0.00688	870	0.0000664	**39**
	Field crop, typical: Guar; Lentils; Peas, Dried Type; Peas, Pigeon; Strawberry; Tuberous and Corm Vegetables;	37.6	SL/G	0.0219	APF10 R	0.50 lb ai/A	80 A	0.0188	320	0.000011	240
		29.1	DL/G					0.0145	410		
		8.6	EC	0.083	EC			0.0043	1400	0.0000415	**63**
	Field crop, high acreage: Alfalfa; Clover	37.6	SL/G	0.0219	APF10 R	1.5 lb ai/A	200 A	0.141	**43**	0.0000821	**32**
		29.1	DL/G					0.109	**55**		
		8.6	EC	0.083	EC			0.0323	190	0.000311	**8.4**

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Field crop, high acreage: Barley; Coniferous/Evergreen/Softwood (non-food); Corn, Field; Corn, Pop; Cotton; Fallowland; Peanuts; Peas (Unspecified); Rice; Safflower; Sorghum; Soybean; Sugarcane; Sunflower; Tyfon; Wheat	37.6	SL/G	0.0219	APF10 R	1.0 lb ai/A	200 A	0.094	**64**	0.0000548	**47**
		29.1	DL/G					0.0728	**82**		
		8.6	EC	0.083	EC			0.0215	280	0.000208	**13**
	Field crop, high acreage: Legume Vegetables; Mint	37.6	SL/G	0.0219	APF10 R	0.80 lb ai/A	200 A	0.0753	**80**	0.0000438	**59**
		29.1	DL/G					0.0583	100		
		8.6	EC	0.083	EC			0.0173	350	0.000166	**16**
	Field crop, high acreage: Grasses Grown for Seed; Potato, White/Irish (or Unspecified)	37.6	SL/G	0.0219	APF10 R	0.60 lb ai/A	200 A	0.0564	110	0.0000329	**79**
		29.1	DL/G					0.0436	140		
		8.6	EC	0.083	EC			0.0129	470	0.000125	**21**
	Field crop, high acreage: Beans, Dried-Type; Hops; Pastureland; Peas, Dried-Type; Peas, Pigeon; Tuberous and Corm Vegetables	37.6	SL/G	0.0219	APF10 R	0.50 lb ai/A	200 A	0.047	130	0.0000274	**95**
		29.1	DL/G					0.0364	160		
		8.6	EC	0.083	EC			0.0108	560	0.000104	**25**
	Field crop, high acreage: Root and Tuber Vegetables	37.6	SL/G	0.0219	APF10 R	0.30 lb ai/A	200 A	0.047	130	0.0000164	160
		29.1	DL/G					0.0219	270		
		8.6	EC	0.083	EC			0.00645	930	0.0000623	**42**
Applicator											
Spray (all starting formulations), Aerial	Field crop, typical: Asparagus; Brassica (head and stem) Vegetables; Carrots (Including Tops); Corn, Sweet; Cucurbit; Vegetables; Eggplant; Fruiting Vegetables; Leafy Vegetables;	2.08	EC	0.0049	EC	1.0 lb ai/A	350 A	0.0091	660	0.0000215	120

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Lettuce; Melons; Peas (Unspecified); Pepper; Sugar Beet; Tomato; Turnip Greens Orchard/Vineyard; Almond										
	Field crop, typical: Legume Vegetables; Sage, Clary	2.08	EC	0.0049	EC	0.80 lb ai/A	350 A	0.00728	820	0.0000171	150
	Field crop, typical: Lentils; Peas, Dried Type; Tuberous and Corm Vegetables; Orchard/Vineyard; Grapes	2.08	EC	0.0049	EC	0.50 lb ai/A	350 A	0.00455	1300	0.0000107	240
	Field crop, typical: Root and Tuber Vegetables	2.08	EC	0.0049	EC	0.30 lb ai/A	250 A	0.00195	3100	0.0000046	570
	Field crop, high acreage: Alfalfa; Clover	2.08	EC	0.0049	EC	1.5 lb ai/A	1200 A	0.0468	130	0.00011	**24**
	Field crop, high-acreage; Barley; Beans, Dried-Type; Corn, Field; Corn, Pop; Cotton; Deciduous/Broadleaf/Hardwood; Fallowland; Forestry; Grasses Grown for Seed; Mint; Nonagricultural Areas; Pastureland/Rangeland; Peas (Unspecified); Potato, White/Irish (or Unspecified); Rice; Root and Tuber Vegetables; Safflower; Sorghum; Soybeans; Sugarcane; Sunflower; Tuberous and Corm Vegetables; Wheat	2.08	EC	0.0049	EC	1.0 lb ai/A	1200 A	0.0313	190	0.0000735	**35**
	Field crop, high acreage: Legume Vegetables	2.08	EC	0.0049	EC	0.80 lb ai/A	1200 A	0.025	240	0.0000588	**44**
	Field crop, high acreage: Peas, Dried-Type	2.08	EC	0.0049	EC	0.50 lb ai/A	1200 A	0.0156	380	0.0000368	**71**
Spray (all starting formulations), Groundboom	Nursery (ornamentals, vegetables, trees, container stock)	5.1	EC	0.043	EC	1.0 lb ai/A	60 A	0.00383	1600	0.0000323	**80**
	Orchard/Vineyard: Arecola (West Indies Cherry); Apple; Apricot: Avocado; Banana; Bushberries; Caneberries; Citrus; Cocoa; Coffee; Fig; Grapes; Guava; Kiwi; Nectarine;	5.1	EC	0.043	EC	1.0 lb ai/A	40 A	0.00255	2400	0.0000215	120

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Olive; Papaya; Passion Fruit (Granadilla); Peach; Pear; Persimmon; Pistachio; Plum; Prune; Subtropical/Tropical Fruit; Tree Nuts										
	Orchard/Vineyard: Macadamia Nut (Bushnut)	5.1	EC	0.043	EC	0.50 lb ai/A	40 A	0.00128	4700	0.0000108	240
	Field crop, typical: Artichoke; Asparagus; Brassica (head and stem) Vegetables; Carrots (Including Tops); Corn, Sweet; Cucurbit Vegetables; Eggplant; Flowering Plants; Fruiting Vegetables; Garlic; Ginger; Leafy Vegetables; Lettuce; Manioc (Cassava); Melons; Okra; Onions; Peas (Unspecified); Pepper; Pineapple; Root and Tuber Vegetables; Rhubarb; Sugar Beet; Tomato; Turnip Greens; Yam	5.1	EC	0.043	EC	1.0 lb ai/A	80 A	0.0051	1200	0.000043	**60**
	Field crop, typical: Tobacco	5.1	EC	0.043	EC	0.94 lb ai/A	80 A	0.0048	1300	0.0000404	**64**
	Field crop, typical: Legume Vegetables; Sage, Clary; Taro; Vegetables (Unspecified)	5.1	EC	0.043	EC	0.80 lb ai/A	80 A	0.00408	1500	0.0000344	**76**
	Field crop, typical: Guar; Lentils; Peas, Dried Type; Peas, Pigeon; Strawberry; Tuberous and Corm Vegetables;	5.1	EC	0.043	EC	0.50 lb ai/A	80 A	0.00255	2400	0.0000215	120
	Field crop, high acreage: Alfalfa; Clover	5.1	EC	0.043	EC	1.5 lb ai/A	200 A	0.0191	310	0.000161	**16**
	Field crop, high acreage: Barley; Coniferous/Evergreen/Softwood (non-food); Corn, Field; Corn, Pop; Cotton; Fallowland; Peanuts; Peas (Unspecified); Rice; Safflower; Sorghum; Soybean; Sugarcane; Sunflower; Tyfon; Wheat	5.1	EC	0.043	EC	1.0 lb ai/A	200 A	0.0128	470	0.000108	**24**

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Field crop, high acreage: Legume Vegetables; Mint	5.1	EC	0.043	EC	0.80 lb ai/A	200 A	0.0102	590	0.000086	**30**
	Field crop, high acreage: Grasses Grown for Seed; Potato, White/Irish (or Unspecified)	5.1	EC	0.043	EC	0.6 lb ai/A	200 A	0.00765	780	0.0000645	**40**
	Field crop, high acreage: Beans, Dried-Type; Hops; Pastureland; Peas, Dried-Type; Peas, Pigeon; Tuberous and Corm Vegetables	5.1	EC	0.043	EC	0.5 lb ai/A	200 A	0.00638	940	0.0000538	**48**
	Field crop, high acreage: Root and Tuber Vegetables	5.1	EC	0.043	EC	0.3 lb ai/A	200 A	0.00383	1600	0.0000323	**80**
Flagger											
Spray (all starting formulations), Aerial	Field crop, high acreage: Alfalfa; Clover	12	SL/G	0.035	APF10 R	1.5 lb ai/A	350 A	0.0788	76	0.00023	**11**
	Field crop, typical: Asparagus; Brassica (head and stem) Vegetables; Carrots (Including Tops); Corn, Sweet; Cucurbit; Vegetables; Eggplant; Fruiting Vegetables; Leafy Vegetables; Lettuce; Melons; Peas (Unspecified); Pepper; Sugar Beet; Tomato; Turnip Greens Orchard/Vineyard; Almond Field crop, high-acreage; Barley; Beans, Dried-Type; Corn, Field; Corn, Pop; Cotton; Deciduous/Broadleaf/Hardwood; Fallowland; Forestry; Grasses Grown for Seed; Mint; Nonagricultural Areas; Pastureland/Rangeland; Peas (Unspecified); Potato, White/Irish (or Unspecified); Rice; Root and Tuber Vegetables; Safflower; Sorghum; Soybeans; Sugarcane; Sunflower; Tuberous and Corm Vegetables; Wheat					1.0 lb ai/A	350 A	0.0525	110	0.000154	**17**
	Field crop, typical: Legume Vegetables; Sage, Clary					0.80 lb ai/A	350 A	0.042	140	0.000123	**21**

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
	Field crop, typical: Lentils; Peas, Dried Type; Tuberous and Corm Vegetables; Orchard/Vineyard; Grapes Field crop, high acreage: Peas, Dried-Type					0.50 lb ai/A	350 A	0.0263	230	0.0000766	**34**
	Field crop, typical: Root and Tuber Vegetables					0.30 lb ai/A	350 A	0.0158	380	0.000046	**57**
Mixer/Loader/Applicator											
Liquid, Backpack, Ground/soil-directed	All Use Sites	8260	SL/G	0.258	APF10 R	0.015 lb ai/gallon	40 gallons	0.062	**97**	0.00000194	1300
		4120	DL/G					0.0309	190		
	Pastureland	8260	SL/G			0.019 lb ai/gallon		0.0785	**76**	0.00000245	1100
		4120	DL/G					0.0391	150		
Liquid, Backpack, Broadcast	All Use Sites	30500	SL/G	6.91	APF10 R	0.015 lb ai/gallon		0.229	**26**	0.0000519	**50**
		16900	DL/G					0.126	**48**		
	Pastureland	30500	SL/G			0.019 lb ai/gallon		0.29	**21**	0.0000656	**40**
		16900	DL/G					0.16	**38**		
Liquid, Manually-pressurized Handwand, Broadcast	All Use Sites	430	SL/G	430	APF10 R	0.015 lb ai/gallon		0.00323	1900	0.0000225	120
		365	DL/G					0.00274	2200		
	Pastureland	430	SL/G			0.019 lb ai/gallon		0.00409	1500	0.0000285	**91**
		365	DL/G					0.00346	1700		
Liquid, Mechanically-pressurized	All Use Sites	2050	SL/G	0.868	APF10 R	0.015 lb ai/gallon	1000 gallons	0.385	**16**	0.000163	**16**
		1360	DL/G					0.255	**24**		

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Paraquat											
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control[2]**	**Inhalation Unit Exposure[1] (µg/lb ai)**	**Level of PPE or Engineering control**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Dermal LOC = 100**		**Inhalation LOC = 100**	
								Dose[5] (mg/kg/day)	**MOE[6]**	**Dose[7] (mg/kg/day)**	**MOE[8]**
Handgun, Broadcast (foliar); Drench/Soil-/Ground-directed	Pastureland	2050	SL/G			0.019 lb ai/gallon		0.488	**12**	0.000206	**13**
		1360	DL/G					0.323	**19**		
Loader/Applicator											
Liquid, Backpack, Broadcast	Rights-of-Way	30500	SL/G	6.91	APF10 R	0.015 lb ai/gallon	40 gallons	0.229	**26**	0.0000519	**50**
		16900	DL/G					0.126	**48**		

1. Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline, PPE, Eng. Controls.
2. SL/G = single layer clothing/gloves; DL/G = double layer clothing/gloves; APF 10 R = assigned protection factor 10 respirator; EC = engineering control.
3. Based on registered labels as summarized in the Line by Line, and Maximum Use Scenario Pesticide Label Usage Summary (PLUS) Reports as generated by OPP's Biological and Economic Analysis Division (BEAD).
4. Exposure Science Advisory Council Policy #9.1.
5. Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) × DAF (%) ÷ BW (80 kg).
6. Dermal MOE = Dermal NOAEL (6 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
7. Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
8. Inhalation MOE = Inhalation NOAEL (0.0026 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).