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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

March 25, 2002

MEMORANDUM

SUBJECT: **Diquat Dibromide** HED Risk Assessment for Tolerance Reassessment Eligibility Document (TRED.) PC Code No: 032201; DP Barcode: D281890; Submission Barcode: S611057

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Attached is the Health Effects Division (HED's) revised risk assessment conducted to support a Tolerance Reassessment Eligibility Decision (TRED) for diquat dibromide. This document updates the March 6, 2001 version by incorporating revisions to the drinking water exposure assessment provided by the Environmental Fate and Effects Division (EFED). The disciplinary science chapters and other supporting documents are included as appendices as follows:

Use Closure Memo. Tyler Lane (10/31/01)
Report of the Hazard Identification Assessment Review Committee. Linda Taylor (12/14/01, HED DOC NO 014670)
Report of the FQPA Safety Factor Committee. C. Christiansen (11/27/10, TXR NO. 0050293)
Report of the Metabolism Assessment Review Committee. T. Morton (9/13/01, D277764)
Product & Residue Chemistry Chapter. T. Morton (12/12/01, D277710)
Residential Exposure Assessment. T. Brennan (12/14/01, D279507)
Dietary Exposure and Risk Estimates for Tolerance Reassessment. B. Daiss (12/11/01, D277766)
Incident Report. M. Spann and J. Blondell, Ph.D (10/15/01, D278482)
Tier I Drinking Water and Aquatic Ecological Exposure Assessments for Diquat Dibromide. J Breithaupt (3/5/02, D281199)
Toxicology Chapter, Linda Taylor (12/14/01, D279696)

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Chemical:	**6,7-Dihydrodipyrido(1,2-a:2',1'-c)pyrazi**
PC Code:	**032201**
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1.0 EXECUTIVE SUMMARY

EPA issued a Reregistration Eligibility Decision (RED) for diquat dibromide in July, 1995. The RED recommended revisions to some of the existing tolerances for diquat dibromide. The purpose of this document is to reassess the findings and conclusions presented in the RED to determine whether infants and children exhibit enhanced sensitivity from dietary and/or residential exposure to diquat dibromide. This action is required under the Food Quality Protection Act (FQPA) of 1996. Occupational exposure/risk is not considered for this TRED. However, a separate but concurrent reassessment of occupational exposure/risk is also being conducted to address the registrant's request to modify diquat dibromide label requirements (T. Brennan, D279612).

Use Profile

Diquat dibromide is a non-selective contact herbicide, algicide, dessicant, and defoliant. As a herbicide/algicide, it is used to control aquatic and terrestrial weeds. It is used as a preharvest dessicant/defoliant to facilitate the harvest of potatoes and various crops grown for seed. Its largest use is as a dessicant on potato crops. Other minor food use applications include use as a dessicant on crops grown for seed that is used for feed, i.e., alfalfa, sorghum, soybean, and clover. Additionally, use of irrigation water containing residues of diquat may result in diquat residues in plants and livestock. Non-food use applications include use as a preharvest dessicant on carrot, radish and turnip grown for seed; as a post-harvest dessicant on cantaloupe, cucumber, pepper, squash, tomato, and watermelon; and as a dessicant/defoliant for commercial greenhouses and nurseries, ornamental seed crops, and commercial and residential landscaping and grounds maintenance. Diquat dibromide is rapidly absorbed by green plant tissue and interacts with the photosynthesis process. It works as an herbicide/dessicant by reacting with molecular oxygen to produce a superoxide anion in treated plants. The oxidative activity, which occurs subsequent to formation of the oxygen radicals, rapidly destroys plant cell membranes. Herbicidal activity is usually quite rapid with effects visible in a few days.

Diquat dibromide is formulated as a soluble concentrate and ready-to-use liquid. As an herbicide/algicide used to control algae and aquatic weeds, it is applied by direct pouring, hand-held or mechanical sprayer, and injection below the water surface. As a terrestrial herbicide and crop dessicant/defoliant, it is applied by hand-held sprayer, aircraft, or ground equipment.

Currently, 43 products containing the active ingredient diquat dibromide are registered and marketed under the trade name diquat dibromide. The largest markets for diquat, in terms of total pounds of active ingredient, include: aquatic uses (40%), potatoes (35%), home & garden (10%), and alfalfa for seed (5%). Most of the usage is in FL, ME, ND, NY, WA, and WI (T. Lane, Use Closure Memo, 10/31/01).

Regulatory History

In July, 1995, EPA issued a RED for diquat dibromide. In the RED, the Agency recommended changes to published tolerances for several commodities, including fish (increase from 0.1 to 2.0 ppm) and fruiting vegetables (increase from 0.02 to 0.05 ppm). The recommended changes to the tolerances have not yet been implemented. Based on the risk assessment conducted for the RED, EPA concluded that acute and chronic dietary risks from exposure to diquat are minimal, but found risks of concern for some worker and residential exposure scenarios. To address these risks EPA required the following: closed mixing/loading of diquat dibromide for aerial applications; a longer interim restricted entry level (REI) and more stringent personal protective equipment (PPE) for uses within the scope of the Worker Protection Standard for Agricultural Pesticides; a four-day reentry interval to reduce post-application exposure for workers not covered by the worker protection standard (e.g., golf course workers); and a ban on broadcast treatments to reduce the potential for post-application residential exposure. Diquat labels have not yet been revised in accordance with the requirements outlined in the RED. The RED also addressed the occurrence of ethylene dibromide (EDB) which is used as a starting material in the manufacture of diquat dibromide and may be present as a process impurity in final formulations. EDB is considered a carcinogen and all pesticide uses of EDB have been canceled. Previous EPA assessments indicate that the presence of EDB in diquat formulations does not pose a significant dietary risk. In addition, the registrant certified an upper limit of 10 ppm EDB in diquat dibromide, and demonstrated that EDB does not persist as an impurity in diquat dibromide.

In January, 1998, HED conducted a human health risk assessment to evaluate the effect of a change in application and use patterns on potatoes and a new use on dried shelled peas and beans (W Cutchin, 1/23/98, D220714). Results from the 1998 assessment were consistent with the RED, as were the recommendations for additional restricted entry and PPE requirements.

Only manufacturing use products (MPs) are subject to a reregistration eligibility decision. There are currently only 2 diquat dibromide MPs; 41.1% and 37.3% a.i. formulation intermediates. Both of these MPs are currently registered to Syngenta Crop Protection, Inc. The products were transferred from Zeneca to Syngenta and the product chemistry information for the Zeneca MPs was a repack of a registered product which is now canceled. From the confidential statements of formula provided by Syngenta, it appears that the manufacturing process for the current MPs has changed. Therefore, the product chemistry data submitted for the canceled products do not satisfy the requirements for the Syngenta products and a complete updated product chemistry data package on the currently registered technicals must be submitted to support continued registration.

Hazard Identification and Dose Response Assessment

The toxicology data base is adequate to characterize the toxicity of diquat dibromide, Diquat dibromide exhibits low acute toxicity *via* the oral (Toxicity Category II for technical, III for formulation) and inhalation (Toxicity Category III) routes of exposure but is moderately-to-severely toxic *via* the dermal route of exposure (Toxicity Categories I for technical and II for

formulation). Diquat dibromide is not an acute skin irritant (Toxicity Category IV) nor a dermal sensitizer, but it is considered a moderate-to-severe eye irritant (Toxicity Category II).

Subchonic and chronic studies in several species indicate multiple target sites for diquat dibromide toxicity. In subchronic dermal exposure studies in rats, diquat dibromide showed evidence of severe systemic toxicity, i.e. high mortality and clinical signs. In subchronic inhalation study in rats, the lung was determined to be the primary target site for inhalation toxicity. Chronic feeding studies in dogs, rats, mice, and rabbits indicate that target sites include the eyes and kidneys in both males and females and the adrenals and epididymides in males. Developmental toxicity was observed in rat, rabbit, and mouse studies, and reproductive toxicity was observed in the rat in both generations. Rat and rabbit studies provided evidence of maternal toxicity. Acute and subchronic studies in mice and rats provided no evidence of neurotoxicity. Available data provide no evidence of endocrine disruption following exposure to diquat dibromide. Carcinogenicity studies in rats and mice provided no evidence of an increased tumor incidence and diquat dibromide was classified as a Category E (evidence of non-carcinogenicity to humans) by the HED Cancer Peer Review Committee based on the 1999 *EPA Draft Proposed Guidelines for Carcinogen Risk Assessment*. The weight of the evidence was predominantly negative for mutagenicity. The data provided no indication of increased sensitivity of rats, mice, or rabbits to in utero and/or early postnatal exposure to diquat dibromide. HED's FQPA committee determined that the FQPA safety factor could be removed (1x) in assessing the risk posed by this chemical because the toxicological database is complete for FQPA assessment, there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure, a developmental neurotoxicity study is not required, and the dietary (food and drinking water) and residential exposure assessments will not underestimate potential exposures for infants and children. There are no toxicological study data gaps at this time.

Risk assessments were conducted for the exposure scenarios listed below. Route-specific endpoints were selected for all but the dermal scenario. The dermal exposure endpoint is based on oral toxicity studies and therefore requires application of a dermal absorption factor (4.1%).

– acute dietary(general population):	NOAEL= 75 mg/kg/day	RfD=0.75 mg/kg/day
– chronic dietary:	NOAEL= 0.5	RfD = 0.005 mg/kg/day
– short-term oral:	NOAEL= 1 mg/kg/day	MOE=100
– short-term dermal:	NOAEL= 1 mg/kg/day	MOE=100

Exposure Assessment

Analysis of dietary, drinking water, and residential exposure pathways were included in the risk assessment for the diquat TRED. Sources of dietary exposure include potatoes and various crops grown for seed that is used for feed (e.g. alfalfa, sorghum) to which diquat has been applied as a dessicant. Residues in plants and livestock feeds may also occur through irrigation of crops with water containing diquat residues, resulting in dietary exposure through consumption of crops and secondary residues in livestock tissues. Drinking water exposure may occur due to run-

off from terrestrial use of diquat and use of diquat in lakes, ponds, streams, etc., to control aquatic weeds. Residential application and post-application exposure may occur through the use of diquat on turf grass and weeds. Potential residential exposure routes include inhalation and dermal exposure to adult applicators/handlers, postapplication dermal exposure to adults and children, and incidental ingestion of residue by toddlers via hand-to-mouth activity and ingestion of grass or soil from a treated area.

Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary, drinking water, and residential exposure pathways. An aggregate assessment of risk from the combined food, drinking water and residential pathways was also conducted. A cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity has not been conducted for this TRED because HED has not yet determined if there are any other chemical substances that have a mechanism of toxicity common with that of diquat dibromide.

Food Pathway Exposure and Risk

HED conducted acute and chronic dietary exposure analysis using the Dietary Exposure Evaluation Model (DEEM™). The acute and chronic dietary exposure/risk analyses were conducted using a conservative deterministic (Tier I) methodology. The Tier I analysis assumes that; 1) residues are present at published tolerances for registered uses and at recommended tolerances for proposed new uses, and 2) 100% crop treated (CT) for all commodities with existing and/or recommended tolerances. Tier I acute and chronic dietary analyses were conducted for the general U.S. population and all population subgroups.

The acute and chronic dietary risks are expressed as a percentage of the acute or chronic Population Adjusted Dose (aPAD or cPAD). A dietary risk of 100% of the PAD is the target level of exposure that should not be exceeded, (i.e., the estimated risk that is less than 100% of PAD is not of concern). The Population Adjusted Dose (PAD) is the Acute reference dose (RfD) or the Chronic RfD modified by the FQPA Safety Factor. In the acute dietary assessment for diquat, acute exposure (mg/kg/day) was compared to the aPAD which is based on the acute RfD and a FQPA safety factor of 1x.. For the chronic dietary assessment, chronic exposure was compared to the cPAD which is based on the chronic RfD and an FQPA factor of 1x. Based on these analyses, acute and chronic dietary risk associated with exposure to diquat from existing and proposed uses are below the Agency's level of concern for the general US population and population subgroups. The 95th percentile acute exposure estimates were < 100% of the aPAD. The highest acute exposures (0.0054 mg/kg/day) were in Children 1-6 years old (<1% aPAD). The chronic exposure estimates were <100% of the cPAD, with the highest chronic exposure (0.0031 mg/kg/day) occurring in children 1-6 years old (62% cPAD).

Residential Pathway Exposure and Risk

Potential residential scenarios include exposures to handlers (mixers, loaders, applicators, etc.) that occur during handling and application of diquat and/or to persons entering treated sites after its application. This TRED estimates exposure and risk for four residential handler scenarios four post-application scenarios, and two recreational scenarios. Residential handler scenarios include: 1) mixing, loading, and applying with a low pressure handwand (for lawns and backyard ponds), 2) mixing, loading, applying with a backpack sprayer(for lawns and backyard ponds), 3) applying with an aerosol sprayer (for lawns), and 4) applying with a trigger pump sprayer. Postapplication scenarios include: 1) dermal exposure to treated turf grass (adults and children); 2) toddler ingestion of treated turf grass via object-to-mouth activities; 3) toddler ingestion of residue via hand-to-mouth activity while on treated turf grass; and 4) toddler ingestion of soil from treated areas. Recreational exposures include: 1) golfer exposure from playing on treated turf grass; and 2) exposure from swimming in treated lakes and ponds. A target Margin of Exposure (MOE) of 100 is considered adequate for all residential exposure routes. With one exception, the MOEs estimated for all of the residential exposure scenarios described above showed no risks of concern (i.e. all MOEs were 100 or greater). An assessment of aggregate residential risks to children 1-6 years from post-application exposure to broadcast treated lawns resulted in an estimated MOE of 70, which exceeds the Agency's level of concern. The residential aggregate risk combines screening level risk estimates from individual exposure pathways and should be viewed as a highly conservative estimate which is certain to over-estimate risk. A refined analysis would result in lower exposure estimates and higher MOEs.

Drinking Water Pathway Exposure and Risk

The Environmental Fate and Effects Division (EFED) performed a Tier I drinking water assessment for diquat dibromide for both terrestrial and aquatic uses. EFED used both computer models and monitoring data to estimate environmental concentrations of diquat in surface and ground water. For terrestrial uses, EFED assessed preharvest application to potatoes, alfalfa, and clover with aerial and ground equipment and application to clover trees, vines, small fruits, and vegetables using directed spray from ground equipment. The FQPA Index Reservoir Screening Tool (FIRST) model was used to estimate environmental concentrations in drinking water from surface water contaminated by terrestrial use of diquat. The surface water estimated environmental concentrations (EECs) generated by FIRST ranged from 6.3- 13.2 ug/L (ppb) for peak exposure and 0.2-0.4 ug/L for average annual exposure.

EFED relied on monitoring data to estimate concentrations in groundwater contaminated by terrestrial uses. Based on municipal monitoring data, EFED recommends use of EPA's Office of Waters (OW) maximum contaminant level (MCL) of 20 ppb for both peak and average annual EECs for groundwater concentrations due to terrestrial use of diquat. EFED also used monitoring data to estimate surface water and ground water concentrations from aquatic uses of diquat. For surface water, EFED recommends use of the MCL of 20 ppb for both acute (peak) and chronic (annual average) EECs. For the aquatic use EFED relied on use information from the U.S. Corp of

Engineers and the states of Florida, Minnesota, and Michigan. The assessed aquatic uses include application to lakes and flowing streams. EFED also recommends use of the MCL of 20 ppb for both acute and chronic EECs for groundwater. EFED recommends use of the same EECs for both surface and groundwater contaminated by aquatic uses of diquat because diquat is used near wells located next to lakes and ponds resulting in interaction between surface and ground water.

Aggregate Exposures and Risks

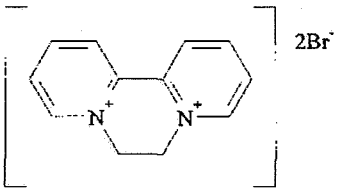
The aggregate risk assessment combines the exposure assessments conducted for dietary, drinking water, and residential exposure. Since there is potential for concurrent exposure via the food, water, and residential pathways, the combined or aggregate exposures are estimated and expressed in terms of an aggregate MOE. The aggregate MOE is compared with the target MOE to determine whether there is an aggregate exposure of concern. All routes of diquat dibromide exposure were considered in the aggregate assessment for this TRED. Aggregate exposure pathways for adults include dietary, drinking water, and dermal exposures from application and post-application activities. Aggregate exposure pathways for children include dietary, drinking water, oral and dermal exposures from post-application exposure. A target MOE of 100 is considered adequate for aggregate exposure/risk. Acute and chronic aggregate MOEs were not a risk concern, nor was the short term aggregate MOE for adults. The short-term screening level aggregate MOE for the toddler (child 1-6) exposure scenario was 55. The short-term aggregate risk combines screening level risk estimates from individual exposure pathways and should be viewed as a highly conservative estimate which is certain to over-estimate risk. A refined analysis would result in lower exposure estimates and higher MOEs.

Data Gaps

All product chemistry data are required for the Syngenta 41.1% and 37.3% Formulation Intermediates (EPA Reg. Nos. 10-1062 and 100-1063). Magnitude of the residue in plants studies are required for sorghum aspirated grain fractions and soybean aspirated grain fractions.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Common Name:	Diquat Dibromide
Chemical Name:	6,7-dihydrodipyrido(1,2-a;2',1'-c)pyrazinediium dibromide
Trade Names:	Reglone, Weedkiller D, Aquacide, Dextrone, FB 2, Reglox, Reward
Empirical Formula:	$C_{12}H_{12}Br_2N_2$
CAS No.:	85-00-7
PC Code:	032201
Structure:	



Molecular Weight:	344 [Cation - 184]
Physical State:	Crystals
Color:	Colorless to Yellow
Odor:	Odorless
Solubility in Water:	700 g/L at 20°C
Vapor Pressure:	< 0.03 mPa
Melting Point:	300°C
Density:	1.22-1.27 at 20°C

Pure diquat dibromide is an odorless, colorless to yellow crystal. It is very soluble in water, slightly soluble in alcohol and hydroxylic solvents, and insoluble in non-polar organic solvents. It is susceptible to ultraviolet decomposition. Ethylene dibromide (EDB) may be present as a process impurity in final formulations of diquat dibromide. However, the registrant has certified an upper limit of 10 ppm EDB in diquat dibromide and has demonstrated that EDB does not persist as an impurity in diquat dibromide and will slowly dissipate over time.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicity data base for diquat dibromide is adequate for the selection of doses and endpoints for use in risk assessment. HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the acceptable studies available in the database and established acute and chronic reference doses (RfD), as well as doses and endpoints for short and intermediate-term incidental oral exposure, and short-term, intermediate-term, and long-term dermal and inhalation exposure scenarios. The Acute Reference Dose (Acute RfD) is an estimate (with uncertainty spanning an order of magnitude or greater) of a single day oral exposure level for the human population, including the sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects. The Chronic Reference Dose (Chronic RfD) is an estimate (with uncertainty spanning an order of magnitude or greater) of a daily oral exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. The acute RfDs are calculated by dividing the NOAEL by the Uncertainty Factors (UF). Uncertainty Factors are used to account for differences between humans (intraspecies variability) and for differences between the test animals and humans (interspecies extrapolation). For residential exposures, uncertainty factors are used to determine adequate margins of exposure (MOEs). The MOE is the ratio of the route appropriate NOAEL to estimated exposure. The HIARC also evaluated available studies to determine if there is a special sensitivity for infants and children. The toxicological data are summarized below.

3.1.1 Acute Toxicity

Diquat dibromide exhibits low acute toxicity *via* the oral (Toxicity Category II for technical, III for formulation) and inhalation (Toxicity Category III) routes of exposure but is

moderately-to-severely toxic *via* the dermal route of exposure (Toxicity Categories I for technical and II for formulation). Diquat dibromide is not an acute skin irritant (Toxicity Category IV) nor a dermal sensitizer, but it is considered a moderate-to-severe eye irritant (Toxicity Category II). Acute toxicity categories for diquat are shown in Table 1.

Table 1. Acute Toxicity Data on DIQUAT DIBROMIDE

Guideline No.	Study Type	MRID # (S)	Results	Toxicity Category
870.1100	acute oral - rat Diquat Water Weed Killer	00081506	rat LD_{50} = 810 mg/kg ♂ rat LD_{50} = 600 mg/kg ♀	III
870.1200	acute dermal - rat Diquat Water Weed Killer	00100614	rabbits LD_{50} = 262 mg/kg ♂ rabbits LD_{50} = 315 mg/kg ♀ rabbits LD_{50} = 288.5 mg/kg ♂+♀	II
870.1300	acute inhalation - rat Diquat Water Weed Killer	26385♪	rat LC_{50} = 0.80 mg/L ♂ rat LC_{50} = 1.09 mg/L ♀ rat LC_{50} = 0.97 mg/L ♂+♀	III
870.2400	primary eye irritation - Diquat Water Weed Killer	00081507	rabbit slight to severe eye irritant	II
870.2500	primary skin irritation - Diquat Water Weed Killer	00107903	slight irritation	IV
870.2600	*Dermal Sensitization*	*00107903*	*not a dermal sensitizer*	N/A

♪ Accession No.; With the exception of the dermal sensitization study, which was conducted with the technical diquat [Diquat Herbicide Concentrate], the above studies were conducted with the end-use products [Diquat Water Weed Killer and Diquat 2 Spray (eye irritation study only)] and not in terms of the Diquat ion. Because the only difference between the technical diquat and the end-use products is 2.15% of water, *studies with the end-use products have been accepted to satisfy the generic data requirements for acute studies.* The above LD and LC values are expressed in terms of the test material and not, as is commonly done with diquat, in terms of the diquat cation.

3.1.2 Toxicity Profile

Table 2 identifies and summarizes guideline studies conducted for diquat dibromide.

Table 2. Toxicity Profile of DIQUAT DIBROMIDE

GUIDELINE	STUDY	MRID	RESULTS
OPPTS 870.3100	90-day oral toxicity - rat		no study available
OPPTS 870.3150	subchronic nonrodent oral toxicity - 90-day		no study available
OPPTS 870.3200	repeated dose dermal toxicity -21/28 days - rat 20.64% diquat cation [doses: 0, 5, 20, 40, and 80 mg/kg/day] Classification: Acceptable/Guideline	40308101	Dermal Toxicity NOAEL < 5 mg/kg/day Dermal Toxicity LOAEL = 5 mg/kg/day, based on dermal irritation at application site [erythema, edema, atonia, and desquamation] and tissue destruction [necrosis and eschar formation].. Systemic Toxicity NOAEL = 5 mg/kg/day Systemic Toxicity LOAEL = 20 mg/kg/day, based on a dose-related mortality and clinical signs [hypothermia, hypoactivity, dyspnea, cyanosis, pale extremities, general poor condition, and emaciated appearance]. Based on the severity of the effects observed [death and clinical signs (hypothermia, hypoactivity, dyspnea, cyanosis, pale extremities, general poor condition, and emaciated appearance)] and the extent of skin toxicity [dermal irritation (erythema, edema, and desquamation) and tissue destruction (necrosis and eschar formation); sores, severe erythema, fissures, acute necrotizing purulent dermatitis, and degeneration of the hair follicles and sebaceous glands] observed at the site of application in one or both sexes, it was concluded that the study was not appropriate for use in risk assessment since the NOAEL is artificially low due to the fact that the skin is compromised

Table 2. Toxicity Profile of DIQUAT DIBROMIDE			
GUIDELINE	STUDY	MRID	RESULTS
OPPTS 870.3200	repeated dose dermal toxicity -20 days - rabbit [doses: 20, 40, 80, 160 mg diquat cation/kg/day] Classification: Acceptable/Non-Guideline	00140576	Dermal Toxicity NOAEL = <20 mg/kg/day Dermal Toxicity LOAEL = 20 mg/kg/day, based on erythema and scabbing. Systemic Toxicity NOAEL = 20 mg/kg/day Systemic LOAEL = 40 mg/kg/day, based on weight loss, unsteadiness, muscular weakness and inability to stand, and pathological changes in the distal convoluted renal tubules with cell necrosis [thought to be associated with an electrolyte imbalance].
OPPTS 870.3250	subchronic dermal toxicity - 90 days		no study available
OPPTS 870.3465	subchronic inhalation toxicity [21-day] 21.6% and 23.5% diquat cation [doses: 0, 0.49, 1.1, 3.8 μg/L; 0, 0.1 μg/L] Classification: Acceptable/Guideline, when both studies are considered together. NOTE: Duration of study is 21 days, not 90 days.	40301701 40640801	NOAEL: 0.1 μg/L/day [males 0.024 mg/kg/day; females 0.026 mg/kg/day], based on increased lung weights and microscopic lesions [mottling and reddening of the lungs in females, multifocal, chronic, interstitial pneumonia and alveolar macrophages in both sexes] in the lungs at the LOAEL of 0.49 μg/L [males 0.117 mg/kg/day; females 0.128 mg/kg/day].
OPPTS 870.3500	preliminary developmental toxicity screen		no study
OPPTS 870.3600	inhalation developmental toxicity study		no study
OPPTS 870.3700	prenatal developmental toxicity study - rat 26.2% diquat cation [doses: 0, 4, 12, 40 mg/kg/day] Classification: Acceptable/Guideline	41198902	Maternal NOAEL: 4 mg/kg/day Maternal LOAEL: 12 mg/kg/day, based on decreased body-weight gains and food consumption during dosing. At HDT, there was one death [GD 15], and clinical signs [piloerection and subdued activity] were observed [GD 13-22]. Developmental NOAEL: 12 mg/kg/day Developmental LOAEL: 40 mg/kg/day, based on decreased fetal, litter, and gravid uterine weights, an increased incidence of fetuses with hemorrhagic kidney, and delayed skeletal ossification [increased incidence of minor skeletal variations, including unossified ventral tubercle, unossified cervical vertebral centra, and delayed ossification of the 2nd and 5th sternebrae].
OPPTS 870.3700	prenatal developmental toxicity study - rabbit 26.2% diquat cation [doses: 0, 1, 3, 10 mg/kg/day] Classification: Acceptable/Guideline	41198901	Maternal NOAEL: 1 mg/kg/day Maternal LOAEL: 3 mg/kg/day, based on body-weight loss [GD 7-10] and decreased food consumption [GD 7-10]. At HDT, there were deaths and clinical signs [diarrhea, subdued activity, thin appearance, mucus, blood, little or no feces in tray] Developmental NOAEL: 3 mg/kg/day Developmental LOAEL: 10 mg/kg/day, based on decreased fetal body weight, an increased incidence of friable/mottled livers, and an increased incidence of minor skeletal alterations [partially ossified ventral tubercle of cervical vertebrae, partially ossified 6th sternebrae, and unossified 6th sternebrae and presacral vertebrae].

Table 2. Toxicity Profile of DIQUAT DIBROMIDE			
GUIDELINE	STUDY	MRID	RESULTS
OPPTS 870.3700	prenatal developmental toxicity study - mouse analytical standard [doses: 0, 1, 2, 4 mg/kg/day] Classification: Acceptable/Non-Guideline	00061637	Maternal NOAEL: 1 mg/kg/day [as diquat cation] Maternal LOAEL: 2 mg/kg/day, based on mortality, clinical signs [piloerection, respiratory sounds], and decreased body-weight gain [during dosing period]. At HDT, additional clinical signs [abnormal posture (hunched or tail raised), lethargy, tremors, unsteadiness on feet, emaciation, ptosis] and a slight decrease in body weight [91% of control] at termination were observed also. NOTE: Poor dosing technique; incidental exposure into lungs. Developmental NOAEL: 2 mg/kg/day Developmental LOAEL: 4 mg/kg/day, based on decreased fetal body weight and an increased incidence of overall skeletal alterations.
OPPTS 870.3800	reproduction and fertility effects 20.09% diquat cation [doses: 0, 16, 80, 400/240 ppm (0, 0.8, 4, 20/12 mg/kg/day)] Classification: Acceptable/Guideline	41531301	Parental NOAEL: 16 ppm [0.8 mg/kg/day] Parental LOAEL: 80 ppm [4 mg/kg/day], based on clinical signs, ulceration of the tongue, and partial/total cataract. At HDT, increased incidence of clinical signs including ophthalmoscopic signs and lack of grooming, and gross and microscopic findings [ulceration of the tongue and partial/total cataract]. Reproductive/Developmental NOAEL: 80 ppm [4 mg/kg/day] Reproductive/Developmental LOAEL: 400/240 ppm [12 mg/kg/day], based on decreased number of live pups per litter on days 1-22, decreased pup body-weight gain during lactation, and increased incidence of kidney lesions.
OPPTS 870.4100	chronic toxicity [feeding] study - beagle dog 26.7% diquat cation [doses: 0, 0.5, 2.5, 12.5 mg/kg/day for 52 weeks] Classification: Acceptable/Guideline	41730301	NOAEL: 0.5 mg/kg/day LOAEL: 2.5 mg/kg/day, based on unilateral cataracts in females, and decreased weights of epididymides and adrenals in males. At the HDT, bilateral lenticular opacity [cataracts], macroscopically and microscopically [in all dogs, both sexes]; inflammatory lesions in the large intestine [in all dogs, both sexes]; increased kidney weight [both sexes].
OPPTS 870.4200	carcinogenicity -CD-1 mouse 21.09% diquat cation [doses: 0, 30, 100, 300 ppm (males 0, 3.56, 11.96, 37.83 mg/kg/day; females 0, 4.78, 16.03, 48.27 mg/kg/day)] for 104 weeks Classification: Acceptable/Guideline	42219801 42880701 42905901 42919501	NOAEL = 30 ppm [356/4.78 mg/kg/day] LOAEL: 100 [11.96/16.03 mg/kg/day], based on clinical signs [eye discharge (males), subdued behavior (females)], and decreased body weight/body-weight gain [males]. Diquat dibromide was not carcinogenic in male or female CD-1 mice.
OPPTS 870.4300	combined chronic toxicity/carcinogenicity - rat 26.5% diquat cation [doses: 0, 5, 15, 75, and 375 ppm (0, 0.19, 0.58, 2.91, and 14.88 mg/kg/day for males and 0, 0.24, 0.72, 3.64, and 19.44 mg/kg/day for females)] for 104 weeks. Classification: Acceptable/Guideline	00145855 00155474 41085601	NOAEL: 15 ppm [0.58/0.72 mg/kg/day] LOAEL: 75 ppm [2.91/3.64 mg/kg/day], based on eye lesions [total cataracts]. NOTE: The incidence of eye lesions increased with time on study, and effect observed at lower dose level with time. Opacity first occurred in week 10 at 75 ppm and week 11 at 375 ppm. There was no treatment-related increase in tumor incidence in either sex.

Table 2. Toxicity Profile of DIQUAT DIBROMIDE			
GUIDELINE	STUDY	MRID	RESULTS
OPPTS 870.5100-5915	genetic toxicity tests Classification: Acceptable/Guideline		negative for mutagenicity in a bacterial gene mutation [Ames] assay.; however, positive for gene mutations in a mammalian cell line [mouse lymphoma] but at cytotoxic doses. Also, clastogenic in cultured human lymphocytes, but the response was generally weak and observed at cytotoxic levels. In contrast, there was no evidence of clastogenicity in somatic cells [*mouse bone marrow*] or germinal cells [mouse spermatogonia] or unscheduled DNA synthesis [UDS] in rat hepatocytes in a series of *in vivo* studies. Overall, the data suggest that there is no concern for mutagenicity.
OPPTS 870.6100	delayed neurotoxicity of OPs following acute/28-day exposures	-	no study
OPPTS 870.6200	neurotoxicity screening battery - acute [rat] 20.1% diquat cation [doses: 0, 25, 75, and 150 mg/kg] Classification: Acceptable/Guideline	42666801	NOAEL = 75 mg/kg LOAEL = 150 mg/kg/day, based on clinical signs [piloerection, diarrhea, staining around nose, urinary incontinence, upward curvature of the spine, tip toe gait, hunched posture, subdued behavior, and pinched sides] and decreased body-weight gains. NOTE: Agency concluded that signs may not be due to direct *neurotoxicity*.
OPPTS 870.6200	subchronic neurotoxicity - Alpk:APfSD rats 20.8% diquat cation doses: 0, 20, 100, and 400 ppm [males 0, 1.6, 8.0, 32.4 *mg/kg/day/females* 0, 1.9, 9.5, and 38.5 *mg/kg/day*] Classification: Acceptable/Guideline	42616101	Systemic Toxicity NOAEL = 100 ppm [8.0/9.5 mg/kg/day Systemic Toxicity LOAEL = 400 ppm [32.4/38.5 mg/kg/day, based on evidence of cataracts and decreased body-weight gain and food utilization in both sexes. **There was no evidence of neurotoxicity at any dose level.**
OPPTS 870.6300	developmental neurotoxicity study	-	no study
OPPTS 870.7485	metabolism and pharmacokinetics [disposition and *metabolism*] Classification: Acceptable/Guideline when considered with other two studies	00065592	Diquat dibromide did not accumulate in tissues and was slowly absorbed following either oral or iv exposure to single doses of [^{14}C] Diquat dibromide to rats or mice of both sexes. Following a single dose of 60 mg/kg, only 5.5% of the radiolabel was excreted in urine within 7 days. Following an oral [feeding] dose of unlabeled Diquat dibromide [250 ppm] to rats of both sexes for 2, 4, or 8 weeks, no retention of Diquat was observed in the brain, liver, lung, stomach, small and large intestine, muscle, and blood, and little retention in the kidneys [0.18, 0.25, and 1.17 ppm during weeks 2, 4, and 8, respectively]. Ten minutes after iv injection, there were indications that Diquat concentrated in cartilaginous tissues, liver, and urinary bladder, as well as the brain and spinal cord. After 24 hours, radiolabel was detected only in the urinary bladder and intestines.
	Metabolism - excretion Classification: Acceptable/Guideline when considered with other two studies	00065593	Rats excreted 6.3% and 89.3% of [^{14}C] in the urine and feces, respectively, within 4 days following oral exposure, with most being excreted within the first 48 hours In urine, most [5.3%] of the [^{14}C] was unchanged Diquat, whereas the remaining 1% was associated with: diquat monopyridone [0.2%], diquat dipyridone [0.1%], and unidentified *metabolites* [0.3%]. *In feces*, 65.5% of excreted [^{14}C] was detected in sulfuric acid-extractable fraction and 15.7% in the ammonium sulfate-unextractable fraction. In the sulfuric acid fraction, [^{14}C] was distributed as follows: unchanged diquat [57.1%], diquat monopyridone [4.3%], and unidentified material [4.1%].

Table 2. Toxicity Profile of DIQUAT DIBROMIDE			
GUIDELINE	STUDY	MRID	RESULTS
	Metabolism *Classification: Acceptable/Guideline when considered with other two studies*	00055107	Following oral dosing, ≈90% of [^{14}C] was eliminated in the feces, indicating that Diquat was poorly absorbed for the gastrointestinal tract. Following a subcutaneous injection of [^{14}C]-Diquat to circumvent the intestine, nearly all [^{14}C] was recovered in the urine within 2 days.
OPPTS 870.7600	dermal penetration Classification: Acceptable/Guideline	41238701	dermal absorption of Diquat dibromide through intact rat skin is considered very low.
OPPTS 870.7800	immunotoxicity	-	no study

3.1.3 Hazard Characterization

The toxicity data base for diquat is complete and clearly defines the toxicity of the compound. Subchonic and chronic studies in several species indicate multiple target sites for diquat dibromide toxicity. In subchronic dermal exposure studies in rats, diquat dibromide showed evidence of severe systemic toxicity, i.e. high mortality and clinical signs. While a dermal study was available, the dermal endpoint is based on a rabbit developmental gavage study because the dermal study was determined to be inappropriate for endpoint selection. Route specific endpoints are available for all other exposure pathways. In a subchronic inhalation study in rats, the lung was determined to be the primary target site for inhalation toxicity. Chronic feeding studies in dogs, rats, and mice indicate that target sites include the eyes and kidneys in both males and females and the adrenals and epididymides in males. Developmental toxicity was observed in rat, rabbit, and mouse studies, and reproductive toxicity was observed in the rat in both generations. Rat and rabbit studies provided evidence of maternal toxicity. The acute and subchonic neurotoxicity studies in rats provided no evidence of neurotoxicity. Available data provide no evidence of endocrine disruption following exposure to diquat dibromide. Carcinogenicity studies in rats and mice provided no evidence of increase tumor incidence and diquat dibromide was classified as a Category E (evidence of non-carcinogenicity to humans) by the HED Reference Dose (RfD)/Peer Review Committee based on the 1999 *EPA Draft Proposed Guidelines for Carcinogen Risk Assessment*. The weight of the evidence was predominantly negative for mutagenicity. The data provided no indication of increased sensitivity of rats, mice, or rabbits to in utero and/or early postnatal exposure to diquat dibromide. The terminal residue of concern is the parent compound, diquat cation. There is no indication that metabolites are present in significant quantities.

3.2 FQPA Considerations

HED's FQPA committee determined that the FQPA safety factor could be removed (1x) in assessing the risk posed by this chemical because the toxicological database is complete for FQPA assessment, there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure, a developmental neurotoxicity study is not required, and the dietary (food and drinking water) and residential exposure assessments will not underestimate the potential exposures for infants and children. The HIARC and FQPA Committee determined that a developmental neurotoxicity study was not required for diquat dibromide based

on the fact that (1) there is no indication of abnormalities in the development of the fetal nervous system in prenatal developmental toxicity studies in rats, mice, and rabbits at oral dose levels that were maternally toxic, (2) there was no evidence of neuropathology in either the acute or subchronic neurotoxicity studies, (3) the clinical and functional observational battery observations in the acute neurotoxicity study, which could not be unequivocally correlated to an effect on the nervous system, were not observed in the subchronic neurotoxicity study, and (4) no neurotoxic effects were observed in the brain weights or histopathology of the nervous system in the chronic toxicity studies with diquat in several species.

3.3 Dose Response Assessment

Doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for Diquat for Use in Human Risk Assessment

Exposure Scenario	Dose	Endpoint	Study
Acute Dietary general population incl infants and children	NOAEL= 75 mg/kg UF = 100	LOAEL of 150 mg/kg based on clinical signs and decreased body-weight gain.	Acute neurotoxicity rat
	FQPA = 1x Acute RfD = 0.75 mg/kg Acute PAD = 0.75 mg/kg		
Chronic Dietary	NOAEL = 0.5 mg/kg/day UF = 100	LOAEL of 2.5 mg/kg/day based on cataracts in females and decreased adrenal and epididymides weights in males.	chronic toxicity dog
	FQPA = 1x Chronic RfD = 0.005 mg/kg/day Chronic PAD = 0.005 mg/kg/day		
Short-Term Oral (1day - 1 month)	NOAEL = 1 mg/kg/day MOE = 100	LOAEL of 3 mg/kg/day based on body-weight loss and decreased food consumption.	Developmental toxicity - rabbit
Short-Term Dermal [a] (1 day - 1 month)	NOAEL = 1 mg/kg/day MOE = 100	LOAEL of 3 mg/kg/ day based on body-weight loss and decreased food consumption.	Developmental toxicity - rabbit
Short-Term Inhalation (1 day - 1 month)	NOAEL = 0.1 ug/l (0.024 mg/kd/d male, 0.026 mg/kd/d female) MOE = 100	LOAEL of 0.49 ug/L (0.117 mg/kg/day male, 0.128female) due to increased mean lung weight in males, mottling and reddening of lungs in females, and lung lesions.	21-day inhalation toxicity rat

[a] Since an oral value was selected, route-to-route extrapolation should be followed. A dermal absorption factor is required for this risk assessments.

3.3.1 Dietary Exposure Endpoints

3.3.1.1 Acute Reference Dose

The HIARC selected an acute RfD of 0.75 mg/kg based on an acute neurotoxicity gavage study in the rat which showed clinical signs of systemic toxicity (e.g., piloerection, diarrhea, urinary incontinence, upward curvature of the spine, subdued behavior) and decreased body-weight

gains at the systemic Lowest Observed Adverse Effect Level (LOAEL). The study is considered appropriate for selection of an acute endpoint because effects were seen after a single dose. The HIARC recommended a (UF) of 100x (10x for interspecies and 10x for intraspecies is extrapolation) for calculation of the RfD.

The acute endpoint selected by the HIARC for the current risk assessment differs from that used in assessments conducted for the 1995 RED and 1998 assessment of risk based new and revised uses. The acute dietary endpoint used in previous assessments was based on a rat developmental study, which showed transitory decrease in mean body-weight gain of the maternal rat following four days of exposure to diquat dibromide. The HIARC concluded that this endpoint was not a single dose effect and so was not appropriate for use in an acute risk assessment. The rabbit and mouse developmental toxicity studies were also re-evaluated by the HIARC for the current analysis. The rabbit study was deemed inappropriate because the maternal body-weight loss observed during gestation was not a single dose effect. The mouse study was rejected for endpoint selection because of poor dosing technique which caused inappropriate introduction of test material into the lungs.

$$\text{Acute RfD} = \frac{\text{75 mg/kg (NOAEL}}{\text{100 (UF)}} = 0.75 \text{ mg/kg}$$

3.3.1.2 Chronic Reference Dose

The HIARC selected a chronic RfD of 0.005 mg/kg/day from a chronic oral dog toxicity study. The endpoint is based on unilateral cataracts in males and females and decreased adrenal and epididymides weights in males at the LOAEL of 2.5 mg/kg/day. The study is considered appropriate for selection of an endpoint for a chronic exposure scenario because cataracts and decreased adrenal and epididymides weights are found consistently in repeat exposure studies in both the dog and the rat. The rat chronic toxicity/carcinogenicity study which also showed evidence of cataracts, was considered co-critical for this endpoint. The HIARC recommended a UF of 100 (10 interspecies; 10 intraspecies). The chronic endpoint selected for the current analysis was used in both of the previous diquat risk assessments.

$$\text{Chronic RfD} = \frac{\text{0.5 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = 0.005 \text{ mg/kg/day}$$

3.3.2 Residential Exposure Endpoints

3.3.2.1 Short-Term Oral Exposure (1 day - 1 month)

A short-term oral NOAEL of 1 mg/kg/day was selected from a rabbit developmental gavage study which showed maternal body-weight loss during gestation days (GD) 7-10 and

decreased food consumption during dosing (GD 7-10) at the LOAEL of 3 mg/kg/day. The study is considered appropriate as a basis for endpoint selection for infants and children, the population of concern for incidental oral exposure. A target MOE of 100 was determined to be adequate for this exposure pathway by the HIARC. A short-term oral endpoint was not included in previous HIARC or risk assessment documents for this chemical.

3.3.2.2 Short-Term Dermal Exposure (1 day - 1 month)

The HIARC selected a short-term dermal NOAEL of 1 mg/kg/day. The endpoint is based on a rabbit developmental gavage study which resulted in maternal body-weight loss during gestation days (GD) 7-10 and decreased food consumption during dosing (GD 7-10) at the LOAEL of 3 mg/kg/day. The rat chronic toxicity/carcinogenicity study was considered co-critical for this endpoint. The recommended target MOE was 100. For the diquat risk assessment conducted for the 1995 RED, and endpoint from a 20 day dermal toxicity study in rabbits was selected for use in assessing risk from dermal exposure. For the 1998 revised assessment, the HIARC determined that the 21-day rat dermal toxicity study was more appropriate for use in selecting a dermal endpoint because the rabbit study is a non-guideline study. Only 3 rabbits/group were used and hematology, clinical chemistry, and urinalysis parameters were not monitored. The guideline states that ten animals/sex/dose are needed for a NOAEL for risk assessment. The HIARC then re-evaluated the rat dermal toxicity study for this TRED. Based on the most recent review, the HIARC concluded that the rat study was inappropriate for use in endpoint selection because the animal's skin was compromised resulting in increased severity of effects and an artificially low NOAEL.

3.3.2.3 Dermal Absorption

Since the dermal exposure endpoints were selected from oral toxicity studies, a dermal absorption factor is required to convert the oral dose to an equivalent dermal dose for the risk assessment. In an acceptable/guideline *in vivo* per cutaneous absorption study, three aqueous doses of [^{14}C] diquat dibromide were applied dermally to 12 Sprague-Dawley rats (four rats per dose). The rats were dermally dosed at levels of 0.05, 0.5, and 5 mg diquat cation/rat for exposure periods of 2, 10 and 24 hours. The respective 2, 10, and 24 hour absorption rates were 4.1, 5.5, and 7.4% at the low dose (0.05 mg/rat), absorption was 2.8, 5.3, and 4.7% at the middle dose (0.5 mg/rat), and 2.6, 2.5, and 3.3% at the high dose (5 mg/rat). (Total percent absorbed = percent absorbed + percent remaining in/on the skin.)

The 4.1% (dermal absorption factor corresponding to the 2 hour, low dose (0.05 mg/rat) exposure was used for the non-occupational handler and postapplication exposure scenarios where children and adults are assumed to have a 2 hour exposure duration. This is a conservative assumption in which total percent absorbed = percent absorbed (1.2%) + percent remaining in/on the skin (3.9%).

3.3.2.4 Short Term Inhalation Exposure (1 day - 1 month)

The selected NOAEL for inhalation exposure is 0.1 μg/L (0.023 mg/kd/day male, 0.027 mg/kg/day female) based on a repeated dose 21-day inhalation toxicity study in rats which resulted in on increased lung weights and microscopic lesions in the lungs at the LOAEL of 0.49 μg/L (0.113 mg/kg/day male, 0.134 female). The route and duration of exposure are appropriate for selecting a short term inhalation endpoint.

3.3.2.5 Intermediate and Long-Term Endpoints - The HIARC also selected endpoints for intermediate-term oral, and intermediate, and long-term dermal and inhalation exposure scenarios. However, since only short-term exposures are anticipated for residential uses, endpoints for longer term exposures were not used in the exposure and risk assessments for this TRED.

3.3.2.6 Common Toxicological Endpoints for Exposure Routes

A common toxicological endpoint (decrease in maternal body weight and food consumption) was selected for assessment of short-term incidental oral and dermal (oral equivalent) exposures. Therefore, these exposure routes can be aggregated. The toxicological endpoint (increased lung weight and microscopic lung lesions) observed via the inhalation route is unique. Therefore, this exposure route cannot be aggregated with the oral and dermal exposures.

3.4 Endocrine Disruptor Effects

Available toxicity data suggest that there is no evidence of endocrine disruption following exposure to diquat dibromide. EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, diquat dibromide may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Currently registered uses are summarized in Table 4. Table 5 summarizes the volume of diquat dibromide usage by crop.

Table 4. Diquat Dibromide Use Groups and Sites

Use Group	Use Sites
Aquatic Food Crop	agricultural drainage & irrigation systems; lakes/ponds/reservoirs with human or wildlife use
Aquatic Non-food Industrial	drainage systems, lakes/ponds/reservoirs without human or wildlife use
Aquatic Non-food Outdoor	aquatic and intermittently flooded areas, streams/rivers/channeled water
Aquatic Non-food Residential	ornamental ponds/aquaria
Greenhouse Food Crop	in-use greenhouse
Indoor Food	storage areas - empty and full
Indoor Non-food	empty greenhouse
Outdoor Residential	residential lawns, household/domestic dwellings outdoor premises
Terrestrial Feed Crop	alfalfa, Bermuda grass, clover
Terrestrial Non-Food Crop	carrot, cucumber, melons, pepper, radish, squash, turnip, tomato
Terrestrial Food & Feed Crop	potato, sorghum, soybeans
Terrestrial Non-food Crop	agricultural fallow/idleland, structures/equipment, rights-of way/fence rows/hedge rows, and uncultivated areas; airports/landing fields; commercial/industrial lawns, premises and equipment (outdoor); golf course turf; nonagricultural outdoor structures/rights-of-way/fence rows/hedge rows

Table 5. Volume of Diquat Dibromide Usage by Crop

Crop	% Treated	Pounds A.I. (1000)	Application Rate (lbs A.I)	Major States
Alfalfa/Seed	50	25	0.4	CA, OR, WA
Potatoes	30	170	0.3	ME, ND, NY
Soybeans	<1	1	0.4	-
Sorghum	<1	2	0.4	-
Dry Beans	<1	1	0.3	-

Table 5. Volume of Diquat Dibromide Usage by Crop				
Crop	% Treated	Pounds A.I. (1000)	Application Rate (lbs A.I)	Major States
Grapes	<1	1	0.4	-
Home & Garden	<1	100	0.3	-
Aquatic Uses	<1	200	1.5	CA, FL
Total		500		

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

4.2.1.1 Nature of the Residue - Plants and Livestock

Plants

The reregistration requirements for plant metabolism are fulfilled (T. Morton, 11/20/01, D277710). The qualitative nature of the residue in plants is adequately understood based on an acceptable potato metabolism study and a rat bioavailability study. The HED Metabolism Assessment Review Committee (MARC) has concluded that the terminal residue of concern in plants is the diquat cation (T. Morton, 11/8/01, D277765). The established tolerance expression for residues of diquat dibromide in/on plant commodities is appropriate and no changes are required.

The potato metabolism study indicated that no metabolism of diquat occurred in potato tubers following preharvest application of [^{14}C]diquat as a desiccant to potato stalks and stems. Previously submitted soybean and wheat metabolism studies were deemed marginal because of inadequate characterization and identification of ^{14}C-residues in the commodities of concern. In lieu of additional crop metabolism studies, the Agency recommended several alternatives for this requirement. The registrant opted to conduct a bioavailability study. The results of the bioavailability study showed that diquat plant residues are largely not bioavailable; $\leq$5% of the ^{14}C is absorbed as a result of feeding diquat field residues in/on wheat chaff to rats. The retention of diquat residues in tissues was negligible ($\leq$0.004 ppm diquat equivalents) following dosing at $\geq$25x the maximum human dietary intake.

Livestock

The reregistration requirements for animal metabolism are fulfilled. The qualitative nature of the residue in livestock is adequately understood based on acceptable poultry, ruminant, and fish metabolism studies. The HED Metabolism Assessment Review Committee (MARC) has concluded the residue of concern for livestock is the diquat cation (T. Morton, 11/8/01, D277765).

The established tolerance expression for residues of diquat dibromide in animal commodities is appropriate and no changes are required.

In the poultry metabolism study, laying hens were dosed with ring-labeled [^{14}C]diquat at 32 ppm in the diet for 4 days. The total radioactive residues (TRR; expressed as diquat equivalents) ranged from <0.001-0.004 ppm in egg yolks, egg whites, fat, and muscle, 0.042-0.058 ppm in kidney, and 0.030-0.045 ppm in liver. The predominant metabolites identified were diquat cation (48% of TRR in liver), and diquat monopyridone (15.1% of TRR in kidney)

The metabolism of diquat dibromide in ruminants has been extensively investigated. Ruminant data confirm that the residue of concern in ruminant milk and tissues is diquat cation. Ethylene bridge-labeled [^{14}C]diquat dibromide was administered at 5 ppm to three cows. In addition, one cow was dosed with ethylene bridge-labeled [^{14}C]diquat at 20 ppm and with bypyridyl-labeled [^{14}C]diquat at 5 ppm. The highest TRR value in milk was 0.077 ppm in the 72-hour milk sample from the cow dosed at 20 ppm. In milk samples from the high-dose cow, residues of diquat per se were quantitated at <0.002 ppm and did not concentrate in the fat, casein or whey. No residues (<0.01 ppm) were found in the leg muscle samples from one of the cows dosed at 5 ppm. A bull calf was administered ethylene bridge-labeled [^{14}C]diquat dibromide at 8 ppm and sacrificed 24 hours after dosing. The TRR were 1.071 ppm in kidney, 0.033 ppm in liver and <0.04 ppm in other tissues. Residues of diquat cation were 0.03 ppm and <0.01 ppm in the kidney and liver samples, respectively.

In the fish metabolism study, trout and carp were exposed to an initial concentration of 1 ppm of bridge-labeled [^{14}C]diquat in the water for 7 days. The TRR (expressed as diquat equivalents) in carp head and tail, viscera, and body with skin were 0.025-0.077 ppm, 0.135-0.946 ppm, and 0.013-0.024 ppm, respectively. The TRR in skin and flesh without skin were 0.015-0.023 ppm and 0.006-0.016 ppm, respectively. The TRR in trout head, tail, and flesh were 0.025-0.051 ppm, 0.059-0.239 ppm, and 0.008-0.01 ppm, respectively. Approximately 65% of the radioactivity in carp flesh and trout viscera was identified as diquat.

4.2.1.2 Residue Analytical Method - Plants and Livestock

Enforcement methods

The Pesticide Analytical Manual (PAM) Vol. II. lists a spectrophotometric method, designated as Method A as available for the enforcement of tolerances for residues of diquat in/on plant and in livestock commodities. The limit of detection is 0.01 ppm. The registrant has proposed new enforcement methods, RM-5B-1 and RM-5C, for plant and livestock commodities, respectively. The stated limit of detection is 0.005 ppm for RM-5B-1; the limit of detection for RM-5C is not clearly specified. Both methods have been adequately validated by the registrant; however, an independent laboratory validation must be conducted followed by validation by the Agency's Analytical Chemistry Branch before they can be considered fully adequate for

enforcement purposes. Once a successful EPA method validation has been performed, these methods will be sent to FDA for inclusion in PAM Vol. II.

Data collection

Residue data submitted for tolerance reassessment were collected using the current (PAM Vol. 2 Method A) or proposed (RM-5B and RM-5C) enforcement methods. The registrant provided adequate method validation data to verify the suitability of these methods for data collection.

4.2.1.3 Multiresidue Methods

The FDA's PESTDATA dated 11/6/90 (PAM Vol. I, Appendix) indicates that recovery of diquat dibromide using Multiresidue Protocols is unlikely. The updated PESTDATA dated 08/93 does not have an entry for diquat dibromide.

4.2.1.4 Storage Stability Data

The requirements for storage stability data are fulfilled for purposes of tolerance reassessment. Adequate storage stability data on diquat dibromide are available to support the storage conditions and intervals of samples from magnitude of the residue studies in plants and livestock. Residues of diquat are stable under frozen (-20°C) storage conditions for: up to six months in/on bell pepper, carrot roots, clover (hay and seed), lettuce, potato, rice (grain and straw), sorghum grain, soybean, tomato and tomato processed fractions, and wheat (grain and straw); up to 8 months in processed fractions of sorghum grain and soybean; and up to 2 months in water and seafood samples.

4.2.1.5 Magnitude of the Residue in Crop Plants

All data for magnitude of the residue in plants have been evaluated and deemed adequate except for the following deficiencies: residue data required for sorghum aspirated grain fractions, soybean aspirated grain fractions. All field residue data have been re-evaluated and plant commodity tolerances reassessed (where residue data are available) for TRED purposes. There are no registered uses of diquat dibromide on sugarcane and vetch. Therefore, field residue data for these crops are no longer required and the established tolerance for residues in/on sugarcane should be revoked.

4.2.1.6 Magnitude of the Residue in Processed Food/Feed

The data for magnitude of the residue in processed food/feed have been evaluated and deemed adequate to determine the extent to which residues of diquat concentrate in food/feed items upon processing of raw agricultural commodities. Acceptable potato, soybean, and sorghum processing studies have been submitted and evaluated. Acceptable processing data are also

available for tomato wet pomace, tomato juice, and tomato paste. However, additional residue data are required for sorghum and soybean aspirated grain fractions and tomato puree.

4.2.1.7 Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

The reregistration data requirements for magnitude of the residue in livestock are fulfilled. The HED MARC has concluded that the residue of concern for livestock is the diquat cation (T. Morton 11/08/01) and acceptable animal feeding studies have been submitted and evaluated.

A new maximum dietary burden (MDB) estimate has been calculated based on reassessed established/proposed tolerances of feed commodities and revised Table II of OPPTS 860 Guidelines. (T. Morton, 11/20/01, D277710). The established tolerances of 0.02 ppm for diquat residues in the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep may be raised to 0.05 ppm to achieve compatibility with the Codex maximum residue limit (MRL). The established 0.02-ppm tolerance level for diquat residues in poultry fat, meat, meat byproducts and eggs may be raised to 0.05 ppm to achieve compatibility with the Codex MRL.

4.2.1.8 Magnitude of the Residue in Fish and Shellfish

All data requirements for magnitude of the residue in fish and shellfish have been evaluated and deemed adequate to reassess the tolerances for diquat; no additional data are required regarding this topic. The available data indicate that residues of diquat in fish and shellfish will exceed the established tolerances following tests reflecting the current maximum registered use patterns. The registrant must submit a petition requesting tolerance increases from 0.1 ppm to 2.0 ppm for fish and 20 ppm for shellfish to cover all residues of diquat which may occur as a result of the currently registered uses.

4.2.1.9 Magnitude of the Residue in Irrigated Crops

The available data concerning diquat residues following irrigation of carrot, corn (sweet), cowpea, peach, and rice are adequate to support the established 0.02 ppm tolerances for diquat residues in/on all members of the crop groups containing these commodities. However, the data also indicate that residues in/on cowpea, blackberry, strawberry, orange, mustard greens, pasture grass, and tomato may exceed the tolerances for the respective crop groups. The registrant must propose a higher tolerance level of 0.05 ppm for citrus fruit, small fruits, fruiting vegetables, legume vegetables, and Brassica leafy vegetables. The registrant is required to propose a higher tolerance level of 0.20 ppm for forage grasses.

No data are available for the commodities avocado, cottonseed, hops, and sugarcane for which tolerances currently exist. However, data for other crops can be translated to these commodities. Based on the highest residues found in other crops irrigated with water containing diquat residues, HED recommends that the registrant propose tolerances of 0.20 ppm for these crops. If lower tolerances are desired, additional data will be required.

4.2.1.10 Confined and Field Accumulation in Rotational Crops

The data requirements for confined rotational crops have been reviewed and deemed adequate by the Environmental Fate and Effects Division (EFED). The requirements for field rotational crop studies have been waived at this time.

4.2.1.11 Codex/International Harmonization

Several maximum residue limits (MRLs) for diquat have been established by Codex in various commodities. Tolerance levels for some commodities with an MRL have been revised in the TRED to achieve compatibility with Codex. The U.S. tolerance for eggs, poultry, meat, and offal (mammalian) may be raised to 0.05 ppm to achieve harmonization. Further harmonization of U.S. tolerances and Codex MRLs on other commodities are not feasible at this time because of differences in agricultural practices.

4.2.2 Dietary Exposure/Risk Assessment

4.2.2.1 Consumption Data and Dietary Risk Analysis

Diquat acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.73, which incorporates consumption data from USDA's Continuing Surveys of Food Intake for Individuals (CSFII), 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and in total represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire US population and within population subgroups (e.g., children one to six years old) for chronic exposure assessment, but are retained as individual consumption items for acute exposure assessment.

For chronic exposure and risk assessment, estimates of average residues for foods (e.g., orange) or food-forms (e.g., orange-juice) of interest are multiplied by the averaged consumption estimate of each food/food-form of each population subgroup. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD.

For acute exposure assessments, individual one-day consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita basis.

4.2.2.2 Acute Dietary Exposure/Risk Assessment

An acute dietary exposure analysis was conducted for diquat dibromide using the DEEM™ software (B. Daiss, D277766, 12/11/01). The acute dietary exposure/risk analysis was conducted using a conservative deterministic (Tier I) methodology. The Tier I analysis assumes that; 1) residues are present at published tolerances for registered uses and at recommended tolerances for proposed new uses, and 2) 100% crop treated (CT) for all commodities with existing and/or recommended tolerances. Tier I acute dietary analyses were conducted for the general U.S. population and all population subgroups. Based on this analyses, acute dietary risk associated with exposure to diquat from existing and proposed uses are below the Agency's level of concern for the general US population and population subgroups. The 95th percentile acute exposure estimates were < 100% of the acute Population Adjusted Dose (aPAD). The highest acute exposure (0.0054 mg/kg/day) was in children 1-6 years old (<1% aPAD). The results are presented in Table 6.

Table 6. Acute Dietary (Food) Exposure Estimate and Percent of Acute RfD at the 95th Percentile - Tier 1 Exposure Analysis (Assumes 100% Crop Treated and Tolerance Level Residues)

Subgroups	95th Percentile Exposure (mg/kd/day)	% aPAD at 95th Percentile Exposure
US Population (total)	0.0039	< 1
All Infants (<1 year old)	0.0035	< 1
Children 1-6 years old	0.0054	< 1
Children 7-12 years old	0.0033	< 1
Females 13-50 years old	0.0032	< 1
Males 13-19 years old	0.0030	< 1
Males 20+ years old	0.0035	< 1
Seniors 55+ years old	0.0023	< 1

4.2.2.3 Chronic Dietary Exposure/Risk Assessment

A chronic dietary exposure analysis was conducted for diquat dibromide using the DEEM™ software. The chronic dietary analysis was conducted using a conservative deterministic (Tier I) methodology (i.e., residues present at tolerance levels and 100 %CT). Tier I chronic dietary analyses were conducted for the general U.S. population and all population subgroups. Based on this analyses, chronic dietary risk associated with exposure to diquat from existing and proposed uses are below the Agency's level of concern for the general US population and population subgroups. The chronic exposure estimates were < 100% of the chronic PAD (cPAD) with the highest chronic exposure (0.0031 mg/kg/day) occurring in children 1-6 years old (62% cPAD). Results are presented in Table 7.

Table 7. Chronic Dietary (Food) Exposure Estimate and Percent of Chronic RfD - Tier 1 Exposure Analysis (Assumes 100% Crop Treated and Tolerance Level Residues)		
Subgroups	Mean Exposure (mg/kd/day)	% cPAD at Mean Exposure
US Population (total)	0.0019	38
All Infants (<1 year old)	0.0017	33
Children 1-6 years old	0.0031	62
Children 7-12 years old	0.0021	42
Females 13-50 years old	0.0017	34
Males 13-19 years old	0.0018	26
Males 20+ years old	0.0019	38
Seniors 55+ years old	0.0015	31

4.3. Drinking Water Exposure/Risk Pathway

4.3.1. Environmental Fate Assessment

Diquat is persistent but essentially immobile in the environment, indicating that it will most likely be associated with the soil and sediment instead of water. The primary route of environmental dissipation of diquat used in terrestrial settings is strong adsorption to soil. When used as an aquatic herbicide, diquat is removed from the water column by adsorption to sediment, aquatic vegetation, and organic matter. Based on acceptable guideline studies, diquat does not hydrolyze or photodegrade and is resistant to microbial degradation under aerobic and anaerobic conditions. There were no major degradates isolated from any of the environmental fate studies. Environmental fate data indicate that diquat is miscible in water (7×10^5 ppm), is stable to hydrolysis and photolysis, and metabolism, but is essentially immobile in soil and sediment. The extent of adsorption appears to be related to soil pH, with is consistent with cation exchange in soil.

4.3.2 Estimated Environmental Concentrations/Monitoring Results

The Environmental Fate and Effects Division (EFED) performed a Tier I drinking water assessment for diquat dibromide for both terrestrial uses and aquatic uses (D281199, J. Breithaupt, 3/5/01). EFED used both computer models and monitoring data to estimate environmental concentrations of diquat in surface and ground water. For terrestrial uses, EFED assessed preharvest application to potatoes, alfalfa, and clover with aerial and ground equipment and application to clover trees, vines, small fruits, and vegetables using directed spray from ground equipment. The assessed aquatic uses include application to lakes and flowing streams.

4.3.2.1 Terrestrial Uses

Surface Water

The FQPA Index Reservoir Screening Tool (FIRST) model was used to estimate environmental concentrations in drinking water from surface water contaminated by terrestrial use of diquat. FIRST is based upon the linked Pesticide Root Zone Model (PRZM) which simulates pesticides in field run-off and Exposure Analysis Modeling System (EXAMs) which simulates pesticide fate and transport in an aquatic environment. However, where previous PRZM-EXAMs models used a standard field pond scenario, FIRST uses an Index Reservoir which is based on Shipman City Lake in Illinois (13 acres in area, 9 feet deep, and a watershed area of 427 acres). In addition, FIRST uses a Percent Cropped Area (PCA) factor which translates to reduction of area within the reservoir that is planted to modeled crop. Due to the change from the standard pond to Index Reservoir, the physical scenario as well as the treatment of spray drift is different in FIRST. FIRST is designed to produce more realistic estimates of pesticides in surface water that is used as a source of drinking water.

FIRST was used to model the following diquat scenarios: trees/vines/small fruits/vegetables (maximum use rate of 1 lb a.i./A, single application, 87 PCA); potatoes (0.5 lb a.i./A, 2 applications, 14 day application interval, 87 PCA); and alfalfa/clover/non-crop (0.5 lb a.i./A, 1 application, single application, 87 PCA) . The surface water estimated environmental concentrations (EECs) generated by FIRST ranged from 6.3- 13.2 ppb (ug/L) for peak exposure and 0.2-0.4 ppb for annual average exposure.

Groundwater

EFED used the Screening Concentration in Ground Water (SCI-GROW) model to estimate diquat concentrations in groundwater contaminated by terrestrial uses. SCI-GROW is a regression-based model that uses few input parameters: pesticide's organic carbon partition coefficient (Koc), aerobic soil degradation half-life, and product label application rate and frequency (Barrett, 1997). It provides a groundwater screening concentration for use in determining potential risk to human health from drinking water contaminated with a pesticide. The groundwater concentration is estimated based on the maximum application rates in areas where groundwater is exceptionally vulnerable to contamination. These vulnerable areas are characterized by high rainfall, rapidly permeable soil, and shallow aquifer. The SCI-GROW model estimated terrestrial use groundwater EECs of 0.006 ppb. However, EFED recommends that monitoring data be used in lieu of the SCI-GROW results because higher concentrations were observed from monitoring data.

The sources of available monitoring data include the South Florida Water Management District (SFWMD), and potable water modeling studies from the registrant, and monitoring data from the EPA Office of Water (OW). The SFWMD data contained a total of 42 samples that were taken from April 1992 to November 2000 on approximately a 1-3 month interval. For diquat, the

only detection observed in surface water was 0.0045 ppm in 1994. Further monitoring beyond 1994 has not shown any detections in surface water. Also in the SFWMD, diquat was detected in 9 sediment samples from canals with a maximum concentration of 3.1 ppm (LOD of 2.5 ppm, Miles and Pfeuffer, Pesticides in Canals of South Florida, Arch. Environ. Contam. Toxicol. 32:337-345, 1997). In the potable water modeling studies, highly variable estimates of water concentrations have been observed. The modeling concentrations at reservoir pumps ranged from non-detections (LOD of 0.003 ppm) to 0.26 ppm. These modeling estimates were not used in this assessment because of available monitoring data obtained by OW. OW has monitored for diquat at intake pumps at drinking water utilities that use surface water and ground water. Data from eight states in the years 1993-1997 were included in the report. In these eight states, 0.06 percent of combined surface water and ground water systems reported exceedences of the 0.02 ppm (mg/L) Maximum Contaminate level (MCL) set by OW, resulting in a population exceedence of 0.27 % (Occurrence of Regulated Contaminants in Drinking Water: First Stage Occurrence and Exposure Report for Six-Year Regulatory Review, Working Draft 5/12/2000). Based on municipal monitoring data, EFED recommends use of the MCL of 0.02 ppm (20 ppb) for both peak and average terrestrial use EECs for groundwater.

4.3.2.2 Aquatic Uses

EFED also relied on monitoring data to estimate surface water and ground water concentrations from aquatic uses of diquat. For the aquatic use, EFED also included use information from the U.S. Corp of Engineers and the states of Florida, Minnesota, and Michigan. For aquatic use, EFED recommends use of the MCL of 0.02 ppm (20 ppb) for both peak and annual average EECs. EFED recommends use of the same annual average EECs for both surface and groundwater contaminated by aquatic uses of diquat because diquat is used near wells located next to lakes and ponds resulting in interaction between surface water and ground water. EFED notes that, while concentrations in excess of 20 ppb in private wells cannot be ruled out, they are unlikely because of the tendency of diquat to sorb nearly irreversably to soil and sediment.

EECs for surface and groundwater terrestrial and aquatic uses are provided in the Tables 8 and 9 respectively.

Table 8. FIRST EEC's for Diquat for Drinking Water Assessment from Surface Water

Type of Use	Use Site	Peak (ppb)	Average Annual (ppb)
Terrestrial	Trees, vines, small fruits, vegetables	13.2	0.4
	Alfalfa, Clover	6.3	0.2
	Non-Crop (fallow land)	6.6	0.2
	Potatoes	12.7	0.4
Aquatic	Ditches, reservoirs, and rivers	20[1]	20

[1] MCL from Office of Water

Table 9. Monitoring EEC's for Diquat for Drinking Water Assessment from Ground Water			
Type of Use	Use Site	Peak (ppb)	Average Annual (ppb)
Terrestrial	Trees, vines, small fruits, vegetables, alfalfa, clover, non-crop (fallow land), and potatoes	20	20
Aquatic	Ditches, reservoirs, and rivers	20	20

4.4 Residential Exposure/Risk Assessment

A regulatory review of residential exposure to diquat dibromide was conducted for this TRED because there is potential exposure to non-occupational (residential) handlers (mixers, loaders, applicators, etc.) during handling and application of diquat and/or to persons entering treated sites after its application (T. Brennan, 12/14/01, D279507). Only short-term exposures are expected/assessed for residential exposure scenarios.

4.4.1 Home Uses

4.4.1.1 Handler

Handler Exposure Scenarios

Diquat dibromide can be applied to turf and backyard ponds for general weed control and can be used in and around home & garden sites for weed control and landscape uses by residential handlers. Diquat dibromide is applied to residential turf grass at application rates ranging from 0.25 to 0.5 lb ai/acre. Therefore, for this assessment both low end and high end MOEs were assessed based on the range of application rates. Diquat dibromide is formulated for residential uses both as a Liquid Ready to Use, and as a Soluble Concentrate/Liquid that can be mixed with water and then applied with a low pressure handwand or backpack sprayer. This TRED estimates exposure and risk for four residential handler scenarios:

1) Mixing, loading, and applying with a low pressure handwand - This residential handler scenario estimates exposure and risk to a mixer, loader, applicator applying diquat dibromide with a low pressure handwand to control weeds in and around lawns, gardens, around buildings, driveways, fence lines and other such edge areas. The dermal and inhalation unit exposures for this scenario were obtained from the Outdoor Residential Exposure Task Force (ORETF) chemical handler exposure studies.

2) Mixing, loading, applying with a backpack sprayer - This scenario estimates exposure and risk to a mixer, loader, applicator applying diquat dibromide with a backpack sprayer to control residential weeds in edge areas.

3) Applying with an aerosol sprayer - This scenario estimates exposure and risk to an applicator applying diquat with an aerosol spray can to control residential weeds in edge areas.

4) Applying with a trigger pump sprayer - This scenario estimates exposure and risk to an applicator applying diquat dibromide with an trigger pump sprayer to control residential weeds. The dermal and inhalation unit exposures for this scenario were obtained from a carbaryl Occupational and Residential Exposure Task Force (ORETF) study on ready-to-use insect sprayer application to home garden vegetables.

The handler assessment was developed using standard residential application techniques and PHED unit exposure data. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available. PHED was designed by a task force of representatives from the US. EPA, Health Canada, the California Department of Pesticide Regulation, and members of the American Crop Protection Association. PHED is a software system consisting of two parts; 1) a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions, and 2) a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). For the handler scenarios female adult applicators were assessed for dermal exposures because the dermal toxicity endpoint was based on developmental toxicity effects. A complete summary of the handler dermal exposure and risk calculations, critical assumptions, and results is provided in Table 10. Handler exposure assumptions are summarized below.

Handler Exposure Assumptions

The following assumptions were made in the exposure calculations:

- Average body weight of an adult handler is 70 kg/day.
- Application rates range from a low-end rate 0.009 to a high-end 0.018 lb ai/gallon of sprayer.
- Backpack sprayers and low pressure handwands were applied at a rate of 5 gallons per day. Aerosol cans and triggers sprayers were applied at a rate of 0.125 gallons per day.
- No protective clothing was factored into the assessment for these residential handler exposure/risk scenarios. Clothing assumptions include short pants, short-sleeved shirt, and no gloves.
- Exposure frequency - The residential handlers are expected to have a short-term exposure duration (less than 30 days).

Handler Exposure and Risk Estimates

A target MOE of 100 for the dermal and inhalation routes are considered adequate for the handler risk assessment. Results of handler exposure assessment are presented in Table 10 and are summarized below.

1) Low pressure handwand scenario - The adult applicator dermal MOEs were 670 for the low end scenario and 330 for the high end scenario. The inhalation MOEs were 8,800 for the low end scenario and 4,400 for the high end scenario.

2) Backpack sprayer scenario - The adult applicator dermal MOEs were 7,500 for the low end scenario and 3,700 for the high end scenario. The inhalation MOEs were 1,400 for the low end scenario and 720 for the high end scenario.

3) Aerosol can scenario - The adult applicator dermal MOEs were 6,900 for the low end scenario, and 3,500 for the high end scenario. The inhalation MOEs were 720 for the low end scenario, and 360 for the high end scenario.

4) Trigger pump spray scenario - The adult applicator dermal MOEs were 24,390 for the low end scenario, and 14,000 for the high end scenario. The inhalation MOEs were > 24,000,000 for the low end scenario, and > 12,000,000 for the high end scenario.

Table 10: Diquat Dibromide Residential Handler Short Term Exposure and Risk Assessment

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb a.i)	Inhalation Unit Exposure (ug/lb a.i)	Crop (rate)	Application Rate (lb ai per gal)	Amount Treated (gal per day)	Dermal Absorbed Dose* (mg/kg/d)	Dermal MOE*	Inhalation Dose* (mg/kg/d)	Inhalation MOE*
Mixer/Loader/Applicator									
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (1)[a]	100	30	high end	0.018	5	0.003	330	0.0000055	4400
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (2)[a]	100	30	low end	0.009	5	0.0015	670	0.0000028	8800
Mixing/Loading/Applying Liquids for Backpack sprayer application (3)[b]	5.1	30	high end	0.018	5	0.00027	3700	0.000038	720
Mixing/Loading/Applying Liquids for Backpack sprayer application (4)[b]	5.1	30	low end	0.009	5	0.00013	7500	0.000019	1400
Applicator									
Aerosol can application (5)[b]	220	2400	high end	0.018	0.125	0.00029	3500	0.000077	360
Aerosol can application (6)[b]	220	2400	low end	0.009	0.125	0.00014	6900	0.000039	720
Trigger Sprayer (7)[a]	53	0.067	high end	0.018	0.125	0.00007	14000	2E-09	12000000
Trigger Sprayer (8)[a]	53	0.067	low end	0.009	0.125	0.000041	24390	1E-09	24000000

Footnotes:

a Baseline dermal and inhalation exposure derived from the ORETF chemical handler exposure studies.

b Baseline dermal unit exposure represents short pants, short-sleeved shirt, no gloves, open mixing/loading, open cab/tractor. Values from PHED V1.1. Baseline inhalation unit exposure represents no respirator. Values from PHED V1.1.

c Dermal daily dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x amount handled per day (acres) / bw (60 kg).
d Dermal MOE = NOAEL (1 mg/kg) / [daily dose (mg/kg/day) x dermal absorption factor (4.1%)].
e inhalation daily dose (mg/kg/day) = inhalation unit exposure (µg/lb ai) x application rate (lb ai/acre) x amount handled per day (acres) x conversion factor (1 mg/1,000 µg) / body weight (70 kg).
f Inhalation MOE = NOAEL (0.1 µg/L) / daily dose (mg/kg/day).

4.4.1.2 Postapplication

Diquat dibromide is used on dormant turf grass for weed control. Diquat dibromide will kill all types of vegetation and can be used to kill turf grass. Based on this and a review the labels, HED conducted a lawn post-application analysis. Diquat dibromide is specifically labeled to be applied on dormant Bermuda and zoysia grass. Therefore re-entry must be addressed. Only short-term exposures (1 to 30 day period of exposure) are assessed because residents can have post-application exposure to treated lawns in the initial hours and days following treatment. Diquat dibromide is applied to residential turf grass at application rates ranging from 0.25 to 0.5 lb ai/acre. Therefore, for this assessment both low end and high end MOEs were assessed based on the range of application rates.

Postapplication Exposure Scenarios

Four post-application scenarios were assessed:

1) Dermal exposure to treated turf grass - adults and children - This post-application scenario estimates the dermal exposures and risk to adults and toddlers from dermal contact with turf treated with diquat dibromide. This scenario assumes that diquat dibromide residues are transferred to the skin of adults/toddlers who enter treated yards for recreation, yard work, or other homeowner activities.

2) Toddler ingestion of treated turf grass via object-to-mouth activities - This post-application scenario estimates doses among toddlers from incidental ingestion of residential turf grass that has been previously treated with pesticides. This scenario assumes that turf is ingested (or just mouthed) by toddlers who play in the treated areas.

3) Toddler ingestion of residue via hand-to-mouth activity while on treated turf grass - This post-application scenario estimates potential ingestion of pesticide residues from previously treated turf. This scenario assumes that pesticide residues are transferred to the skin of toddlers playing on treated yards and are subsequently ingested as a result of hand-to-mouth transfer.

4) Toddler ingestion of soil from treated area - This post-application scenario estimates doses among toddlers from incidental ingestion of soil containing pesticide residues. This scenario assumes that pesticide residues in soil are ingested by toddlers who play in treated areas.

The turf, post-application assessments were developed using the Residential SOP guidance. The exposure and risk calculations, critical assumptions, and results are provided in Table 11 for

postapplication dermal scenarios and in Table 12 for postapplication incidental oral exposure. Post-application exposure assumptions are summarized below.

Postapplication Exposure Assumptions

The following assumptions were made in the dermal postapplication exposure calculations:

- Application rates range from a low-end rate of 0.25 to a high-end rate of 0.50 lbs ai/acre.
- Turf transferable residue is equal to 5 % of the application rate.
- Turf transfer coefficient is 14,500 cm^2/hr for adult and 5,200 cm^2/hr for children.
- Exposure duration is 2 hours for exposure to residential lawns, and 4 hours for exposure to golf course turf.
- Body weight is 70 kg for adults, and 15 kg for toddlers.

The following assumptions were made in the oral postapplication exposure calculations:

- Application rates range from a low-end rate of 0.25 to a high-end rate of 0.50 lbs ai/acre.
- Hand and object transfer efficiency is equal to 5 % of the application rate available for transfer from treated turf to wet hands and objects.
- Surface portion of hand put in mouth is 20 cm^2.
- Hand-to-mouth exposure frequency is 20/times per hour.
- Body weight is 15 kg for toddlers.
- Exposure time 2 hours.
- Saliva extract factor (for hand-to-mouth only) is 50 percent.

Postapplication Exposure and Risk Estimates

A target MOE of 100 for both the dermal and incidental oral routes is considered adequate for the postapplication risk assessment. Results of post application assessment are presented in Tables 11 and 12 and are summarized below.

1) Dermal exposure to treated turf grass - adults and children - The adult MOEs for re-entering treated lawns were not a risk concern with a low end MOE of 480, and a high end

MOE of 220. The toddler MOEs for this scenario were also not a risk concern with a low end MOE of 270 and a high end MOE of 130.

2) Toddler ingestion of treated turf grass via object-to-mouth activities - The toddler MOEs for ingesting (or mouthing) of treated turf grass were not a risk concern with the low end MOE of 1,110, and a high end MOE of 560.

3) Toddler ingestion of residue via hand-to-mouth activity while on treated turf grass - The toddler MOEs from incidental exposure arising from hand-to-mouth transfer of diquat dibromide were not a risk concern with the low end scenario MOE of 290 and the high end scenario MOE of 145.

4) Toddler ingestion of soil from treated area - The toddler MOEs for ingesting (or mouthing) of treated soil were not a risk of concern with the low end MOE of 83,300, and a high end MOE of 41,670.

Table 11. Dermal Post-application Risks to Toddlers and Adults When Reentering Treated Lawns on Day 0 after Sprays have Dried

Scenario	Range Finder[1]	Application Rate (lb ai/acre)	Fraction of Residue Retained	Transfer Coefficient (cm^2/hr)	Exposure Duration (hours)	Body Wt (kg)	Daily Dermal Dose[2] (mg/kg/d)	Dermal MOE[3]
Toddler	Low End	0.25	0.05	5,200	2	15	0.09	270
	High End	0.5	0.05	5,200	2	15	0.19	130
Adult	Low End	0.25	0.05	14,500	2	70	0.051	480
	High End	0.5	0.05	14,500	2	70	0.11	220

[1] Low end ranges are derived from the lowest labeled application rates, while the high end ranges are derived from the highest labeled rates EPA Reg. No. 10182-404. These application rates represent broadcast application to dormant, established turf grass.

[2] Dermal potential dose rates are calculated as follows:

$$PDR_t = DFR_t * CF1 * Tc * ET$$

where:

PDR_t = potential dose rate on day "t" (mg/day).
DFR_t = dislodgeable foliar residue on day "t" (ug/cm^2).
CF1 = weight unit conversion factor to convert ug units in the DFR to mg for the daily dose (0.001 mg/ug)
Tc = transfer coefficient (cm^2/hr).
ET = exposure time (hr/day).

and

$$DFR_t + AR * F * (1-D)^t * CF2 * CF3$$

where:

AR = application rate (lbs ai/ft^2 or lb ai/acre).
F = fraction of ai retained on foliage (unitless).
D = fraction of residue that dissipates daily (unitless).
t = post-application day on which exposure is being assessed.
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the DFR value (4.54E8 ug/lb)
CF3 = area unit conversion factor to convert the surface area units (ft^2) in the application rate to cm^2 for the DFR value (1.08E-3 ft^2/cm^2 or 24.7E-9 acre/cm^2 if the application rate is per acre)

[3] Post-application Dermal MOE = Oral NOAEL (1 mg/kg/day)/[Daily Dermal Dose (mg/kg/day) x Dermal Absorption Value (4.1%)]. MOEs are reported to two significant figures.

Table 12. Oral Post-application Risks to Toddlers from Oral Exposures When Reentering Treated Lawns

Type of Exposure	Range Finder[1]	Application Rate (lb ai/acre)	Fraction of Residue Available on Foliage	Ingestion Rate or Other Assumptions	Saliva Extraction Factor	Exposure Duration (hours)	Body Wt (kg)	Daily Oral Dose[2] (mg/kg/d)	MOE [3]
Exposure to Treated Turf Grass via object-to-mouth activities[5]	Low End	0.25	0.20	25 cm^2/day ingestion	NA	2	15	0.0009	1,110
	High End	0.5						0.0018	560
Hand-to-Mouth Activity While on Treated Turf Grass	Low End	0.25	0.05	20 hand-to-mouth events per hour; 20 cm^2/day exposed surface area per event	50%			0.0035	290
	High End	0.5						0.007	145
Soil[6]	Low End	0.25	NA	100 mg/day ingestion	NA			0.000012	83,330
	High End	0.5						0.000024	41,670

[1] Low end ranges are derived from the lowest labeled application rates, while the high end ranges are derived from the highest labeled rates EPA Reg. No. 10182-404. These application rates represent broadcast application to dormant, established turf grass.

[2] **Object-to-mouth exposure to treated turf grass potential dose rates from ingestion are calculated as follows:**

$$PDR_t = GR_t * IgR * CF1$$

where:

PDR_t = potential dose rate on day "t" (mg/day)
GR_t = grass (and plant matter) residue on day "t" (ug/cm^2)
IgR = ingestion rate of grass (cm^2/day)
CF1 = weight unit conversion factor to convert ug units in the DFR to mg for the daily dose (0.001 mg/ug)

Hand-to-mouth potential dose rates from ingestion are calculated as follows:

$$PDR_t = DFR_t * SA * FQ * SEF * ET * CF1$$

where:

PDR_t = potential dose rate on day "t" (mg/day).
DFR_t = dislodgeable foliar residue on day "t" (ug/cm^2 turf).
SA = surface area of the hands (cm^2/event).
SEF = saliva extraction factor (%)
FQ = frequency of hand-to-mouth activity (events/hr).
ET = exposure time (hr/day).
CF1 = weight unit conversion factor to convert ug units in the DFR value to mg for the daily exposure (0.001 mg/ug)

Ingestion of soil from treated area potential dose rates from ingestion are calculated as follows:

$$PDR_t = SR_t * Ing * CF1$$

where:

PDRt = potential dose rate on day 't" (mg/day)
SRt = soil residues on day "t" (ug/g)
IgR = ingestion rate of soil (mg/day)
CF1 = weight unit conversion factor to convert ug units in the residues on the soil to g for the daily dose (1.0E-6 g/ug)

[3]Postapplication oral MOE = Oral NOAEL(1 mg/kg/day)/Daily Oral Dose(mg/kg/day). Oral NOAEL determined from a rabbit developmental study. MOEs are reported to two significant figures; an acceptable MOE is at least 100.

Aggregate Post-Application Exposure and Risk Estimate

The short term aggregate post-application risk is the estimated risk associated with combined risks from the short term dermal and oral post-application exposures. Given the observed effects at the recommended NOAELs for oral and dermal pathways, HED believes that risk from these exposure routes can be reasonably added. The inhalation risks are not aggregated because the NOAEL for this exposure pathway is based on a distinct target organ effect.

Aggregate post-application risk is estimated for the child exposure scenario only since the child may be exposed via both oral and dermal pathways while the adult exposure is from the dermal route only. The short term aggregate MOE for the child is calculated by adding exposure estimates from the oral and dermal pathways using the formula presented below. The child aggregate risk combines the highest exposures from the post-application scenarios (i.e., high-end oral and dermal post-application reentry exposure). The calculated short-term aggregate MOE is presented in Table 13. The short-term aggregate post-application MOE for the high-end exposure scenario for 1-6 year old children is 70. The residential aggregate risk combines screening level risk estimates from individual exposure pathways and should be viewed as a highly conservative estimate which is certain to over-estimate risk. The estimated risk from the individual pathways is based on high-end assumptions, i.e., highest application rates, child reentry/play on the day of treatment, and a high-end turf transferable residue factor of 5%. In addition, based on a human dermal absorption study cited by the registrant which shows dermal absorption of 0.3%, use of a 4.1% dermal absorption factor is likely to result in a further overestimation of risk. A refined analysis would result in lower exposure estimates and higher MOEs.

$$\text{MOE Post-Application}_{\text{CHILD}} = \frac{1}{\frac{1}{\text{MOE}_{\text{DERMAL}}} + \frac{1}{\text{MOE}_{\text{ORAL}}}}$$

where:

$\text{MOE}_{\text{DERMAL}}$ = Short Term Dermal NOAEL (mg/kg/day) ÷ (Short Term Dermal Exposure (mg/kg/day) x Dermal Absorption Factor)
MOE_{ORAL} = Short Term Oral NOAEL (mg/kg/day) ÷ Short Term Oral Exposure (mg/kg/day)

Table 13. Short Term Aggregate Post-Application Risk to Child

Population Subgroup	Short Term Oral NOAEL mg/kg/d	Short Term Dermal NOAEL mg/kg/d	Short Term Dermal Re-entry Exposure mg/kg/d[1]	Short Term Oral - Hand to Mouth - Exposure mg/kg/d	Oral MOE	Dermal MOE	Post-Application Aggregate MOE
Child 1-6	1	1	0.0078	0.007	145	130	70

[1] Includes Dermal Absorption Factor of 4.1% (0.19 mg/kg/d x 0.041 = 0.0078)

4.4.2 Recreational

Two recreational post-application exposure scenarios were assessed:

1) Recreational golfer exposure from playing on treated turf grass (adults) - This post-application scenario estimates dermal exposures and risk to adult golfers from dermal contact with turf grass on golf courses that has been previously treated with diquat dibromide. The scenario assumes that a golfer re-enters the course after diquat dibromide sprays have dried and then play a four hour round of golf.

2) Swimming exposure to treated ponds and lakes - This post-application scenario estimates dermal exposures and risk to adult and 7-10 year old swimmers who re-enter

treated ponds and lakes. Several of the diquat dibromide labels intended for aquatic weed control uses have swimming re-entry intervals of 0 days (example: EPA Reg. No. 10182-404).

The exposure and risk calculations, critical assumptions, and results for the recreational golfer exposure scenarios are provided in Table 14. Exposure assumptions for the golfer scenario are summarized below.

Recreational Golfer Exposure Assumptions

The following assumptions were made in the dermal exposure calculations for recreational golfer exposure:

- Application rates range from a low-end rate of 0.25 to a high-end rate of 0.50 lbs ai/acre.
- Turf transferable residue is equal to 5 % of the application rate.
- Turf transfer coefficient is 14,500 cm^2/hr for adult
- Exposure duration 4 hours for exposure to golf course turf.
- Body weight is 70 kg for adults

Table 14. Dermal Post-application Risks Adults When Reentering Golf Courses on Day 0 after Sprays have Dried

Scenario	Range Finder[1]	Application Rate (lb ai/acre)	Fraction of Residue Retained	Transfer Coefficient (cm^2/hr)	Exposure Duration (hours)	Body Wt (kg)	Daily Dermal Dose[2] (mg/kg/d)	Dermal MOE[3]
Adult Golfer	Low End	0.25	0.05	500	4	70	0.0034	7,100
	High End	0.5	0.05	500	4	70	0.0077	3,200

[1] Golfer durations are assumed to be 4 hours for an 18-hole round of golf.
[2] Dermal potential dose rates are calculated as follows: $PDR_t = DFR_t * CF1 * Tc * ET$
[3] Post-application Dermal MOE = Oral NOAEL (1 mg/kg/day)/[Daily Dermal Dose (mg/kg/day) x Dermal Absorption Value (4.1%)]. MOEs are reported to two significant figures.

Swimmer Exposure Assumptions

In order to assess potential exposures to swimmers who re-enter treated ponds and lakes, HED used the Swimmer Exposure Assessment Model (SWIMODEL). The SWIMODEL was developed for estimating the human exposure doses to the pesticides and toxic pollutants in swimming pools. This model is a modification of a study used by J. A. Beech (1980) for estimating exposure to Trihalomethanes (THM) in swimming pools. Clearly swimming in ponds and lakes is different than pools in many ways; however, the basic exposure to chemicals in the water column are similar enough to warrant using this model for this TRED.

The model is based on exposure routes and age-specific contact factors, exposure duration and frequency, chemical/physical properties of the pollutant, and pollutant concentration, total exposure doses can be approximated by the model. For this TRED child (age 7-10) and adult swimmers were modeled. One diquat dibromide concentration in the lake was modeled for this analysis: 20 ppb – the maximum contaminant goal which was reported by EFED as a high end, monitoring data endpoint. The exposure and risk calculations, critical assumptions, and results for the swimmer scenario are provided in Table 15.

Table 15. Child and Adult Exposure and Risk to Swimming in Treated Lakes on Day 0

Exposed Population	Concentration in Lake (ppm)[1]	Total Exposure (mg/event)[2]	Body Weight (kg)[3]	Total Dose (mg/kg/day)[4]	MOE[5]
Child (age 7-10)	20	0.062	37.8	0.0016	630
Adult	20	0.0087	84.4	0.0001	10,000

[1] The concentration in the lake was run at 20 ppb (the maximum contaminant goal reported by EFED as a high end, monitoring data endpoint).
[2] Total exposure is a combination of exposures via the following routes: oral, dermal, buccal/sublingual, orbital/nasal, aural, and inhalation.
[3] Body weights represent the 90% for the population being modeled.
[4] Total dose (mg/kg/day) = Total exposure (mg/event) / body weight (kg)
[5] MOE = Oral NOAEL 1 mg/kg/day / Total dose (mg/kg/day)

Recreational Exposure and Risk Estimates

A target MOE of 100 for both the dermal and incidental oral routes is considered adequate for the recreational risk assessment. Results of the recreational exposure assessment are presented in Tables 14 and 15 and are summarized below.

1) The MOEs for an adult playing a round of golf on a treated golf course were not a risk concern. MOEs ranged from 7,100 for the low-end exposure scenario to 3,200 for the high-end scenario.

2) Estimated MOEs were not a risk of concern for child or adult swimmers. MOEs for children age 7-10 ranged from 630 to 180. MOEs for adults ranged from 10,000 to 770.

4.5 Incident Reports

The vast majority of incident reports for diquat fall into one of two categories: (1) people exposed while handling the product for its intended purpose; and, (2) people who drank the pesticide either by accident or on purpose (i.e., in order to harm themselves) (M. Spann and J. Blondell, 10/15/01, D278482). According to a several of pesticide incident sources, diquat dibromide ranked relatively high on the list of pesticides with reported incidents. Detailed descriptions of 112 cases submitted to the California Pesticide Illness Surveillance Program (1982-

1999) were reviewed. In 76 of these cases, diquat was used alone or was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. Diquat ranked 50th as a cause of systemic poisoning in California based on data for 1982 through 1999. Similarly, on the list of the top 200 chemicals for which National Pesticide Telecommunications Network received calls from 1984-1991 inclusively, diquat was ranked 54th with 74 incidents in humans reported. From the review of California data, it appears that a majority of cases involved systemic, eye, and skin illnesses such as eye irritation/pain, skin rash, chemical burns, chemical conjunctivitis, nausea, and vomiting. Poison Control Center data tend to support the California data, eye irritation/pain, erythema, rash, skin itching, corneal abrasion, lacrimation, dyspnea, coughing, and choking were the most common effects reported due to exposure. Oral exposure to even modest amounts can lead to severe poisoning and even death.

4.5.1 Residential Handler Incidents

Of all the handler incident reports, "applicator" was associated with more exposures than any other category. These illnesses included symptoms of burning and itching eyes, dizziness, nausea, dyspnea, rashes, chemical conjunctivitis, vomiting, dermatitis, and chemical burns.

4.5.2 Postapplication and Recreational Incidents

Not many cases of post-application exposures have been reported, however there was one incident involving swimmers. In this case, two boys swam in a lake that had been treated with diquat three days prior to the activity. Both boys developed a rash, one much more severe than the other. The nine year old boy with the more serious rash was treated by a physician while the other boy was treated at home. No information was provided on levels of diquat in the treated lake.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

The aggregate risk assessment integrates the assessments conducted for dietary and residential exposure. Since there is potential for concurrent exposure via the food, water and residential pathways, the combined exposures are estimated using the methodology described below and are compared with monitoring-based estimates of drinking water contamination determined by EFED. All routes of diquat dibromide exposure have been considered. Aggregate exposure pathways for adults include dietary, drinking water, and dermal and inhalation exposures from application and post-application activities. Aggregate exposure pathways for children include dietary, drinking water, and dermal and oral exposures from post-application exposure.

5.1 Acute Aggregate Risk Assessment

The acute aggregate risk is the estimated risk associated with combined acute food and drinking water exposure. The acute aggregate MOE is calculated by adding acute dietary exposure estimates with drinking water levels obtained from monitoring data using the formula presented below. The target MOE for acute aggregate risk is 100. The calculated acute aggregate

MOEs are presented in Table 16. Acute aggregate risk MOEs are below EPA's level of concern (i.e., ≥to 100) for all population subgroups. Since the estimated risk from the individual pathways are considered to be screening level, the aggregates should be considered as a highly conservative estimate of risk.

$$\text{MOE Aggregate}_{acute} = \frac{1}{\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{WATER}}}$$

where:

MOE_{FOOD} = Acute Dietary NOAEL (mg/kg/day) ÷ Acute Dietary Exposure (mg/kg/day)
MOE_{WATER}= Acute Dietary NOAEL (mg/kg/day) ÷ Acute Water Exposure (mg/kg/day).

and:

$$\text{Acute Water Exposure (mg/kg/d)} = \frac{\text{Acute Water EEC (mg/L) x Drinking Water Consumption (L/day)}}{\text{Body Weight (kg)}}$$

Table 16. Acute Aggregate Risk

Population Subgroup	Acute Dietary NOAEL (mg/kg/day)	Acute Dietary Exposure (mg/kg/day)	Acute Water EEC (mg/L)	DW Consumption (L/day)	Body Weight (kg)	Acute Water Exposure (mg/kg/day)	Acute Aggregate MOE
US Population (total)	75	0.0039	0.02	2	70	0.00057	16773
All Infants (<1 year old)	75	0.0035	0.02	1	10	0.002	13636
Children 1-6 years old	75	0.0054	0.02	1	10	0.002	10135
Children 7-12 years old	75	0.0033	0.02	1	10	0.002	14151
Females 13-50 years old	75	0.0032	0.02	2	60	0.00067	19397
Males 13-19 years old	75	0.0030	0.02	2	70	0.00057	21000
Males 20+ years old	75	0.0035	0.02	2	70	0.00057	18421
Seniors 55+ years old	75	0.0023	0.02	2	70	0.00057	26119

5.2 Short-Term Aggregate Risk Assessment

The short term aggregate risk is the estimated risk associated with combined risks from the following pathways: chronic dietary intake, average annual drinking water exposures, and short term dermal and oral (if applicable) exposures. Given the observed effects at the recommended NOAELs for each of these pathways, HED believes that risk from these exposure routes can be reasonably added. The inhalation risks are not aggregated because the NOAEL for this exposure pathway is based on a distinct target organ effect. The short term aggregate MOE is calculated by adding exposure estimates from each of these pathways using the formula presented below. The adult aggregate risk combines the highest exposures from the various application and post-application scenarios (i.e., high-end, low pressure handwand applicator exposure, and high-end

adult reentry exposure). Likewise, the highest dermal and oral exposures from the assessed scenarios are added for the estimated child risk aggregate. The calculated short-term aggregate MOEs are presented in Table 14. The short term aggregate MOE for the high-end exposure scenario for the adult applicator is 100. The short-term aggregate MOE for the high-end toddler exposure scenario is 55.

The short-term aggregate risk combines screening level risk estimates from individual exposure pathways and should be viewed as a highly conservative estimate, certain to over-estimate risk. A refined analysis would result in lower exposure estimates and higher MOEs. Possible refinements include: 1) revising the dietary assessment to account for actual percent crop treated (i.e., no use involves 100% crop treated; most involve <1% CT) and to reflect residues based on field trial data, which are generally much lower than tolerance levels; 2) revising estimated environmental concentrations in drinking water sources to reflect lower concentrations in a sizeable majority of monitoring samples (i.e., monitoring data from 1993-1997 showed an MCL exceedence rate of < 1%); and 3) refining the residential exposure scenarios to include more plausible assumptions regarding a) the use of protective clothing for applicators (i.e., no protective clothing was factored into assessments of residential exposure), b) application rates (i.e., highest rates are assumed), c) day of reentry (i.e., children and adults are assumed to reenter and work/play on the lawn on the day of treatment), d) turf transferable residue (i.e., TTR is assumed to be 5% of the application rate - a high-end assumption), and e) dermal absorption factor (i.e., dermal absorption is assumed to be 4.1% based on a rat study; a human dermal absorption study cited by the registrant estimates dermal absorption to be about 0.3% (Feldman RJ and Maibach HI, "Percutaneous penetration of some pesticides and herbicides in man" Tox. Appl. Pharm. 28 126-132, 1974)).

$$\text{MOE Aggregate}_{\text{SHORT TERM}} = \frac{1}{\frac{1}{\text{MOE}_{\text{FOOD}}} + \frac{1}{\text{MOE}_{\text{WATER}}} + \frac{1}{\text{MOE}_{\text{DERMAL}}} + \frac{1}{\text{MOE}_{\text{ORAL}}^{*}}}$$

* If applicable

where:

MOE_{FOOD} = Short Term Oral NOAEL (mg/kg/day) ÷ Chronic Dietary Exposure (mg/kg/day)
$\text{MOE}_{\text{WATER}}$ = Short Term Oral NOAEL (mg/kg/day) ÷ Chronic Water Exposure (mg/kg/day)
$\text{MOE}_{\text{DERMAL}}$ = Short Term Dermal NOAEL (mg/kg/day) ÷ (Short Term Dermal Exposure (mg/kg/day) x Dermal Absorption Factor)
MOE_{ORAL} = Short Term Oral NOAEL (mg/kg/day) ÷ Short Term Oral Exposure (mg/kg/day)

and:

$$\text{Water Exposure (mg/kg/d)} = \frac{\text{Chronic Water EEC (mg/L)} \times \text{Drinking Water Consumption (L/day)}}{\text{Body Weight (kg)}}$$

Table 17. Short Term Aggregate Risk

Population Subgroup	Short Term Oral NOAEL mg/kg/d	Chronic Dietary Exposure mg/kg/d	Annual Avg Water Exposure mg/kg/d	Short Term Dermal NOAEL mg/kg/d	Short Term Dermal Exposure - Handwand Applicator mg/kg/d[1]	Short Term Dermal Exposure Re-entry mg/kg/d[1]	Short Term Oral - Hand to Mouth - Exposure mg/kg/d	Short Term Aggregate MOE
Male 20+	1	0.0018	0.00057	1	0.003	0.0045	NA	100
Child 1-6	1	0.0031	0.002	1	NA	0.0078	0.007	55

[1] Includes Dermal Absorption Factor of 4.1% (0.11 mg/kg/d x 0.041 = 0.0045; 0.19 mg/kg/d x 0.041 = 0.0078)

5.3 Chronic Aggregate Risk Assessment

The chronic aggregate risk is the estimated risk associated with combined chronic food and drinking water exposure. The chronic aggregate MOE is calculated by adding chronic dietary exposures and estimated average annual drinking water concentrations using the formula presented below. The target MOE for chronic aggregate risk is 100. The calculated chronic aggregate MOEs are presented in Table 18. Chronic aggregate risk MOEs are below EPA's level of concern (i.e., ≥to 100) for all population subgroups. Again, since the aggregate combines screening level risks from individual exposure pathways, the chronic aggregate risk estimate is highly conservative.

$$\text{MOE Aggregate}_{\text{CHRONIC}} = \frac{1}{\frac{1}{\text{MOE}_{\text{FOOD}}} + \frac{1}{\text{MOE}_{\text{WATER}}}}$$

where:

MOE_{FOOD} = Chronic Dietary NOAEL (mg/kg/day) ÷ Chronic Dietary Exposure (mg/kg/day)
$\text{MOE}_{\text{WATER}}$ = Chronic Dietary NOAEL (mg/kg/day) ÷ Chronic Water Exposure (mg/kg/day)

and:

$$\text{Chronic Water Exposure (mg/kg/d)} = \frac{\text{Chronic Water EEC (mg/L)} \times \text{Drinking Water Consumption (L/day)}}{\text{Body Weight (kg)}}$$

Table 18. Chronic Aggregate Risk

Population Subgroup	Chronic Dietary NOAEL (mg/kg/day)	Chronic Dietary Exposure (mg/kg/day)	Chronic Water EEC (mg/L)	DW Consumption (L/day)	Body Weight (kg)	Annual Avg Water Exposure (mg/kg/day)	Chronic Aggregate MOE
US Population (total)	0.5	0.0019	0.02	2	70	0.00057	202
All Infants (<1 year old)	0.5	0.0017	0.02	1	10	0.002	135
Children 1-6 years old	0.5	0.0031	0.02	1	10	0.002	98
Children 7-12 years old	0.5	0.0021	0.02	1	10	0.002	122
Females 13-50 years old	0.5	0.0017	0.02	2	60	0.00067	211
Males 13-19 years old	0.5	0.0018	0.02	2	70	0.00057	211
Males 20+ years old	0.5	0.0019	0.02	2	70	0.00057	202
Seniors 55+ years old	0.5	0.0015	0.02	2	70	0.00057	241

6.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a

common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this TRED for diquat dibromide because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of diquat dibromide. For purposes of this TRED, EPA has assumed that diquat dibromide does not have a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether diquat dibromide shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for diquat dibromide need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with diquat dibromide, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by December 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 DATA NEEDS/LABEL REQUIREMENTS

All product chemistry data are required for the Syngenta 41.1% and 37.3% Formulation Intermediates (EPA Reg. Nos. 10-1062 and 100-1063). Magnitude of the residue in plants studies are required for sorghum aspirated grain fractions and soybean aspirated grain fractions.