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MEMORANDUM

SUBJECT: **Difenzoquat**. HED Human Health Risk Assessment for the Tolerance Reassessment Eligibility Decision (TRED). PC Code: 106401. Case 0223. DP Barcode D279988.

FROM: William J. Hazel, Ph.D., Risk Assessor
Reregistration Branch 1
Health Effects Division (7509C)

THROUGH: Whang Phang, Ph.D., Branch Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

TO: Tawanda Spears/Betty Shackleford
Reregistration Branch 3
Special Review and Reregistration Division (7508C)

The following human health risk assessment has been prepared by the Health Effects Division (HED) for Phase 1 (Registrant Error Correction) of the tolerance reassessment eligibility decison (TRED) process for difenzoquat methyl sulfate. The HED chapter reflects the Agency's current guidelines concerning the retention of the Food Quality Protection Act (FQPA) safety factor and risk assessment. The chapter is based upon the toxicology review by Elizabeth Mendez (RRB1), the product chemistry, residue chemistry, and dietary exposure/risk analysis by Felecia Fort (RRB1), the human incidents report by Jerome Blondell (CEB), and the drinking water exposure assessment by Mark Corbin of the Environmental Fate and Effects Division (EFED). The risk assessment and characterization were performed by William Hazel (RRB1).

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1.0 Executive Summary

The following human health risk assessment has been prepared by the Health Effects Division (HED) for Phase 1 (Registrant Error Correction) of the tolerance reassessment eligibility decison (TRED) process for difenzoquat methyl sulfate. The Difenzoquat Reregistration Standard Guidance Document was issued 12/88.

Difenzoquat (1,2-dimethyl-3,5-diphenyl-1*H*-pyrazolium ion) is an herbicide frequently considered to be a bipyridylium compound; it is, in fact, a pyrazole compound bearing two phenyl rings that has similar biological activity to the bipyridyliums such as paraquat. Difenzoquat is used largely for the selective control of wild oats in wheat and barley, its mode of action being rapid destruction of cell membranes. In addition, there are Special Local Needs [24(c)] labels granted for the states of Washington, Oregon, and Idaho. In these states, difenzoquat may be used for the control of wild oats in Kentucky bluegrass grown for seed production (i.e., not a turf use). There are no residential use scenarios for difenzoquat. The current U.S. tolerances for difenzoquat, expressed in terms of parent compound only, range from 20 ppm in wheat and barley straw to 0.05 ppm in fat, meat, and meat byproducts. Difenzoquat is marketed as the methyl sulfate salt and formulated as a 2 lb cation/gal soluble concentrate/liquid (SC/L) and a 92.5% water dispersible granule (WDG). A single postemergence application is made at a maximum rate of 1 lb cation/A at up to the 7-leaf or tiller stages. Currently, labels prohibit grazing or cutting of forage for hay or silage; although this is not considered to be practical, this restriction should remain on labels while barley and wheat forage and hay residue trials are being conducted. There are 235 thousand pounds of difenzoquat active ingredient used in the U.S. annually.

Difenzoquat has a moderate acute toxicity profile (acute oral LD_{50} = 485 mg/kg bw, Toxicity Category II; acute dermal LD_{50} = 3.45 g/kg bw, Toxicity Category III; inhalation LC_{50} = 0.5 mg/L, Toxicity Category II).

The relevant data on the carcinogenic potential of difenzoquat was evaluated by RfD Peer Review Committee in 1994. Difenzoquat has been classified as a Group E chemical (a compound showing evidence of non-carcinogenicity in humans). This classification is based on the lack of carcinogenicity in studies in rats and mice and is confirmed by the evaluations of IARC, OSHA, and NTP.

The toxicity profile for difenzoquat indicates that it is extremely irritating to the gastrointestinal (GI) tract. The only acute effects noted in the database (suggestive of irritation) were considered to be artifacts of the method of administration of the test article (gavage) or were not elicited by a single dose. In a Chronic Oral Toxicity Study in Dogs with capsule administration, no effects were seen at a dose of 30 mg/kg/day. The lowest dose at which effects were reported was 44 mg/kg/day. The effects included: 1) increased mortality, 2) increased incidence of clinical signs of toxicity (lateral recumbency, tremors, lethargy, irregular gait, and dilated pupils), 3) decreased body weight gain, and 4) necropsy findings (stomach lesions). The animals did not tolerate

exposure to higher doses of the test article. These clinical signs of toxicity were considered to reflect the impact of the severe degeneration of the GI tract (necrosis of the esophagus, stomach, small and large intestine). Interestingly, similar effects were not observed in the Subchronic Oral Toxicity Study in Dogs; in this study the test compound was incorporated into the food supply. In the Combined Chronic/Oncogenicity Study in Rats, effects were seen at the 125 mg/kg/day dose level. Toxicity at this dose level was manifested by consistent decreases in body weight and body weight gain in the absence of decreased food consumption. Similar effects were also reported in the Oncogenicity Study in Mice at dose levels ≥69 mg/kg/day. No neoplastic lesions were reported in any of the long-term toxicity studies.

In contrast to the severe GI irritation induced by oral administration of difenzoquat (capsule or gavage), a 21-Day Dermal Toxicity Study revealed no signs of systemic toxicity after topical application of the test article up to the limit dose (1000 mg/kg/day). In fact, dermal toxicity at the high dose level was limited to slight edema observed prior to the last application of the test compound. These data suggest that dermal absorption of difenzoquat is low; probably similar to the absorption through the GI tract (1-7%) reported in the rat metabolism study.

Reproductive and developmental parameters that may be affected by exposure to difenzoquat were studied in a Multigeneration Reproduction Toxicity Study, a Developmental Toxicity Study in Rabbits, and a Developmental toxicity Study in Rats. The Developmental Toxicity studies in Rats and Rabbits indicate that there is no enhanced susceptibility of the offspring after *in utero* exposure to difenzoquat. In the Developmental Toxicity Study in rats, maternal toxicity is observed at dose levels that do not elicit developmental effects. The developmental effects seen in the rabbit study (resorptions and skeletal effects) are reported at the same dose level causing mortality in maternal animals and are not considered to result from a single dose. Though a Multigeneration Reproduction Toxicity Study has been submitted to the Agency, this study is considered unacceptable by the HIARC. This study has numerous deficiencies, ranging from testing at only two dose levels to insufficient parameters evaluated, which severely compromised the interpretation of the results.

The mutagenicity database for difenzoquat indicates that this chemical has no mutagenic or genotoxic activity. Negative mutagenic responses were noted for the *In Vitro* Mammalian Cell Gene Mutation Test, the *In Vitro* Mammalian Chromosome Aberration Test, and the Unscheduled DNA Synthesis in Mammalian Cells in Culture Test.

Currently the difenzoquat database does not contain Acute or Subchronic Neurotoxicity Studies. Though Acute and Subchronic Neurotoxicity Studies were initially requested in the 1994 Reregistration Eligibility Decision Document (RED), the registrant later requested and was granted data waivers for these studies. The basis for the data waivers was that the apparent signs of neurotoxicity in existing studies were "not indicative of a direct effect of difenzoquat on the nervous system but were secondary

effects of the systemic toxicity resulting from the marked irritation to the GI tract. Further, as the majority of animals died within a few days of the onset of neurological signs, the findings were indicators that the animals were near death."[1]

The rat metabolism study showed that difenzoquat was poorly absorbed through the GI tract since only 1-7% of the administered radioactivity was recovered in the urine. Most of the radioactivity was eliminated in the feces as the parent compound (63-80% of the administered dose) within 24 hours. Negligible amounts of the administered radioactivity were found in any tissue (≤0.01 ppm).

An acute dietary risk assessment was not conducted because an acute reference dose (aRfD) was not established. The only acute effects noted in the database (suggestive of irritation) were considered to be artifacts of the method of administration of the test article (gavage) or did not result from a single dose.

The chronic dietary risk estimate did not exceed the Agency's level of concern for any population subgroup. The NOAEL of 25 mg/kg/day from the combined rat chronic/oncogenicity study was selected for chronic risk assessment based on consistent decreases in body weight and body weight gain in the absence of decreased food consumption seen at the LOAEL of 125 mg/kg/day. The chronic RfD (cRfD) is 0.083 mg/kg/day reflecting application of the following factors: 10x for intraspecies extrapolation, 10x for interspecies variation, 3x for lack of a multigeneration reproduction study, and 1x reduced FQPA safety factor. An unrefined Tier 1 chronic dietary risk assessment was conducted for all supported (i.e., currently registered and proposed) difenzoquat food uses. Dietary risk estimates are provided for the general U.S. population and various population subgroups. This assessment concludes that for all included commodities, the **chronic risk estimates are below the Agency's level of concern (<100% cPAD)** for the general U.S. population (<1% of the cPAD) and all population subgroups (<1% cPAD). No cancer endpoint has been identified.

Aggregate chronic risk estimates include the contribution of risk from food and water dietary sources. There are no uses of difenzoquat registered in a residential setting. The Agency concludes with reasonable certainty that residues of difenzoquat in food and drinking water would not likely result in an aggregate chronic risk to infants and children or other population subgroups above the Agency's level of concern. The Agency based this determination on a comparison of estimated concentrations of difenzoquat in surface water and groundwater to Drinking Water Levels of Comparison (DWLOCs) for difenzoquat.

The database for difenzoquat is considered adequate for risk assessment necessary for the conduct of this TRED. However, data deficiencies have been identified. Studies

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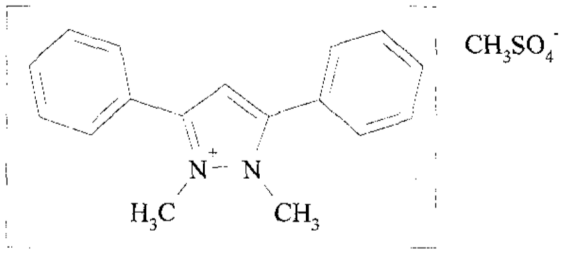
[1] Desiree L. Little memorandum (American Cyanimid Co.) to Andrew Ertman (SRRD) dated May 2, 1995

required by the Agency include: (i) multigeneration reproduction toxicity study (870.3800), (ii) UV/visible absorption (830.7050); (iii) wheat and barley hay and wheat forage field trial residue studies (860.1500), the concomitant proposal of tolerances in these commodities, and the eventual deletion of the forage/hay grazing/cutting restriction upon submission of the field trials.

2.0 Physical and Chemical Properties

Difenzoquat (1,2-dimethyl-3,5-diphenyl-1*H*-pyrazolium methyl sulfate) is a selective pyrazole herbicide formulated as a soluble concentrate/liquid (SC/L) and a water dispersible granule (WDG). The sole registrant in the U.S. is BASF. Some information and properties are presented below.

Identity:	1,2-dimethyl-3,5-diphenyl-1*H*-pyrazolium methyl sulfate
Class:	pyrazole
Empirical Formula:	$C_{18}H_{20}N_2O_4S$
Molecular Weight:	360.4
CAS Registry No.:	43222-48-6
PC Code:	106401
Color:	clear to pale yellow
Physical state:	solid
Odor:	odorless
Melting point:	156-158 C
Bulk density:	0.796 g/ml
Water solubility:	76% @ 25 C
vapor pressure:	Being a salt, vp is expected to be negligible
log P_{ow}:	Expected to be very low due to high water solubility and low solubility in organic solvents



Difenzoquat methyl sulfate exhibits high water solubility and low lipophilic potential and thus is not likely to be significantly absorbed through the skin or to bioaccumulate. The vapor pressure of difenzoquat methyl sulfate is very low which would somewhat reduce inhalation exposure. No impurities of known or suspected toxicological concern are contained within the difenzoquat technical grade of the active ingredient (TGAI). Although there is the potential for exposure to the chemical via all routes (oral, dermal and inhalation), this TRED will assess the exposure and risks via the oral route (food and water pathways) only because there are no residential uses and occupational exposure will not be considered in this assessment.

3.0 Hazard Characterization

3.1 Hazard Profile

The acute toxicity profile of difenzoquat is presented in Table1. A summary of relevant studies pertaining to the toxicity of difenzoquat methyl sulfate is presented in Table 2 below. All studies were performed using difenzoquat methyl sulfate as the test substance.

Table 1. Acute toxicity profile of Difenzoquat methyl sulfate.

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	41325406	LD_{50} = 485 mg/kg[a]	II
81-2	Acute Dermal	00041883	LD_{50} = 3540 mg/kg	III
81-3	Acute Inhalation	41325408	LC_{50} = 0.5 mg/L[b]	II
81-4	Primary Eye Irritation	00041883	slight eye irritant (At 72 hrs after exposure, conjunctival irritation was present in 4/6 test rabbits)	
81-5	Primary Skin Irritation	00041883	Not a skin irritant	
81-6	Dermal Sensitization	41325409	not a dermal sensitizer	

a: Mortality occurred at 400 mg/kg or above within 2-8 hrs post-dosing. Clinical signs of toxicity such as salivation at 200 mg/kg or above, decreased activity and prostration at doses $\geq$400 mg/kg. Diuresis was seen at 800 mg/kg.

b: At $\geq$0.255 mg/L, Signs of toxicity included inactivity, closed eyes, wet or stained nose, ruffled fur, tremors, and unsteady gait.

Table 2. Toxicity Profile of Difenzoquat methyl sulfate.

Study Type/Dose Level/MRID	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Acute Oral Toxicity/Rat: 200, 400, 800 mg a.i./kg MRID No. 41325406		LD_{50} Males = 617 mg/kg Females = 373 mg/kg Combined = 485 mg/kg	Mortality occurred at 400 (3/5 ♀ only) and 800 (4/5 ♂ and 5/5 ♀)mg/kg. [2] Clinical signs were observed including salivation (all dose levels), decreased activity and prostration (≥ 400 mg/kg), and diuresis (800 mg/kg) within the first 24 hours of treatment. Gross necropsy findings for animals that died during the study included congested livers and kidneys as well as enlarged fluid-filled intestines. **Toxicity Category II**
Acute Dermal Toxicity /Rabbit 625, 1250, 2500, 5000, and 10000mg/kg for 24 hrs. MRID No. 00041883		LD_{50} Males = 3,450 mg/kg	Lethargy and slight erythema noted. **Toxicity Category III**
Acute Inhalation/Rats 0, 0.255, 0.438, 0.579, 1.14, or 1.72 mg/L for 4 hrs. MRID No. 41325408		LC_{50} Males = 0.62 mg/L Females = 0.36 mg/L Combined = 0.5 mg/L	All animals died during the exposure period at concentrations ≥ 1.14 mg/L . Clinical signs of toxicity including inactivity, closed eyes, wet or stained noses, ruffled fur and unsteady gait reported at concentrations of 0.255 mg/L and higher. **Toxicity Category II**
Primary Eye Irritation/Rabbit MRID No. 00041883			Slight eye irritant. Conjunctivae involvement persisting for 72 hrs.
Primary Skin Irritation/Rabbit 0.5 g test article applied for 24 hrs. MRID No. 00041883			Not a dermal irritant. **Toxicity Category IV**
Dermal Sensitization/Guinea Pigs MRID 41325409			Not a dermal sensitizer.

[2] Symbols: ♂ = male; ♀ = female

Study Type/Dose Level/MRID	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
21-Day Dermal Toxicity Study/Rabbits. 0, 250, 500, and 1000 mg/kg/day. MRID No. 41325410	Systemic = 1000 (HDT)[3] Dermal = 250	Systemic: Not established Dermal = 500	No systemic signs of toxicity. Mild edema at the application site in males at ≥ 500 mg/kg/day. **Acceptable/guideline**
Subchronic Oral Toxicity Study/Dog. 0, 100, 500, and 2500 ppm (0, 2.5, 12.5, 62.5 mg/kg/day). MRID No. 00037922	62.5 (HDT)	Not established	Study conducted in 1973, clinical chemistry parameters (e.g. bilirubin, creatinine , etc.) were not evaluated. No effects noted at the highest dose tested (HDT) which was well below the limit dose. **Unacceptable/non-guideline.**
Developmental Toxicity Study/Rabbits: 0, 50, 100, and 250 mg/kg/day during GD 7-19. MRID No. 144521	Maternal: 100 Developmental: 100	Maternal: 250 based on diarrhea and mortality. Developmental: 250 based on resorptions and vertebral central abnormalities indicative of delayed ossification	Only 17 fetuses (6 litters) available for evaluation at the high-dose due to maternal mortality (61%). Nonetheless, sufficient data are available to assess developmental toxicity and offspring susceptibility **Acceptable/guideline.**
Developmental Toxicity Study/Rats: 0, 30, 60, 120, and 240 mg/kg/day during GD 6-15. MRID No. 41521203	Maternal: 60 Developmental: 240	Maternal. 120 based on excessive salivation, decreased food consumption and body weight gain. Developmental: **Not established**	At the 240 mg/kg/day dose level (HDT), maternal animals exhibited similar effects to the ones reported at 120 mg/kg/day. **Acceptable/Guideline**
Multi-Generation Reproduction Toxicity Study/Rat: 0, 500, and 2500 ppm (Males: 0, 38, 190 mg/kg/day; Females: 0, 46, 281 mg/kg/day). MRID No. 00037924	Parental: 38 Reproduction: 190(HDT) Offspring: 38	Parental: 190 based on marginal but statistically significant decreases in body weight and body weight gain. Reproduction: **Not established.** Offspring: 190 based on statistically significant decreases in pups weight at weaning.	This study had numerous deficiencies that severely compromised the interpretation of the results. **Unacceptable/guideline.**

[3]Abbreviations: HDT = Highest dose tested; UDS = Unscheduled DNA Synthesis

Study Type/Dose Level/MRID	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Combined Chronic/Oncogenicity Study/Rats: 0, 100, 500, and 2500/5000 ppm (0, 5, 25, and 125/250 mg/kg/day). High-dose increased from 2500 to 5000 ppm on week 30 of the study. MRID No. 00036710	25	125 based on consistent decrease in body weight and body weight gain.	No evidence of carcinogenicity. **Acceptable/non-guideline**
Oncogenicity Study/Mouse: 0, 200, 500, and 1000 ppm (Males: 0, 26.9, 69.4, and 150.1 mg/kg/day; Females: 0, 39.7, 97.9, and 202.4 mg/kg/day). MRID No. 42800402	26.9	69.4 based on decreased body weight gain in males.	No evidence of carcinogenicity. **Effects reported at 1000 ppm:** Mean body weights were reduced in males (7-16%) and females (5-10%) compared to control. Body weight gains were decreased in males (30-62%) and females (0-54%). **Acceptable/guideline.**
Chronic Toxicity Study/Dogs Doses (mg/kg): Group I(Control): empty gelatin capsules Group II : 12.5 Group III: 37.5 (days 1- 28) and 20 (days 29-termination) Group IV: 75 (days 1-6) 50 (days 7-8); 44 (days 9-28); and 30 (days 29-termination) Group V: 125 (days 1-4); 100 (days 5-6) 75 (days 7-9 all dogs dead) MRID No. 42800401	30	44 based on mortality, clinical signs (recumbency, tremors, lethargy, irregular gait, and dilated pupils), decreased body weight gain, and necropsy findings (discoloration of the stomach)	Though the decreasing doses complicated the evaluation of this study, animals received the final dose level for sufficient time to make an evaluation of this chemical's toxic effects in dogs. **Acceptable/guideline**

Study Type/Dose Level/MRID	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Metabolism Study/Rats: 5 or 25 mg/kg ^{14}C-difenzoquat by gavage (single dose) or 5 mg/kg/day difenzoquat followed by 5 mg/kg/day ^{14}C-difenzoquat. MRID No. 41844501			^{14}C-difenzoquat was administered to groups of SD rats by gavage. The results indicated that this chemical was poorly absorbed and distributed. Most of the radioactivity was eliminated rapidly in the feces as the parent compound (63-80% of the administered dose) within 24 hrs. The recovery was low in the urine (1.3-6.9% of the administered dose). Bioaccumulation was not seen. With iv administration, approximately 25% of the administered dose was found in the urine while approximately 31% was found in the feces after 24 hrs. Tissue levels was reported to be less than 0.01 ppm.
In Vitro Mammalian Cell Gene Mutation Assay Doses: 500-1600 μg/ml (-S9 activation) and 500-1250 μg/ml (+S9 activation). MRID No. 41325411			Cytotoxicity at ≥ 2000 μg/ml (- S9 activation) and ≥ 1600 μg/ml (+S9 activation). **Difenzoquat did not induce mutations in the absence or presence of S9 activation**
In Vitro Mammalian Chromosome Aberration Assay Doses: 65-5700 μg/ml (-S9 activation) and 24-1900 μg/ml (+S9 activation). MRID No. 41415303			Cytotoxicity was too high at concentrations ≥ 1900 μg/ml both in the absence and presence of metabolic activation. **Difenzoquat did not induce mutations in the absence or presence of S9 activation.**
Unscheduled DNA Synthesis in Mammalian Cells in Culture Assay Doses: 0.26-8000 μg/well			Cytotoxicity was too high at concentrations ≥ 80 μg/well. **Difenzoquat failed to induce UDS when assayed up to cytotoxic levels.**

The toxicology database for difenzoquat is considered adequate for hazard characterization for purposes of this TRED. The toxicity profile of difenzoquat can be characterized for all effects including potential developmental, reproductive, and neurotoxic effects. Difenzoquat is an irritant of the GI tract; all effects elicited appear to be secondary to this irritation. The only acute effects noted in the database (suggestive of irritation) were considered to be an artifact of the method of

administration of the test article (gavage) and no effects attributable to a single dose were observed. In a Chronic Oral Toxicity Study in Dogs with capsule administration, clinical signs of toxicity occurred at the LOAEL of 44 mg/kg/day; these signs are considered to reflect the impact of the severe degeneration of the GI tract (necrosis of the esophagus, stomach, small and large intestine). However, similar effects were not observed in the Subchronic Oral Toxicity Study in Dogs, in which the test compound was administered via the food supply. In the Combined Chronic/Oncogenicity Study in Rats, **selected for risk assessment purposes**, effects seen at the 125 mg/kg/day dose level (consistent decreases in body weight and body weight gain in the absence of decreased food consumption) are consistent with GI irritation. Similar effects were also reported in the Oncogenicity Study in Mice at dose levels ≥69 mg/kg/day. No neoplastic lesions were reported in any of the long-term toxicity studies.

In contrast to the severe GI irritation induced by oral administration of difenzoquat (capsule or gavage), a 21-Day Dermal Toxicity Study revealed no signs of systemic toxicity after topical application of the test article up to the limit dose (1,000 mg/kg/day). In fact, dermal toxicity at the high dose level was limited to slight edema observed prior to the last application of the test compound. These data suggest that dermal absorption of difenzoquat is low; probably similar to the absorption through the GI tract (1-7%) reported in the metabolism study.

Reproductive and developmental parameters that may be affected by exposure to difenzoquat were studied in a Multigeneration Reproduction Toxicity Study, a Developmental Toxicity Study in Rabbits, and a Developmental toxicity Study in Rats. The Developmental Toxicity studies in Rats and Rabbits indicate that there is no enhanced susceptibility of the offspring after *in utero* exposure to difenzoquat. In the Developmental Toxicity Study in rats, maternal toxicity is observed at dose levels that do not elicit developmental effects. The developmental effects seen in the rabbit study (resorptions and skeletal effects) are reported at the same dose level causing mortality in maternal animals and are not considered to be elicited by a single dose. An acceptable Multigeneration Reproduction Toxicity Study is outstanding and must be submitted to permit full evaluation of the hazards associated with difenzoquat exposure, including the sensitivity of infants and children. Based on available data, however, there are no indications of either qualitative or quantitative increases in susceptibility of offspring or young animals to difenzoquat exposure.

The toxicology database for difenzoquat indicates that this chemical has no mutagenic, genotoxic, or carcinogenic activity. Although the difenzoquat database does not contain Acute or Subchronic Neurotoxicity Studies, these studies have been waived because the apparent signs of neurotoxicity in other existing studies are not indicative of a direct effect of difenzoquat on the nervous system but are secondary effects of the systemic toxicity resulting from the marked irritation to the GI tract.

The metabolism study demonstrates that difenzoquat is poorly absorbed through the GI tract since only 1-7% of the administered radioactivity is recovered in the urine. Most of the radioactivity is eliminated in the feces as the parent compound within 24 hours. Negligible amounts of the administered radioactivity were found in any tissue (≤0.01 ppm). These results are consistent with the metabolism of difenzoquat in hens and ruminants although small amounts of parent compound are transferred to liver and kidney.

Difenzoquat methyl sulfate has moderate acute toxicity, with toxicity categories of II for oral (LD_{50} = 485 mg/kg), III for dermal (LD_{50} = 3450 mg/kg), and II for inhalation (LC_{50} = 0.5 mg/L/hr). Difenzoquat induces slight primary eye irritation and is not a dermal sensitizer or a skin irritant.

3.2 FQPA Considerations

HED's FQPA Safety Factor Committee evaluated the sensitivity of infants and children at its1/14/02 meeting. The difenzoquat database has sufficient information available for the selection of endpoints for the purpose of conducting a risk assessment as part of a TRED. The database includes developmental toxicity studies in the rat and rabbit but it does not include an acceptable Multigeneration Reproduction Toxicity Study. The developmental toxicity studies in rats and rabbits do not show evidence of quantitative or qualitative susceptibility following *in utero* exposure. In the developmental toxicity study in rats, maternal toxicity (excessive salivation, decreased food consumption, and decreased body weight gain) was observed at dose levels that do not elicit developmental effects. In the case of the developmental toxicity study in rabbits, developmental effects (vertebral central abnormalities) are reported at the same dose level causing mortality in maternal animals; these effects are due to delayed ossification and are not considered to reflect exposure to a single dose. The multigeneration reproduction toxicity study is considered unacceptable and may not be used to assess susceptibility; although unacceptable, the lack of this study has already been considered and is reflected in a 3x database uncertainty factor applied to the cRfD.

The FQPA SFC concluded that the safety factor should be removed (1x) because:

1. There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* exposure;
2. Although the two-generation reproductive toxicity study in the rat is unacceptable, the lack of this study has been considered and reflected in the application of a 3x database uncertainty factor to the cRfD;
3. A developmental neurotoxicity study is **not** required;
4. The dietary (food and drinking water) assessments will not underestimate the potential exposures for infants and children.

3.3 Dose-Response Assessment

The toxicology database for difenzoquat has been evaluated by the HED in the Office of Pesticide Programs (OPP) in preparation for an FQPA update in compliance with FQPA of 1996 requirement for reassessment of chemicals registered after 1984. On January 8, 2002, HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database for difenzoquat methyl sulfate (Table 2) and established a cRfD for risk assessment (Table 3).

Toxicological endpoints were considered for all exposure scenarios. Acute dietary exposure to the

general population is not assessed since there was no appropriate endpoint attributable to a single-dose in the database. For this TRED for difenzoquat, only the chronic dietary exposure scenario will be assessed because there is no acute hazard and there are no registered uses for difenzoquat in the residential environment. Occupational exposures and risk will not be considered at this time as they were assessed at the time of the reregistration eligibility decision (RED). A characterization of the dose-response relationships for the chronic dietary endpoint follows presentation of Table 3.
(*Difenzoquat (Difenzoquat methyl sulfate) - Report of the Hazard Identification Assessment Review Committee*, HED Doc. No. 0050435, Elizabeth Mendez, January 31, 2002.)

Table 3. Summary of Toxicology Endpoint Selection.

Exposure Scenario	Dose (mg/kg/day)	Endpoint	Study
Acute Dietary	An acute reference dose (aRfD) was not established. The only acute effects noted in the database (suggestive of GI irritation) were considered to be an artifact of the method of administration of the test article (gavage)		
Chronic Dietary	NOAEL = 25 UF = 300* FQPA SF reduced to 1x	Decreased body weight and body weight gain.	Combined Chronic/Oncogenicity Study in Rats (supported by mouse carcinogenicity and dog chronic oral studies
		Chronic RfD = 0.083 mg/kg/day **Chronic RfD = Chronic PAD**	
Incidental Oral, Short-Term		No residential uses	
Incidental Oral, Intermediate-Term		No residential uses	
Dermal, Short-, Intermediate-, and Long-Term		No hazard was identified; therefore, no quantification is required. Systemic toxicity not seen at the limit dose in a Dermal Toxicity Study. Additionally, there are no developmental concerns.	
Inhalation, Short-, Intermediate-, and Long-Term	LOAEL = 44 MOE = 300**	Clinical signs (e.g. inactivity, closed eyes, unsteady gait)	Acute Inhalation Toxicity Study

* 10x intraspecies variation, 10x interspecies extrapolation, 3x for incomplete database (lack of an acceptable Multigeneration Reproduction Study).
** 10x intraspecies variation, 10x interspecies extrapolation, 3x for lack of a NOAEL.

3.3.1 Acute Reference Dose (aRfD)

An acute reference dose (aRfD) was not established. The only acute effect noted in the database was excessive salivation in the Developmental Toxicity Study in Rats which is indicative of localized irritation of the GI tract. Though GI tract irritation is an appropriate endpoint for risk assessment, in this instance, the effect is considered primarily due to the mode of administration (gavage). Since similar effects were not observed at comparable doses in studies in which the test article was incorporated into the food, the irritation observed is considered to be a result of the bolus administration of the test article. Finally, the developmental effects observed in the Developmental Toxicity Study in Rabbits (vertebral central abnormalities due to incomplete ossification) are not believed to be the outcome of a single exposure event.

3.3.2 Chronic Reference Dose (cRfD)

Selection of the Combined Chronic/Oncogenicity Study in Rats as the hazard component of risk assessment (NOAEL/LOAEL = 25/125 mg/kg/day; see cRfD calculation below) is supported by a Carcinogenicity Study in Mice and a Chronic Oral Toxicity Study in Dogs. The Oncogenicity Study in Mice has a NOAEL of 26.9 mg/kg/day and a LOAEL of 69.4 mg/kg/day based on statistically significant decreases in body weight and body weight gain (same effects as those seen in the rat study). The Chronic Oral Toxicity Study in Dogs has a NOAEL of 30 mg/kg/day and a LOAEL of 44 mg/kg/day based on mortality, clinical signs, decreased body weight gain, and necropsy findings (necrosis of the GI tract). The findings reported in the dog study are considered to be secondary to the degeneration of the GI tract. In addition to the 10x for intraspecies variation and 10x for interspecies extrapolation, a 3x uncertainty factor was applied to the NOAEL to account for an incomplete database (lack of an acceptable Multigeneration Reproduction Toxicity Study).

$$\textbf{cRfD} = \frac{\textbf{25 mg/kg/day}}{\textbf{300 (UF)}} = \textbf{0.083 mg/kg/day}$$

3.4 Endocrine Disruption

There is no evidence of endocrine disruption upon exposure to difenzoquat. EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active ingredients 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 were 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, difenzoquat 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 Use Patterns

Difenzoquat methyl sulfate is used largely for the selective control of wild oats in wheat and barley, its mode of action being rapid destruction of cell membranes. In addition, there are Special Local Needs [24(c)] labels granted for the states of Washington, Oregon, and Idaho. In these states, difenzoquat may be used for the control of wild oats in Kentucky bluegrass grown for seed production (i.e., not a turf use). There are no residential use scenarios for difenzoquat. The current U.S. tolerances for difenzoquat range from 20 ppm in wheat and barley straw to 0.05 ppm in fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep *(40 CFR §180.369)*. Adequate single analyte enforcement methods are available for the determination of difenzoquat residues in/on plant and livestock commodities. Difenzoquat is not expected to be recovered by any of FDA's multiresidue analytical enforcement methods.

Difenzoquat is marketed as the methyl sulfate salt and formulated as a 2 lb cation/gal soluble concentrate/liquid (SC/L; Avenge®; EPA Reg. No. 241-266) and a 92.5% water dispersible granule (WDG; EPA Reg. No. 241-354). These products are registered for a single postemergence application per growing season to barley and wheat at a maximum rate of 1 lb cation/A. Broadcast ground or aerial applications are permitted in water spray volumes of 5-20 gal/A and 3-10 gal/A, respectively. Application may be made to: (i) barley when plants are in the 2- to 7-leaf stage; (ii) fall-seeded wheat when plants are in the 4-leaf to tiller stage; and (iii) spring-seeded wheat when plants are in the 5- to 6-leaf stage. Application may be made alone or as a tank mix with other herbicides. No PHI has been established. Rotations to other crops may be made 1 year after treatment. Currently, labels prohibit grazing or cutting of forage for hay or silage; although this is not considered to be practical, this restriction should remain on labels while barley and wheat forage and hay residue trials are being conducted.

A profile of difenzoquat usage has been developed by the OPP Biological and Economic Analysis Division (BEAD; A. Halvorson, April 5, 2001). Based on data from 1995 through 2000, an annual estimate of difenzoquat methyl sulfate total domestic usage averaged 235,000 pounds of active ingredient for over one million acres treated. The largest market in terms of total pounds of active ingredient is allocated to wheat (65%) and barley (35%); use on bluegrass grown for seed is very low. Most of the usage is in Minnesota, Montana, North Dakota, and Washington. Weighted average percents of crop treated are 2% for both barley and wheat. As a Tier 1 assessment was conducted, this information was not used in the dietary exposure analysis.

There are no uses of difenzoquat methyl sulfate in a residential setting. The populations of concern for this assessment are those who may be exposed through consumption of crops treated with difenzoquat, secondary residues in livestock commodities, or water contaminated with difenzoquat.

4.2 Dietary (Food) Exposure/Risk Pathway

4.2.1 Residue Profile

The qualitative nature of the residue in plants and livestock is adequately understood. The qualitative nature of the residue in plants is based on acceptable cereal grain (barley and wheat) metabolism studies. These studies indicated that difenzoquat was absorbed from the foliage and translocated throughout the plant but was not extensively metabolized. The terminal residue of concern in plants is difenzoquat.

In livestock, the qualitative nature of the residue is based on acceptable poultry and ruminant metabolism studies. The residue of concern in both poultry and ruminants is difenzoquat per se. In the poultry metabolism study, laying hens were dosed with [^{14}C]difenzoquat at levels equivalent to 1, 10, and 12 ppm in the diet (20x, 200x, and 240x the estimated maximum theoretical dietary burden, respectively). Residues were nondetectable in eggs, muscle, and fat; difenzoquat was the only residue detected in liver and kidney accounting for >90% of the total radioactive residue in each tissue. In the ruminant metabolism study, goats were administered [^{14}C]difenzoquat at 23 and 98 ppm in the diet (38x and 160x the estimated maximum theoretical dietary burden, respectively). Residues were nondetectable in the milk, fat, and muscle of goats. Difenzoquat was the predominant residue in liver and kidney; the O-4-glucuronide of parent difenzoquat was present as a minor metabolite.

A Metabolism Assessment Review Committee (MARC) decision to delineate the residues of concern in plants and livestock was not required for several reasons. Plant and livestock metabolism studies show that difenzoquat is not extensively metabolized and no other significant metabolites have been identified. Additionally, EFED has stated that no degradates were identified in environmental fate studies. These results are consistent with other chemicals in the related classes of compounds known as the bipyridyliums (eg., paraquat) and the pyrazoles, of which difenzoquat is a member. Consequently, the difenzoquat TRED team concluded that the residue of concern in plants, livestock, and drinking water is the parent compound, difenzoquat.

Adequate residue analytical methods are available for purposes of reregistration. For tolerance enforcement, two GLC/FID methods (Methods I for plant and II for livestock commodities) are listed in the Pesticide Analytical Manual (PAM, Vol. II). For residue data collection, methods based on the enforcement methods with acceptable method validation data, were used for plant (Methods M-411 and M-1417) and livestock matrices (Methods M-457 and M-504). The registrant has submitted adequate validation data for analytical methods M-457 (ruminant) and M-504 (poultry), using liver and kidney samples from metabolism studies.

The requirements for data on the recovery of difenzoquat using FDA Multiresidue protocols have been satisfied and these data have been forwarded to FDA for review.

Adequate storage stability data on difenzoquat are available to support the storage conditions and intervals of samples from metabolism and magnitude of the residue studies in plants and livestock. Residues of difenzoquat *per se* are stable under frozen (-10 C) storage conditions for up to 24 months in/on wheat grain and wheat straw. No storage stability data are needed for livestock tissues since the samples were analyzed within one month of collection.

All data requirements for magnitude of difenzoquat residues in barley and wheat straw and grain have been evaluated and there is confidence in these data to support the reassessment of the established grain and straw tolerances (but not tolerances in livestock commodities). Acceptable field residue data from trials reflecting representative regions and the maximum registered use patterns are available for the grains and straw of barley and wheat. However, the registered uses of difenzoquat on barley and wheat also must be supported by acceptable field residue data on barley hay and wheat forage and hay; the data on these major feed items will permit a more refined reassessment of the livestock commodity tolerances.

Data from 177 samples from field trials conducted in CA (31), CO(36), MN(32), MT(21), ND(43), OR(4), SD(6) and WY(4) pertaining to residues of difenzoquat in or on barley grain and straw following treatment with the 2 lb/gal SC/L formulation have been submitted. The trials most closely representing the maximum exposure potential under registered use directions included 11 straw samples from CO, MN and ND harvested 51-90 days following 1X aerial applications in 2-5 gal water/A, and 13 samples from CO, MN, MT, ND and SD harvested 47-75 days following 1X ground applications in 5-8 gal water/A. No detectable residues were found in or on barley grain (<0.05 ppm) and were <0.1 ppm (ND) - 4.0 ppm in or on barley straw. The data were analyzed using GLC/FID method M-411 and were geographically representative. The data indicate that the current tolerances for barley grain and straw should be lowered to 0.05 ppm and 5.0 ppm, respectively.

Seven wheat grain samples from seven trials conducted in MN (4), and MT(3) harvested 75-83 days following aerial application of 1 lb ai/A in 3-5 gals of water /A; and 24 samples from 24 tests conducted in ID(7), MT(6), MN(3), ND(3), OK(1) and TX(4) harvested 60-83 days following ground application at 1-2x rates in 5-20 gals of water/A bore no detectable residues (<0.05 ppm) of difenzoquat in wheat grain. The data support the current tolerance in wheat grain of 0.05 ppm.

Residue data submitted for wheat straw showed difenzoquat residues of <0.10 (ND) - 4.2 ppm in or on wheat straw samples harvested 60-83 days following a 1-2X aerial or ground application. The field trials were conducted in ID, MN, MT, ND, OK, TX, KS, OR, SD and WA. The data indicate that the current tolerance for wheat straw should be lowered to 5.0 ppm.

The label restriction against the grazing of livestock on treated fields and the cutting of treated forage for silage/hay is not considered to be practical. **Field trial data must be submitted for wheat and barley hay and wheat forage.** These data should reflect the maximum application rate. A PHI should be proposed and reflected in the submitted data unless justification for the adequacy of a crop growth stage for application timing is provided. Tolerances for residues in/on hay and forage must also be proposed.

The submitted data for magnitude of the residue in processed food/feed have been evaluated and

deemed adequate. Acceptable wheat grain processing and aspirated grain fraction data have been submitted; the wheat processing data will be translated to barley. The wheat grain processing data indicated that residues of difenzoquat concentrated 4x and 4.6x in wheat bran and shorts, respectively, and minimal concentration occurred in middlings. Residues did not concentrate in flour. HED recommends for the establishment of a tolerance in wheat bran at 0.25 ppm; in wheat shorts at 0.25 ppm; and in barley bran at 0.25 ppm.

Acceptable livestock feeding studies have been conducted. The cattle feeding study showed no detectable residues of difenzoquat in the muscle, fat, and kidney of beef cattle fed up to 10 ppm. The poultry feeding study showed no detectable residues of difenzoquat in the eggs, muscle, liver, kidney, fat, and skin of laying hens administered up to 0.5 ppm. Finite residues were detected only in the cattle liver; this observation is consistent with the ruminant metabolism study where finite residues were detected only in the liver and kidney of animals dosed at 170x the estimated dietary burden. Currently, no tolerances are needed for residues of difenzoquat in milk and eggs; the presently registered uses of difenzoquat are classified as Category 3 of 40 CFR §180.6(a) with respect to the need for tolerances in milk and eggs i.e., there is no reasonable expectation of finite residues.

The results of these livestock feeding studies ***suggest*** that the established tolerances of 0.05 ppm (based on the limit of detection of the analytical method) for difenzoquat residues in the fat, meat, and meat byproducts of cattle, goats, hogs, horses, sheep, and poultry are adequate. However, actual reassessment of livestock commodity tolerances will be made when the requested residue data for all major livestock feed items have been submitted and following recalculation of maximum dietary burdens. Dietary burden calculations used in the dietary exposure assessment are tentative because data remain outstanding for barley hay and wheat hay and forage which are major ruminant feed items. The need for tolerances in milk as well as the magnitude of the fat, meat, and meat byproduct tolerances will be reassessed upon submission of barley and wheat forage and hay data.

Even in the absence of the forage and hay residue data, the current dietary risk assessment is considered to be very conservative for the following reasons: (i) residues in livestock commodities were nonquantifiable (<0.05 ppm) except for trace amounts in liver and kidney; (ii) feeding studies were conducted at exaggerated feeding levels; (iii) forages and hay of barley and wheat will be fed to beef and dairy cattle at no more than 2.5x or 6x higher percentages of their respective diets than straw; (iv) 100% of crop treated was assumed whereas only 1% of barley and 2% of wheat are actually treated; and (v) tolerance-level livestock commodity residues reflecting tolerance-level feed item residues were used in the dietary risk assessment as opposed to any additional refinements to both the feed residues and the secondary livestock commodity residues. Therefore, dietary exposure is not expected to be underestimated.

No maximum residue limits (MRLs) for difenzoquat have been established by Codex for any agricultural commodity. Canadian labeled uses (presumably meaning that MRLs have been established for difenzoquat per se at the default level of 0.1 ppm) exist for wheat, barley, triticale, canary grass, (underseeded) forage, flax, and pasture and rangeland. Mexican MRLs have been established for residues of difenzoquat per se in wheat at 0.05 ppm and barley at 0.2 ppm. No compatibility questions exist with respect to U.S. tolerances vs. Codex MRLs. Although there is no

apparent compatibility between U.S. tolerances and Canadian and Mexican MRLs in terms of residue definition (difenzoquat per se), there are several numerical differences. These differences are not expected to result in significant trade issues.

4.2.2 Acute Dietary

An appropriate hazard endpoint attributable to a single oral dose was not identified; therefore, an aRfD was not established and an acute dietary exposure and risk assessment is not appropriate.

4.2.3 Chronic Dietary

A difenzoquat chronic dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.73, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by 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 therefore 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 U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the chronic Population Adjusted Dose (cPAD) which is the cRfD taking into account the FQPA safety factor. This procedure is performed for each population subgroup.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups from the general U.S. population which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

HED's level of concern is 100% of the cPAD. That is, estimated exposures above this level are of concern, while estimated exposures at or below this level are not of concern. The DEEM analyses estimate the dietary exposure of the U.S. population and 26 population subgroups.

A Tier 1 chronic dietary risk assessment was conducted for all supported difenzoquat food uses. Dietary risk estimates were calculated for the general U.S. population and various population

subgroups. Tolerance-level exposure values and 100% of crops treated were assumed. The calculated chronic exposure (residue x consumption) was compared to a cPAD of 0.083 mg/kg-bw/day, which reflects a 300x uncertainty factor and removal of the FQPA safety factor (1x). This procedure is performed for each population subgroup. This highly conservative assessment demonstrates that, for all supported registered commodities, the **chronic risk estimates are below the Agency's level of concern** (<100% cPAD) for the general U.S. population and **all** population subgroups (<1% of the cPAD). The Agency is confident that the exposures and risks anticipated through registered use of difenzoquat are not underestimated. The required barley and wheat forage and hay data, upon receipt, are not expected to significantly increase chronic dietary risk. *(Difenzoquat Chronic Dietary Exposure Assessment for the Tolerance Reassessment Eligibility Decision (TRED); P.C. Code 106401; DP Barcode D280316; Case 0223; Felecia Fort; January 22, 2002.)*

4.3 Water Exposure/Risk Pathway

The environmental fate database is sufficiently complete to characterize drinking water exposure. Model simulations demonstrate that difenzoquat may reach surface drinking water supplies but should not reach ground water in considerable amounts due to its immobility in soil. No degradates were identified in environmental fate studies. No monitoring data are available.

Physical properties of difenzoquat include vapor pressure of $<9.06 \times 10^{-8}$ mm Hg at 35 °C and solubility of 765,000 ppm in water at 23 °C. The assessment of the environmental fate of difenzoquat indicates that soil binding appears to be the principal route of dissipation. The assessment is supported by laboratory data demonstrating a high degree of adsorption to soil but no degradation of the parent material. Difenzoquat is persistent (the chemical did not degrade in any of the laboratory studies performed: hydrolyis, aqueous and soil photolysis, and aerobic and anaerobic metabolism). This chemical is relatively immobile (K_ds ranged from 124 to 685, K_{oc}s ranged from 23,071 to 36,231).

Field dissipation studies contrasted somewhat with the laboratory data and indicate that difenzoquat residues decline with time in certain locations. Field data confirm the immobility of the parent material while several of the field studies suggest a faster dissipation rate for the parent. Based on the field data it appears that the potential for difenzoquat to leach to ground water is low. However, it also appears that in certain geographic settings difenzoquat may dissipate at a faster rate than that observed in the laboratory.

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for difenzoquat and its degradates. Therefore, the Agency is presently relying on the computer-generated estimated environmental concentrations (EECs) described below. These models take into account the use patterns and the environmental fate profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal or transformation of pesticides from the source water.

For any given pesticide, the SCI-GROW model generates a single EEC value of pesticide

concentration in *ground* water. That EEC is used in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs. PRZM/EXAMS provides surface water annual daily maximum, an annual mean, as well as a 36-year overall mean value of pesticide concentration in surface water and is used when a refined surface water EEC is needed.

There are a number of inherent limitations with the water model used to estimate concentrations on difenzoquat in surface water. Because the index reservoir represents a fairly vulnerable watershed, the estimated exposure may not reflect actual exposure for most drinking water sources. A single steady flow has been used to represent the flow through the reservoir and this assumption can underestimate or overestimate the concentration in the pond depending upon the annual precipitation pattern at the site. In addition, soils can vary substantially across even small areas, affecting residue concentrations in water, and this variation is not reflected in these simulations. Tile drainage (use of buried tiles or pipes to direct water drainage flow or direction) is not specifically considered in the index-reservoir of PRZM-EXAMS. Tile drainage may cause either an increase or decrease in the pesticide concentration in the reservoir. Turnover occurs when the temperature drops in the fall and the thermal stratification of the reservoir is removed and EXAMS is unable to easily model spring and fall turnover. EFED assumes that the field scale processes simulated by the coupled PRZM and EXAMS models are a reasonable approximation of pesticide fate and transport within a watershed that contains a drinking water reservoir. However, available monitoring data suggest uneven model results. In addition, the use of input parameter values for the parent when assessing the difenzoquat degradates increases the uncertainties in the assessment. All these limitations should be noted when evaluating exposure to difenzoquat through surface water.

Tier II (PRZM version 3.12/EXAMS version 2.97.5) surface water modeling for difenzoquat using the index reservoir and Percent Crop Area adjustment (IR-PCA) was conducted using the North Dakota/ spring wheat scenario. This scenario was chosen by making the best fit between BEAD's usage information and a number of standard crop/region combinations that are representative sites vulnerable to runoff. The North Dakota/spring wheat combination is one of EFED's standard scenarios used in the PRZM/EXAMS model and is quite appropriate to represent the registered uses of difenzoquat. This modeling predicts the 1 in 10 year annual maximum (acute) concentration [also known as an EEC (see above)] of 27.4 µg/L. The 1 in 10 year annual average concentration (non-cancer chronic) of difenzoquat is predicted to be **12.3 µg/L in surface water reflecting a percent cropped area of 56%**. The 36-year annual average concentration (cancer/chronic) of difenzoquat is predicted to be 7.9 µg/L. SCI-GROW (version 2.1) modeling estimates that the acute and chronic concentration of difenzoquat residues **in shallow groundwater is 0.006 µg/L**. Analysis of model outputs suggest that the exposure estimate is predominantly due to runoff and that spray drift (< 3% of total concentration) is not a major contributing factor. The long half-life (>365 days) and high adsorption potential of difenzoquat suggests that difenzoquat will remain available in surface soils for runoff. No degradates to be modeled were identified in the environmental fate studies. The groundwater EEC and the 1 in 10 year annual average EEC listed above will be compared to the Drinking Water Levels of Comparison (DWLOCs) calculated for various population subgroups.

Based on the use patterns, the exposure is expected to be more regional than national. Based on

available pesticide usage information for 1995 through 2000, total annual domestic usage of difenzoquat is approximately 235,000 pounds active ingredient (a.i.). Major use states include Minnesota, Montana, North Dakota and Washington. *[TRED for Difenzoquat (Chemical # 106401, DP Barcode D220028, D278716), Mark Corbin, Environmental Fate and Effects Division, October 29, 2001]*

4.4 Residential Exposure/Risk Pathway

There are currently no registered uses of difenzoquat methyl sulfate in the residential environment. Therefore, there is no expected exposure of homeowners to difenzoquat and aggregation with dietary sources of exposure is not appropriate or necessary. Note, however, that the Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, consisting of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with the application of difenzoquat by aerial as well as other application types where appropriate.

5.0 Aggregate Risk Assessment and Risk Characterization

FQPA amendments to the Federal Food, Drug and Cosmetic Act require for establishing or reassessing a pesticide tolerance "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposure for which there is reliable information." The January 8th, 2002 HIARC meeting resulted in selection of effects/doses (hazard endpoints) to assess risks associated only with chronic dietary exposure and inhalation exposure (all durations). Adverse effects were not associated with dietary exposure to a single dose. Residential exposure is not expected to result from currently registered uses and is not expected in the future. As a TRED, this human health risk assessment will not address occupational exposure and risk. **As a result, only chronic exposure and risk associated with the food and water pathways will be assessed and aggregated in this document.** If new uses are added to the label in the future that include possible exposure to persons in the residential environment, EPA will conduct this analysis. The toxicological endpoints appropriate for the dietary (oral) route of exposure are, therefore, the only hazard endpoints considered in this analysis.

Chronic aggregate risk is comprised of the combined exposures to difenzoquat from food and water sources. Risk estimates are aggregated because it is assumed exposure may occur over the same time period. The chronic dietary aggregate assessment will utilize an endpoint based on a combined chronic/oncogenicity study in rats in which decreased body weight and body weight gain due to GI tract irritation resulted at the LOAEL of 125 mg/kg/day; the NOAEL used for the hazard component of

risk was 25 mg/kg/day. The cRfD was calculated to be 0.083 mg/kg/day by dividing the NOAEL by the total of three factors: 300x reflecting 10x for intraspecies variation, 10x for interspecies extrapolation, and 3x for an incomplete database (lack of an acceptable Multigeneration Reproduction Study). As the FQPA safety factor was reduced to 1x, the cPAD is identical to the cRfD, i.e., 0.083 mg/kg/day.

DWLOCs are used to estimate aggregate risk from drinking water sources. DWLOCs are theoretical upper limits of a pesticide's concentration in drinking water as a component of the total aggregate exposure to a pesticide in food and drinking water. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, and body weight. HED uses DWLOC's internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of reliable monitoring data for pesticides, which can be used directly and quantitatively in the risk assessment, a DWLOC is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not a regulatory standard for drinking water. However, they do have an indirect regulatory impact through aggregate exposure and risk assessments.

HED calculates DWLOCs by a two-step process: dietary exposure is subtracted from the PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When EECs are less than DWLOCs, HED considers the aggregate risk [from food + water exposures] not to be of concern.

5.1 Chronic Risk

5.1.1 Chronic Aggregate Risk Assessment

Chronic risk estimates from exposure to food associated with the use of difenzoquat methyl sulfate **do not exceed** the Agency's level of concern for any population subgroup including the most highly exposed population subgroup, children 1-6 years of age. The chronic dietary (food only) risk estimate for all population subgroups was **<1% of the cPAD**. These estimates of food exposure are considered to be very conservative since tolerance-level exposure values, 100% of crop treated figures, and worst-case livestock diets were assumed. Anticipated residue estimates were not generated although processing factors were used for processed food forms of barley and wheat.

Table 4. Chronic DWLOC Calculations.

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Max. Chronic Water Exp. (mg/kg/day)[2]	Ground Water EEC (ug/L)	Surface Water EEC (ug/L)[3]	Chronic DWLOC (ug/L)[4]
U.S. Population (total)	0.083	0.000185	0.079815	0.006	12.3	2800
All Infants (< 1 year)	0.083	0.000073	0.079927	0.006	12.3	800

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Max. Chronic Water Exp. (mg/kg/day)[2]	Ground Water EEC (ug/L)	Surface Water EEC (ug/L)[3]	Chronic DWLOC (ug/L)[4]
Children 1-6 years[1]	0.083	0.000370	0.07963	0.006	12.3	800
Children 7-12 years	0.083	0.000267	0.079733	0.006	12.3	800
Females 13-50	0.083	0.000146	0.079854	0.006	12.3	2400
Males 13-19	0.083	0.000198	0.079802	0.006	12.3	2800
Males 20+ years	0.083	0.000168	0.079832	0.006	12.3	2800
Seniors 55+	0.083	0.000135	0.079865	0.006	12.3	2800

[1]Children 1-6 are the most highly exposed sub-group.

[2]Maximum Chronic Water Exposure (mg/kg/day) = [Chronic PAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]

[3]The use of difenzoquat on spring wheat in North Dakota was modeled to determine this 1 in 10 year average surface water EEC.

[4]Chronic DWLOC(μg/L) = [maximum chronic water exposure (mg/kg/day) x body weight (kg)] / [water consumption (L) x 10^{-3} mg/μg]

Assumptions: Body weights (70 kg adult male; 60 kg adult female; 10 kg child); water consumption 2 liters/day adult and 1 liter/day infants and children.

As described above, EFED provided a groundwater EEC of 0.006 ppm and a 1 in 10 year (chronic noncancer) EEC of 12.3 ppb. The DWLOC's calculated for chronic aggregate risk range from 800 μg/L for infants and children to 2800 μg/L for the general population (Table 4). The chronic aggregate risk calculations indicate that the expected EEC of difenzoquat in surface drinking water is much less than the allowable levels of difenzoquat in drinking water based upon the DWLOC value for any of the population subgroups. Therefore, residues of difenzoquat in drinking water are not expected to represent a chronic human health risk and the chronic aggregate exposure from residues of difenzoquat in food and drinking water are expected to be far less than the Agency's level of concern for chronic aggregate exposure of any U.S. population subgroup.

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 on human health that may result from dietary, residential, or other nonoccupational 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 the TRED for difenzoquat because HED has not yet initiated a comprehensive review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of difenzoquat. For purposes of this TRED, EPA has assumed that difenzoquat 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 difenzoquat shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for difenzoquat need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with difenzoquat, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has developed a framework for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at:

http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf.

In the 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.

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 Incident Data

Relatively few incidents of illness have been reported due to difenzoquat. Only one report in the Incident Data System involved difenzoquat in an incident with a minor outcome. This report was part of an aggregate report that provided no details on the circumstances of exposure or the reported health effects.

Only three cases were reported in the Poison Control Center Data (1993 through 1998) involving difenzoquat. All three occurred among children under 6 years of age. Only one case was reported to have a minor medical outcome. The other two cases had unknown outcomes; although no symptoms were reported, these were not expected to have anything more serious than a minor outcome based on the reported exposure.

No cases were reported from the California Pesticide Illness Surveillance Program (1982 through 1998).

Difenzoquat was not listed on the list of the top 200 chemicals for which National Pesticide Telecommunications Network (NPTN) received calls from 1984-1991, inclusively.

No recommendations can be made based on the few incident reports available.

8.0 Data Needs

The database for difenzoquat is considered adequate for risk assessment necessary for the conduct of this TRED. However, data deficiencies have been identified. Studies required by the Agency include:

Product Chemistry

1. UV/visible absorption (830.7050)

Toxicology

2. Multigeneration reproduction toxicity study (870.3800)

Residue Chemistry

3. Wheat and barley hay and wheat forage field trial residue studies (860.1500), the concomitant proposal of tolerances in these commodities, and the eventual deletion of the forage/hay grazing/cutting restriction upon submission of the field trials. Several tolerance revisions are necessary based on the reassessment made in this TRED.

REFERENCES:

Difenzoquat (106401) List A Reregistration Case No. 0223: Update to the Product and Residue Chemistry Chapters For The Reregistration Eligibility Document (RED); 1/24/02; DP Barcode D280280.

Difenzoquat (Difenzoquat methyl sulfate) - Report of the Hazard Identification Assessment Review Committee. (HED Doc. No. 0050435) Elizabeth Mendez. 1/31/02.

Difenzoquat - Toxicology Evaluation. Elizabeth Mendez. DP Barcode D280279. 1/15/02.

Difenzoquat Chronic Dietary Exposure Assessment for the Tolerance Reassessment Eligibility Decision (TRED); PC code 106401; DP Barcode D280316; Case 0223; Felecia Fort. 1/22/02.

TRED for Difenzoquat (Chemical # 106401, DP Barcode D220028, D278716). [Drinking Water Assessment for Difenzoquat. Mark Corbin. 10/29/01.

Quantitative Usage Analysis for Difenzoquat. Alan Halvorson. 4/5/01

Difenzoquat - Report of the FQPA Safety Factor Committee. (HED Doc. No. 0050453) Carol Christensen. 2/5/02

Review of Difenzoquat Incident Reports. Jerome Blondell. 2/7/02. DP Barcode D280829, Chemical #106401.

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Chemical:	**Difenzoquat methyl sulfate**
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