UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: September 14, 2009

MEMORANDUM

SUBJECT: Dithianon. Human Health Risk Assessment for Proposed Tolerance on Imported Grapes.

PC Code: 099201
Decision No.: 370013
Petition No.: 6E7103
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: 368428
Registration No.: NA
Regulatory Action: New Tolerance
Case No.: NA
CAS No.: 3347-22-6
40 CFR: 180.621

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1.0 Executive Summary

BASF Corp. has proposed, in PP#6E4781, the establishment of tolerances for residues of the fungicide dithianon [5,10-dihydro-5,10-dioxonaphtho(2,3-*b*)-1,4-dithiin-2,3-dicarbonitrile] in/on grapes at a level of 3 ppm. There are no proposed or existing uses of dithianon in the US, so the proposed tolerances would apply only to imported grapes. Tolerances for imported pome fruit and hops were established in September 2006 (71 FR 54917, September 20, 2006).

BASF previously submitted a petition (PP#6E7103) requesting an 8.0 ppm tolerance on grapes imported into the U.S. from countries having registered uses for dithianon on grapes. In its review of this petition (DP# 333117, D. Davis, 4/15/2008), the Agency concluded that the residue chemistry database was insufficient to support establishing a tolerance for dithianon on imported grapes. In response to the Agency's review, BASF has submitted a revised petition addressing the deficiencies cited by the Agency, along with submissions containing the relevant data.

Dithianon is a broad spectrum multi-site protectant fungicide used outside the U.S. for control of apple and pear scab, black rot, rust, and leaf spot diseases in pome fruit, Peronospora in hops, and downy mildew and anthracnose in grapes. There are no U.S. registrations or proposed registrations of dithianon in the U.S. at this time.

The registrant provided translated labels for the foliar use of dithianon on grapes in Australia, Spain, France, Germany, Italy, Argentina, and Brazil. A Codex Maximum Residue Limit (MRL) has been established for grapes at 3 mg/kg. The proposed tolerance (without U.S. registration) on imported grapes is harmonized with the established Codex MRLs with respect to the residue definition and the proposed level. There are currently no established Canadian or Mexican MRLs for dithianon.

The most recent risk assessment was conducted in support of the tolerances on pome fruit and hops (D. McNeilly, 7/11/06, DP No. 235354).

Hazard Identification and Dose Response Assessment
The toxicology database is sufficient to characterize the hazards associated with dithianon, with the exception of the developmental toxicity study in rabbits, which was classified unacceptable. To account for this database gap, a 10X Food Quality Protection Act (FQPA) database uncertainty factor (UF_{DB}) was retained. Due to the recent modification to the 40 CFR Part 158 Test Guidelines, there are additional datagaps: acute and subchronic neurotoxicity studies and an immunotoxicity study.

The acute toxicity is mild via the oral route (Category III). The toxicologically significant adverse effects of dithianon are similar across species. In studies with shorter durations of exposure, including the subchronic dog and rat studies, the developmental toxicity study in rats, and the two-generation reproduction rat study, decreases in body weight, body weight gain, and/or food consumption were noted in adults. However, with continued exposure, as in the chronic and/or carcinogenicity studies in the rat, mouse, and dog, the kidney is the target organ for toxicity. Signs of renal toxicity include increased absolute and/or relative kidney weights in

the rat, mouse, and dog; non-neoplastic kidney lesions in mice and rats; and renal adenomas and carcinomas in female rats. Post-implantation loss due to early resorptions was observed in the developmental rat study

The available toxicology database does not show any indication of increased qualitative or quantitative susceptibility of the offspring. Dithianon did not cause reproductive or developmental toxicity in the two-generation reproduction study. In the developmental rat study, decreased fetal weights were observed only at a dose higher than that which produced similar maternal effects. The developmental toxicity study in rabbits was classified unacceptable/guideline. However, residual uncertainty due to this data gap is addressed through retention of the 10X FQPA Safety Factor as a database uncertainty factor (UF_{DB}).

Dithianon is not mutagenic. The Cancer Assessment Review Committee (CARC) classified dithianon as "Suggestive Evidence of Carcinogenic Potential", based on the overall weight of the evidence. Quantitation of carcinogenic risk is not required.

Dietary endpoints only are required to support this tolerance assessment. The acute dietary endpoint for women ages 13-49 is based on post-implantation loss due to early resorptions seen in the developmental rat study. No endpoint attributed to a single dose was identified for the general population, so a quantitative risk assessment is not required. The chronic dietary endpoint is based on kidney effects and decreased body weight. A combined uncertainty factor (UF) of 1000, including 10X factors for interspecies variability, intraspecies variability and database uncertainty, was used for all endpoints. The acute population adjusted dose (aPAD) for women ages 13-49 is 0.02 mg/kg/day. The chronic population adjusted dose (cPAD) is 0.006 mg/kg/day.

Dietary Exposure/Risk Assessment
The residue of concern (ROC) in plants and animals is dithianon *per se*. There is no reasonable expectation of finite residues in animal commodities.

Acute and chronic dietary assessments were conducted using Dietary Exposure Evaluation Model – Food Commodity Intake Database (DEEM-FCID^{TM}, version 2.03). Both the acute and chronic dietary assessments are based on empirical processing factors for raisins and grape, apple and pear juices and 100 percent crop treated. The acute assessment is based on tolerance level residues while the chronic analysis is based on anticipated (average) residues from field trial data. With no proposed U.S. registration, there is no expectation that dithianon residues would occur in surface or ground water sources of drinking water. The acute exposure for Females ages 13-49 is at 79% of the acute Population Adjusted Dose (aPAD) at the 95th percentile of exposure, which is below the level of concern. The chronic exposures for all populations assessed are below the level of concern. The chronic exposure for the general U.S. population is at 18% of the cPAD. The most highly exposed sub-group is children (ages 1-2), whose exposure is at 63% of the cPAD. The exposure estimates represent a highly conservative estimate of risk because of the assumption that everything consumed in the U.S. has been treated with dithianon, and the assumption of tolerance-level residues in the acute assessment. Actual exposure is likely to be much lower.

Dithianon is not registered for use in the U.S., so quantitative risk assessments for residential, and occupational exposures were not conducted.

Regulatory Recommendations
The following toxicity data are outstanding: 1) developmental toxicity study in rabbits; 2) acute neurotoxicity study; 3) subchronic neurotoxicity study; 4) immunotoxicity study. Despite these datagaps, HED has sufficient information to characterize dithianon toxicity and select endpoints for risk assessment. Sufficient residue data are available to support the dietary exposure assessment and tolerance assessment. Acute and chronic dietary exposures are below the level of concern. Therefore, HED has no objection to establishing a tolerance for residues of grapes at 3 ppm. This tolerance is harmonized with Codex and the European Union with respect to definition and level.

The Health Effects Division (HED) has recently updated its guidance on the language used in tolerance expressions. The tolerance expression should be modified to the following

> Tolerances are established for residues of dithianon, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only dithianon (5,10-dihydro-5,10-dioxonaphtho(2,3-*b*)-1,4-dithiin-2,3-dicarbonitrile).

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/resources/policies/ej/exec_order_12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

2.0 Ingredient Profile

Dithianon is a broad spectrum multi-site protectant fungicide (with spore inhibitory properties) that is used outside the U.S. for the control of scab, downy mildew, rust, and leaf spot diseases in pome fruit, stone fruit, small fruit, wine grapes, ornamentals, citrus, coffee, and vegetables. It is used in Germany for the control of downy mildew in hops.

2.1 Summary of Registered/Proposed Uses

BASF reported that the following countries currently have registrations for use of dithianon on grapes:

Argentina	Australia	Austria	Belrus	Brazil
Bulgaria	Croatia	France	Georgia	Germany
Hungary	Italy	Japan	Kyrgystan	Luxembourg
Moldova	New Zealand	Romania	Serbia	Slovenia
Slovakia	Switzerland	Thailand	Turkey	Ukraine Uruguay

Of these countries, only Argentina, Australia, Italy, France and Germany are significant exporters of grape commodities to the U.S. Dithianon is not registered in the following countries that are major exporters of grape products to the U.S.: Chile, Mexico, Spain, and South Africa. These countries account for 43% of all imported grape products.

The petitioner submitted copies of labels for dithianon products from the seven countries that are major exporters of grape products to the U.S., along with English translation. In the current petition, the dithianon label from Spain was omitted as there is not a registered use for dithianon in Spain, and the label directions for Australia and New Zealand were included as they are both major exporters of wine to the U.S. A summary of the use directions on grapes from the submitted labels is presented in Table 2.1.

Table 2.1 Summary of Directions for Use of Dithianon on Grapes.

Trade Name; Formulation	Application Type/Timing	Application Rate		Max. No. Applic. Per Season	RTI [1] (days)	Max. Seasonal Applic. Rate (g ai/ha)	PHI (days)	Use Directions Limitations
		g ai/hL	g ai/ha [2]					
Argentina								
DELAN 75; 750 g/L SC	Broadcast foliar applications beginning when vine shoots are 10 cm in length and if climatic conditions favor disease development	49	Not specified (NS)	NS	NS	NS	21	

Table 2.1 Summary of Directions for Use of Dithianon on Grapes.								
Trade Name; Formulation	**Application Type/Timing**	**Application Rate**		**Max. No. Applic. Per Season**	**RTI [1] (days)**	**Max. Seasonal Applic. Rate (g ai/ha)**	**PHI (days)**	**Use Directions Limitations**
		g ai/hL	**g ai/ha [2]**					
Australia								
Delan 700 WG; 70% WDG	Broadcast foliar applications beginning at bud bust through early fruit development	35-52.5	early – 175 late - 525	NS	10-21	NS	21	Apply in a minimum of 500 L/ha early in season and in 1000 L/ha thereafter.
Brazil								
DELAN; 75% WP	Broadcast foliar applications beginning at start of leaf growth and when condition favor disease development	93.75	937.5	NS	NS	NS	28	Apply in a volume of at least 1,000 L/ha.
France								
DELAN WG; 70% WDG	Broadcast foliar applications at leaf emergence and when first leaves open	49	490	2 [3]	NS	980 [3]	14	
Germany								
DELAN WG; 70% WDG	Broadcast foliar applications in early spring after unfolding of the 2nd to 3rd leaf through early berry development (BBCH 75).	35-52.5	early - 210 late – 560	8	NS	NS	49	Apply in a minimum of 400 l/ha, or at 800-1600 l/ha from BBCH 61-75. In areas with steep slopes, apply at 2000 l/ha.
Italy								
DELAN 70 WG; 70% WDG	Broadcast foliar applications depending on weather conditions and disease virulence;	70-84	NS	NS	7-10	NS	40	Apply using only ground equipment
New Zealand								
DELAN WG; 70% WDG	Broadcast foliar applications beginning at bud swell and during conditions favorable to disease development	38.5	early – 252 late - 501	NS	10-14	NS	21	

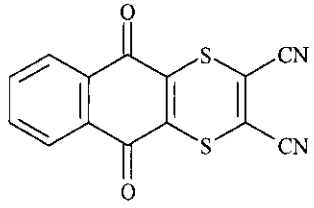
[1] RTI = Retreatment interval.

[2] Several labels from several countries (Australia, Germany and New Zealand) noted that higher rates are used for applications later in the season.

[3] Although the label directions for France do not explicitly state that two applications are allowed per season, the allowed application timings imply that two applications can be may per season.

Although the use directions from each of the above countries specify application rates of dithianon in terms of g ai/hL, the maximum use rates in terms of g ai/ha can only be determined on five of the labels based on the recommended application volumes. None of the labels explicitly state the maximum seasonal use rate (g ai/ha/season) and only the label from Germany specifies a maximum number of applications per season. BASF noted that not all countries require this information to be specified on the label. However, sufficient residue data reflecting a variety of application scenarios have been submitted.

2.2 Structure and Nomenclature

Table 2.2. Dithianon Nomenclature.	
Chemical structure	
Common name	Dithianon
Empirical formula	$C_{14}H_4N_2O_2S_2$
Company experimental names	BAS 216 F; CL37114
IUPAC name	5,10-dihydro-5,10-dioxonaphtho(2,3-*b*)-1,4-dithi-in-2,3-dicarbonitrile
CAS name	5,10-dihydro-5,10-dioxonaphtho(2,3-*b*)-1,4-dithiin-2,3-dicarbonitrile
CAS registry number	3347-22-6
Chemical class	Quinone fungicide
Known impurities of concern	None
End-use products (EPs)	There are no products currently registered in the U.S.; the products identified in the petition were DELAN 75 (750 g/L FlC formulation), DELAN 70 WG (70% WDG formulation), DELAN WG (70% WDG formulation), and DELAN (75% WP formulation).

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Dithianon.			
Parameter	Value		Reference[1]
Melting point/range (°C)	216		MRID #44092604
pH (20 °C)	4.4 to 4.8 (1% wt/wt aqueous dispersion)		MRID #44092604
Density (g/cm^3 at 20 °C)	1.58		MRID #44092604
Water solubility (20 °C)	Nearly insoluble (roughly 0.02 mg/100 mL)		MRID #44092604
Solvent solubility (at 20 °C)	Acetone Dichloromethane Ethyl acetate n-Hexane Methanol Toluene	1.76 g/100 mL 2.01 g/100 mL 0.77 g/100 mL 0.96 mg/100 mL 0.08 g/100 mL 1.59 g/100 mL	MRID #44092604
Vapor pressure (Pa at 25 °C)	2.71×10^{-9}		MRID #44092604
Dissociation constant (pK_a)	Not available (insufficient solubility in water).		MRID #44092604
Octanol/water partition coefficient (log [K_{OW}])	3.2 ± 0.3		MRID #44092604
UV/visible absorption spectrum	Not provided		

[1] See DP# 312241, 7/11/06, W. Drew.

3.0 Hazard Characterization/Assessment

3.1 Hazard Characterization

3.1.1 Sufficiency of studies/data

Only oral toxicity studies are required to support the proposed and existing tolerances on imported commodities, as there are no registrations for the use of dithianon in the U.S., and none are proposed. No new toxicity studies have been submitted since the most recent risk assessment for dithianon (D. McNeilly, 7/11/06, DP No. 235354). The following studies are available to assess toxicity:

- Acute Oral Toxicity
- Subchronic studies in the rat and dog
- Chronic study in the dog
- Chronic/Carcinogenicity studies in the rat and mouse
- Developmental study in the rat
- Reproduction study in the rat

A developmental toxicity in the rabbits was submitted but is unacceptable due to excessive maternal toxicity that resulted in an insufficient number of litters to meet guideline requirements. Therefore, the Agency will retain the 10X FQPA Safety Factor as a database uncertainty factor (UF_{DB}) to account for this deficiency. The Agency has recently modified the test guidelines required to support tolerances (40 CFR Part 158), so additional studies are required to support tolerances, including an acute neurotoxicity study, a subchronic neurotoxicity study, and an immunotoxicity study. Despite these datagaps, the Agency has sufficient information at this time to select endpoints for the proposed import tolerances.

3.1.2 Metabolism and Toxicokinetic data

Rat metabolism studies were conducted reflecting a single dose as well as multiple doses of dithianon. Absorption of dithianon was rapid and not affected by dose level. Based on the amount of radioactivity recovered in the urine and bile, 31-43% of the administered dose was absorbed following a single dose. In tissues other than the gastrointestinal tract, the highest level of dithianon and/or its metabolites was found in the kidneys. Dithianon and/or its metabolites were also detected in the liver, plasma, and whole blood, but it was not detected in the brain or spinal cord. There were no sex-related differences in distribution.

Dithianon was rapidly metabolized to many, mostly polar, compounds. When metabolic fractions were isolated, 15 were found in urine samples, >25 fractions were found in the feces, and many were found in the kidneys and liver. Following a single oral dose, only one metabolic fraction was comprised of >5% of the administered dose; that fraction was from a urine sample checked 8-24 hours after exposure and was identified as a glucuronic acid conjugate. No sex-related differences in metabolism were noted.

There was no bioaccumulation of dithianon. Recovery following repeated dosing was complete

at 120 hours. In both studies, 67-72% of the administered dose was found in the feces, 27-31% in the urine, 0.3-0.4% in the cage wash, and <0.2% in the carcass. A preliminary excretion study found that radioactivity was not detected in exhaled air. Excretion through the biliary route was not examined following the repeat dosing regimen; however, it was found to be a minor pathway following a single exposure, since only 7.2-11.6% of a single dose of 10 or 50 mg/kg dithianon was recovered in the bile 48 hours after exposure. The terminal half-life of dithianon was 46-57 hours. No sex- or dose-related differences on excretion were observed.

3.1.3 Toxicological Effects

The toxicologically significant adverse effects of dithianon are similar across species and generally seen at similar dose levels. In studies with shorter durations of exposure, including the subchronic dog and rat studies, the developmental toxicity study in rats, and the two-generation reproduction rat study, decreases in body weights, body weight gains, and/or food consumption were noted in adults. However, with continued exposure, as in the chronic and/or carcinogenicity studies in the rat, mouse, and dog, it becomes evident that the kidney is the target organ for toxicity. Signs of renal toxicity that were observed include increased absolute and/or relative kidney weights in the rat, mouse, and dog; non-neoplastic kidney lesions in mice and rats; and renal adenomas and carcinomas in female rats. In the developmental toxicity study in rats, increased post-implantation loss due to early resorptions was seen in conjunction with maternal toxicity.

In the species tested, males and females were equally susceptible to the effects of dithianon on body weight, body weight gain, food consumption, kidney weights, and the development of non-neoplastic renal lesions. One major difference between the sexes was seen in the carcinogenicity study in the rat, where females developed renal adenomas and carcinomas, but neoplasms were not found in the males. This sex-related difference is particularly notable because when kidney tumors develop following exposure to a given chemical, which is rare, they are generally observed in males.

The available toxicology database does not show any indication of increased qualitative or quantitative susceptibility of the offspring. Dithianon did not cause reproductive or developmental toxicity in the two-generation reproduction study. In the developmental toxicity study in rats, increased post-implantation loss due to early resorptions (significant only when total litter losses were included) was seen in conjunction with maternal toxicity ($\geq$ 50 mg/kg/day), which included decreased body weights, body weight gains, and food consumption; therefore, there is no increased quantitative susceptibility. These decreased maternal body weights were seen at $\geq$ 50 mg/kg/day, but body weights of the surviving fetuses were significantly decreased only at 100 mg/kg/day. There were no apparent treatment or dose-related external, visceral, or skeletal variations or malformations in the developmental rat study. The developmental toxicity study in rabbits was classified unacceptable/guideline due to excessive maternal toxicity that resulted in an insufficient number of litters to meet guideline requirements and excessive pre-implantation losses at all dose levels.

There is no evidence of neurotoxicity in the toxicology database for dithianon.

Dithianon is not mutagenic. Dithianon produced positive results in an acceptable chromosomal aberration assay that was conducted *in vitro* using Chinese hamster lung fibroblasts (V79 cells); in contrast, a forward gene mutation assay tested in this same cell line was negative. A second forward gene mutation assay with V79 cells was also negative, but it was classified unacceptable due to inadequate cytotoxicity at the highest concentration tested. Negative responses were seen in bacteria (two acceptable reverse gene mutation assays in Salmonella), Wistar rat systems (an acceptable *in vivo* cytogenetic assay and an acceptable *in vitro* UDS assay), and NMRI mice (an unacceptable *in vivo* micronucleus assay).

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March 2005), the Cancer Assessment Review Committee (CARC) classified dithianon as "Suggestive Evidence of Carcinogenic Potential", based on several weight-of-evidence considerations. Quantification of carcinogenic risk is not required. See Section 3.3.4 for details.

3.2 FQPA Considerations

The FQPA SF will be retained as a database uncertainty factor for lack of an acceptable rabbit developmental study. This recommendation is based on the following:

- residual uncertainty concerning the lack of an acceptable developmental toxicity study in rabbits;
- there is no indication of increased quantitative or qualitative susceptibility of rats to *in utero* and/or postnatal exposure to dithianon;
- the dietary food exposure assessment utilizes average residues from crop field trials and 100% crop treated information for all commodities; by using these screening-level assessments, acute and chronic exposures/risks will not be underestimated; and

3.3 Hazard Identification and Toxicity Endpoint Selection

Note: Executive summaries for the toxicity studies used for endpoint selection may be found in the previous risk assessment for dithianon. Endpoints for incidental oral, dermal, and inhalation exposures were not selected since there are no existing or proposed uses of dithianon in the U.S.

3.3.1 Acute Dietary Exposure - Females age 13-49

Study Selected: Developmental toxicity study in rats
MRID Number: 44092611.
Point of Departure: 20 mg/kg/day (NOAEL), based on post-implantation loss due to early resorptions seen at 50 mg/kg/day (LOAEL).
Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)
Comments:
Post-implantation loss resulting from early resorptions can be attributed to a single oral dose and is an appropriate endpoint for the population of concern.

3.3.2 Acute Dietary Exposure - General Population

No appropriate dose and endpoint could be identified to set a reference dose for acute dietary exposure in the general population, including infants and children. Therefore, a quantitative risk assessment is not required.

3.3.3 Chronic Dietary Exposure

Study Selected: Combined chronic toxicity/carcinogenicity study in rats.
MRID Number: 44092616.
Point of Departure: 6 mg/kg/day (NOAEL), based on decreased body weight gain and increased relative to body kidney weights (M&F), grossly observed kidney lesions in males (irregular surfaces, pale kidneys, cysts, and enlarged kidneys) and females (masses), and non-neoplastic lesions of the kidneys in males (tubular nephrosis, renal cysts, and end-stage kidney lesions) and females (tubular nephrosis, proliferative tubules, and glomerulonephropathy) seen at 30 mg/kg/day (LOAEL).
Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)
Comments: The chronic duration and dietary route of exposure in the selected study, as well as the types of adverse effects observed, are appropriate to set a chronic reference dose.

The chronic dog study (MRID 44092608) was considered a co-critical study because the NOAEL, LOAEL, and target organ toxicity were similar to what was seen in the combined chronic/carcinogenicity rat study. In this study, the LOAEL is 37.1/35 mg/kg/day [M/F]), based on increased absolute and relative liver and kidney weights, increased alkaline phosphatase, decreased blood urea nitrogen, hepatocellular hypertrophy, histiocyte pigmentation, and renal pigmentation (M&F). The NOAEL for this study, 6.7/7.6 mg/kg/day [M/F], is well established and could have detected changes in body weights in the 90-day dog study. Therefore, the lower NOAEL found in the 90-day dog study, 2.95/3.00 mg/kg/day [M/F], is an artifact of dose selection.

3.3.4 Classification of Carcinogenic Potential

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March 2005), the Cancer Assessment Review Committee (CARC) classified dithianon as "Suggestive Evidence of Carcinogenic Potential", based on several weight-of-evidence considerations. First, treatment-related rare kidney tumors, primarily adenomas, were seen only at the highest dose tested (600 ppm) in one sex (females) and in one species (rats). The highest dose tested was considered adequate, but not excessive, to assess the carcinogenicity of dithianon; however, significant renal toxicity occurred at this dose. Second, although the CARC concluded that there was not a sufficient or cohesive dataset at the time to fully support a mode of action, the Registrant's hypothesized non-genotoxic mode of action involving nephrotoxicity and sustained regenerative proliferation was considered to be biologically plausible. Finally, there is no mutagenicity concern for dithianon. The CARC determined that quantification of carcinogenic

potential is not required (J. Kidwell, 2/23/06).

3.3.5 Summary of Toxicological Doses and Endpoints

Table 3.1. Summary of Toxicological Doses and Endpoints for Dithianon for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	No appropriate dose and endpoint could be identified for these population groups. Therefore a quantitative risk assessment is not required.			
Acute Dietary (Females 13-49 years of age)	NOAEL = 20 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF (UF_{DB})= 10x	Acute RfD = aPAD = 0.02 mg/kg/day	**Developmental toxicity study in rats** LOAEL = 50 mg/kg/day based on post-implantation loss due to early resorptions
Chronic Dietary (All Populations)	NOAEL = 6 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF (UF_{DB})= 10x	Chronic RfD = cPAD = 0.006 mg/kg/day	**Combined chronic toxicity/carcinogenicity study in rats** LOAEL = 30 mg/kg/day based on decreased body weight gains and increased relative to body kidney weights, grossly observed kidney lesions, and non-neoplastic lesions of the kidney
Cancer	Classification: "Suggestive Evidence of Carcinogenic Potential". A quantitative assessment is not required.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

3.4 Endocrine disruption

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 recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis 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 additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, dithianon may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

There are no registered uses of dithianon in the U.S. Therefore, incident data are not available and it has not been evaluated in any epidemiology studies of which the Agency is aware.

5.0 Dietary Exposure/Risk Characterization

5.1 Residues of Concern

The petitioner has submitted three plant metabolism studies for dithianon on apples, oranges, and wheat. Metabolism of dithianon is similar on all crops. Dithianon does not appear to be highly metabolized in plants, with a significant amount of the unchanged parent compound remaining on the plant surface, and little to no movement from the application site. A confined rotational crop study is not required for import tolerances. The ruminant metabolism study indicated extensive metabolism of dithianon, which is consistent with the results of the rat metabolism study. A poultry study is not required to support the existing or proposed tolerances, as there are no poultry feed items associated with this petition. A summary of the residues of concern for dietary risk assessment and tolerance assessment may be found in Table 5.1.

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

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Dithianon	Dithianon
Plants	Rotational Crop	Not Applicable, since the proposed tolerances are for imported commodities only.	
Livestock	Ruminants	Dithianon	Dithianon
	Poultry	There are no feed items for which tolerances are proposed or established.	
Drinking Water		Not Applicable, since the proposed tolerances are for imported commodities only.	

5.2 Residue Profile

Current and proposed tolerances for dithianon are intended to support imported commodities only and there are no existing or proposed U.S. registrations. Therefore, there is no expectation that dithianon residues would occur in surface or ground water sources of drinking water

Plant metabolism studies indicate that most of the dithianon residues are surface residues, with minimal translocation from the application site in apples and oranges. Some metabolism of residues was observed in the wheat study at longer intervals between application and harvest. The petitioner submitted crop field trials conducted in France, Brazil, Spain, and Italy, and are adequate for dietary exposure assessment. Residues of dithianon are quantifiable at the minimum pre-harvest intervals (PHI) identified on the product labels, and decreased with increasing intervals between application and harvest. The maximum residue observed at the label PHI was 2.6 ppm. Residues of dithianon decreased upon processing into raisins and juice, which is consistent with the apple processing study discussed in the previous dithianon petition.

Exposure to dithianon in livestock commodities is not expected based on the proposed uses of dithianon. There are no feed items associated with the subject commodity, grapes. However, there is a potential for residues of dithianon in livestock commodities from the existing uses. Although it is unlikely that apple wet pomace will be imported into the U.S., or that imported fresh apples will be processed within the U.S., apple wet pomace from dithianon-treated apples may be fed to livestock in the countries in which dithianon is used on apples, and the livestock may be imported into the U.S.. The maximum residues of dithianon observed in the goat metabolism study were 0.011 ppm in kidney from the goat dosed at 30 ppm. Based on these results, HED concludes that the proposed uses of dithianon in this petition result in a 40CFR §180.6[a][3] situation for ruminant commodities; specifically, there is no reasonable expectation of finite residues in ruminant commodities. Therefore, no ruminant feeding study is needed to support the subject petition.

5.3 Dietary Exposure and Risk

5.3.1 Description of Residue Data Used in Dietary Assessment

The existing tolerance levels for pome fruit and hops, as well as the proposed tolerance for grapes were used in the acute dietary assessment. Average residues from crop field trial data were used in the chronic dietary assessment for all commodities. Empirical processing factors were used for pome fruit juices (0.2), grape juice (0.1), and raisins (0.7). DEEM 7.81 default processing factors were used for the dried pome fruits (8.0 for apples and 6.25 for pears).

5.3.2 Percent Crop Treated Used in Dietary Assessment

No percent crop treated data were used in this assessment.

5.3.3 Acute Dietary Risk Assessment

A summary of the dietary assessment may be found in Table 5.3.6. Only exposure for Females ages 13-49 is reported, as no acute endpoint was identified for the general population. The exposure for females (age 13-49) is at 79% of the aPAD at the 95th percentile of exposure, which is below the level of concern. This assessment is highly conservative as it assumes residues are at tolerance level and assumes 100% crop treated.

5.3.4 Chronic Dietary Risk Assessment

The results of the chronic dietary exposure analysis are reported in Table 5.3.6. The exposures for all populations assessed are below the level of concern. The exposure for the general U.S. population is at 18% of the cPAD. The most highly exposed sub-group is children (ages 1-2), whose exposure is at 63% of the cPAD. This assessment is slightly refined with the use of average residue values and empirical processing factors, but is still highly conservative with the assumption of 100% crop treated.

5.3.5 Cancer Dietary Risk Assessment

A quantitative cancer assessment is not required as discussed in Section 3.3.4.

5.3.6 Summary Table of Dietary Exposure/Risk Assessment

Table 5.3.6 Summary of Dietary (Food Only) Exposure and Risk for Dithianon

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD[1]	Dietary Exposure (mg/kg/day)	% cPAD[1]	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	N/A [2]	N/A	0.001082	18	N/A	N/A
All Infants (< 1 year old)			0.003413	57		
Children 1-2 years old			**0.003791**	**63**		
Children 3-5 years old			0.002734	46		
Children 6-12 years old			0.001230	20		
Youth 13-19 years old			0.000420	7.0		
Adults 20-49 years old			0.000881	15		
Adults 50+ years old			0.000862	14		
Females 13-49 years old	**0.01583**	**79**	0.000689	12		

[1]The values for the highest exposed population for each type of risk assessment are bolded.
[2]N/A = Not applicable

5.4 Tolerance Assessment

5.4.1 Enforcement Analytical Method

An adequate LC/MS/MS method (BASF 244882) is available for enforcing the proposed tolerance on grapes. For this method, residues are extracted with acetonitrile:water:2N HCl (70/25/5, v/v/v) and centrifuged. Residues are then analyzed directly by LC/MS/MS using external standards and two ion transitions for quantitation. This method has been adequately validated using fortified samples of grapes, apples, lettuce, oranges, wheat grain, rapeseed, and

dried hop cones. The validated LOQ is 0.01 ppm for each plant, with the exception of dried hop cones (LOQ = 1.0 ppm). Adequate multi-residue method testing data are available for dithianon, and these data have been forwarded to the FDA for evaluation. The data indicate that FDA multi-residue methods are not suitable for determining residues of dithianon.

5.4.2 Tolerance Recommendation

Sufficient residue data are available to support the proposed tolerance. The level proposed by the petitioner, 3 ppm, is appropriate. Processed commodity tolerances are not needed since residues do not concentrate upon processing.

The Health Effects Division (HED) has recently updated its guidance on the language used in tolerance expressions. The tolerance expression should be modified to the following

> Tolerances are established for residues of dithianon, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only dithianon (5,10-dihydro-5,10-dioxonaphtho(2,3-*b*)-1,4-dithiin-2,3-dicarbonitrile).

5.4.3 International Harmonization

There are currently no established Canadian or Mexican maximum residue limits (MRLs) for dithianon on grapes. The proposed tolerance will be harmonized with Codex and the European Union.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed or existing uses of dithianon in the U.S. Tolerances have been proposed or established only on imported commodities. Therefore, there is no expectation that exposure to dithianon residues would occur in residential settings and no residential risk assessment was performed.

7.0 Aggregate Risk Assessments and Risk Characterization

Since dithianon is proposed for use only on imported grapes, and tolerances have been established on imported pome fruit and hops, the only anticipated exposure route for the U.S. population is via dietary (food) exposure. There are no proposed or existing U.S. registrations so there is no expectation of exposure to dithianon in drinking water or in residential settings. Therefore, an aggregate risk assessment is not required.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to dithianon and any other substances, and dithianon does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore,

EPA has not assumed that dithianon has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs (OPP) concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

There are no proposed or existing uses of dithianon in the U.S. Tolerances have been proposed or established only on imported commodities. Therefore, there is no expectation that exposure to dithianon residues would occur via occupational use and no occupational risk assessment was performed.

10.0 Data Gaps

There are no residue chemistry data deficiencies. The following toxicity studies are typically required to support tolerances and are not available in the dithianon database:

- 870.3700b Rabbit developmental Toxicity Study
- 870.6200a Acute neurotoxicity study
- 870.6200b Subchronic neurotoxicity study
- 870.7800 Immunotoxicity study.

11.0 References

The following Agency memoranda were cited in this risk assessment.

Author	DP Number	Date	Title
C. Olinger		In Review	Dithianon. Acute and Chronic Aggregate Dietary (Food Only) Exposure and Risk Assessments for the Proposed Tolerance in/on Grapes
C. Olinger	361351	In Review	Dithianon. Petition for a Tolerance on Imported Grapes. Petitioner's Response to Deficiencies Noted in HED Review dated April 15, 2008. Summary of Analytical Chemistry and Residue Data.
D. Davis	333117	4/15/08	Summary of Analytical Chemistry and Residue Data to Support a Petition for Establishment of Import Tolerance on Grapes.
D. McNeilly	235354	7/11/06	Dithianon. Human Health Risk Assessment for Proposed Food Uses of the Fungicide on Imported Pome Fruit and Hops.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use (tolerances on imported commodities only) of dithianon are in Appendix Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

TABLE A.1. Toxicology Data Requirements.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	no	N/A
870.1300 Acute Inhalation Toxicity	no	N/A
870.2400 Primary Eye Irritation	no	N/A
870.2500 Primary Dermal Irritation	no	N/A
870.2600 Dermal Sensitization	no	N/A
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	no	N/A
870.3250 90-Day Dermal	no	N/A
870.3465 90-Day Inhalation	no	N/A
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	no
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	N/A
870.6100b 90-Day Neurotoxicity (hen)	no	N/A
870.6200a Acute Neurotox. Screening Battery (rat)	yes	no
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	no
870.6300 Develop. Neuro	no	N/A
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	N/A
870.7800 Immunotoxicity	yes	no

A.2 Toxicity Profiles

TABLE A.2 Acute Toxicity Profile for Dithianon.					
Test Material* [% ai]	**Guideline Number**	**Study Type**	**MRID Number**	**Results**	**Toxicity Category**
Technical Product	**870.1100**	Acute oral - rat	44092605	LD_{50} (♂+♀) = 702 mg/kg (95% C.I. = 597-893 mg/kg)	III
Technical Product	**870.1200**	Acute dermal - rat	Not applicable for proposed use pattern (Import tolerance).		
Technical Product	**870.1300**	Acute inhalation - rat	Not applicable for proposed use pattern (Import tolerance).		
Technical Product	**870.2400**	Acute eye irritation - rabbit	Not applicable for proposed use pattern (Import tolerance).		
Technical Product	**870.2500**	Acute dermal irritation - rabbit	Not applicable for proposed use pattern (Import tolerance).		
Technical Product	**870.2600**	Skin sensitization - guinea pig	Not applicable for proposed use pattern (Import tolerance).		

TABLE A.3 Subchronic, Chronic, and Other Toxicity Profile for Dithianon.				
Guideline Number	**Study Type/ *Classification***	**MRID Number**	**Doses**	**Results**
870.3100	90-Day oral toxicity rodents - rat *Acceptable/guideline*	44092606	0, 30, 180, 1080 ppm **M:** 0, 2.53, 14.64, 86.66 mg/kg/day **F:** 0, 2.97, 16.32, 99.53 mg/kg/day	**NOAEL** = 14.64/16.32 mg/kg/day (M/F) **LOAEL** = 86.66/99.53 mg/kg/day (M/F) based on decreased body weights and overall body weight gains in both sexes.
870.3150	90-Day oral toxicity in nonrodents - dog *Acceptable/guideline*	44092607	0, 40, 200, 1000 ppm **M:** 0, 0.63, 2.95, 12.58 mg/kg/day **F:** 0, 0.66, 3.00, 12.61 mg/kg/day	**NOAEL** = 2.95/3.00 mg/kg/day (M/F) **LOAEL** = 12.58/12.61 mg/kg/day (M/F) based on decreased body weights (F only), decreased body weight gains and food consumption (M&F), and increased alkaline phosphatase activity (M&F).

TABLE A.3 Subchronic, Chronic, and Other Toxicity Profile for Dithianon.				
Guideline Number	**Study Type/ *Classification***	**MRID Number**	**Doses**	**Results**
870.3700	Developmental toxicity in rodents - rat *Acceptable/guideline*	44092611 44092612	0, 20, 50, 70, 100 mg/kg/day Dosing period: GD 6-15	**Maternal** **NOAEL** = 20 mg/kg/day **LOAEL** = 50 mg/kg/day based on decreased body weights, body weight gains, and food consumption. At 100 mg/kg/day, 5/25 dams died between GD 13 and 17. **Developmental** **NOAEL** = 20 mg/kg/day **LOAEL** = 50 mg/kg/day based on increased incidence of total litter loss (20-42% at ≥ 50 mg/kg/day) and post-implantation loss due to early resorptions (showed decidual or placental tissues only). At 100 mg/kg/day, weights of the surviving fetuses were decreased.
870.3700	Developmental toxicity in nonrodents - rabbit *Unacceptable/guideline*	44092613 44092614	0, 10, 25, 40 mg/kg/day Dosing period: GD 6-18, beginning prior to implantation.	The Maternal **NOAEL** and **LOAEL** could not be determined due to improper gavage techniques, which resulted in abortions and deaths. The **developmental NOAEL and LOAEL** could not be determined due to excessive pre-implantation loss (44%, 38%, 32%, and 58% per group in the 0, 10, 25, and 40 mg/kg/day dose levels, respectively). High pre-implantation loss alters litter size, fetal weights, and other parameters, hindering the ability to assess post implantation loss. Additionally, the number of litters was insufficient to meet guideline requirements, due to high maternal mortality.

TABLE A.3 Subchronic, Chronic, and Other Toxicity Profile for Dithianon.				
Guideline Number	**Study Type/ *Classification***	**MRID Number**	**Doses**	**Results**
870.3800	Reproduction and fertility effects - rat *Acceptable/guideline*	44092615	0, 35, 200, 600 ppm **M:** 0, 2.2, 12.6, 37.8 mg/kg/day **F:** 0, 2.5, 14.5, 42.7 mg/kg/day	**Parental/Systemic** **NOAEL** = 12.6/14.5 mg/kg/day (M/F) **LOAEL** = 37.8/42.7 mg/kg/day (M/F) based on decreased body weights, body weight gains, and food consumption during pre-mating. **Reproductive** **NOAEL** = 37.8/42.7 mg/kg/day (M/F) **LOAEL** = Not determined. **Offspring** **NOAEL** = 37.8/42.7 mg/kg/day (M/F) **LOAEL** = Not determined.
870.4100	Chronic toxicity - rodents	See 870.4300. This study includes requirements of both 870.4100 and 870.4200.		
870.4100	Chronic toxicity - dog *Acceptable/guideline*	44092608	0, 40, 200, 1000 ppm **M:** 0, 1.5, 6.7, 37.1 mg/kg/day **F:** 0, 1.6, 7.6, 35.0 mg/kg/day	**NOAEL** = 6.7/7.6 mg/kg/day (M/F) **LOAEL** = 37.1/35.0 mg/kg/day (M/F) based on increased absolute and relative liver and kidney weights, increased alkaline phosphatase, decreased blood urea nitrogen, hepatocellular hypertrophy, histiocyte pigmentation, and renal pigmentation (M&F).
870.4200	Carcinogenicity - rat	See 870.4300. This study includes requirements of both 870.4100 and 870.4200.		
870.4200	Carcinogenicity - mouse *Acceptable/guideline*	44092609 44092610	0, 20, 100, 500 ppm **M:** ~ 0, 3, 15, 75 mg/kg/day **F:** ~ 0, 3, 15, 75 mg/kg/day Doses were estimated using the conversion ratio.	**NOAEL** = ~ 15 mg/kg/day (M&F) **LOAEL** = ~ 75 mg/kg/day (M&F) based on increased mortality (M), increased kidney weights, (M&F), and increased incidences and severity of kidney lesions (chronic nephropathy, cortical cysts, tubular dilatation, and infarct) in both sexes. *No evidence of carcinogenicity*

TABLE A.3 Subchronic, Chronic, and Other Toxicity Profile for Dithianon.				
Guideline Number	**Study Type/ *Classification***	**MRID Number**	**Doses**	**Results**
870.4300	Combined chronic toxicity/ carcinogenicity - rat *Acceptable/guideline*	44092616 44092617 44092618	0, 20, 120, 600 ppm **M:** ~ 0, 1, 6, 30 mg/kg/day **F:** ~ 0, 1, 6, 30 mg/kg/day Doses were estimated using the conversion ratio.	**NOAEL** = ~ 6 mg/kg/day (M&F) **LOAEL** = ~ 30 mg/kg/day (M&F) based on decreased body weight gain and increased relative to body kidney weights (M&F), grossly observed kidney lesions in males (irregular surfaces, pale kidneys, cysts, and enlarged kidneys) and females (masses), and non-neoplastic lesions of the kidney in males (tubular nephrosis, renal cysts, and end-stage kidney lesions) and females (tubular nephrosis, proliferative tubules, and glomerulonephropathy). ***Evidence of carcinogenicity:*** renal adenomas and carcinomas observed in 600 ppm females.
870.5100	Gene mutation - bacterial reverse mutation assay *Acceptable/guideline*	44092619 44280401	0.1 - 333.3 µg/plate (-S9) 10 - 3333.3 µg/plate (+S9)	Negative.
870.5100	Gene mutation - bacterial reverse mutation assay *Acceptable/guideline*	44092619 44280402	1 - 333.3 µg/plate (-S9) 33.3 - 3333.3 µg/plate (+S9)	Negative.
870.5300	Cytogenetics - *in vitro* mammalian cell gene mutation test (CHL Cells) *Unacceptable/guideline*	44092619 44280403	0, 20, 50, 100, 200 µg/ml (-S9) 60, 150, 300, 600 µg/ml (+S9)	Negative. This study is unacceptable due to inadequate cytotoxicity at the HDT.
870.5300	Cytogenetics - *in vitro* mammalian cell gene mutation test (CHO Cells) *Acceptable/guideline*	44092619 44280404	**Trial 1**: 0.03-1.33 g/ml (-S9); 0.33-1.33 g/ml (+S9). **Trial 2**: 0.33-1.00 g/ml (-S9); 0.33-1.33 g/ml (+S9). **Trial 3**: 0.10-1.33 g/ml (+S9). **Trial 4**: 0.03-1.00 g/ml (-S9); 0.10-1.33 g/ml (+S9).	Negative.

TABLE A.3 Subchronic, Chronic, and Other Toxicity Profile for Dithianon.				
Guideline Number	**Study Type/ *Classification***	**MRID Number**	**Doses**	**Results**
870.5375	Cytogenetics - *in vitro* mammalian cell chromosome aberration test *Acceptable/guideline*	44092620 44280405	**7 hours fixation**: 0 or 600 ng/ml (-S9); 0 or 5000 ng/ml (+S9). **18 hours fixation**: 0, 25, 500, 600 ng/ml (-S9); 0, 500, 1000, 5000 ng/ml (+S9). **28 hours fixation**: 0 or 300 ng/ml (-S9); 0 or 3500 ng/ml (+S9).	Mutagenic: Evidence of structural chromosome aberrations induced over background.
870.5385	Cytogenetics - mammalian bone marrow chromosomal aberration test (rats). *Acceptable/guideline*	44092620 44280406	0, 22.3, 106.0, 393.5 mg/kg	Negative.
870.5395	Cytogenetics - mammalian erythrocyte micronucleus test (mice) *Unacceptable/guideline*	44092620 44280407	0, 1, 10, 100 mg/kg	Negative. This study is unacceptable due to missing information on test material purity.
870.5550	Other effects - unscheduled DNA synthesis in mammalian cells in culture (rats) *Acceptable/guideline*	44092621	0, 0.1, 1.0, 5.0, 10.0, 15.0, or 20.0 g/ml for 3 hours.	Negative.

TABLE A.3 Subchronic, Chronic, and Other Toxicity Profile for Dithianon.				
Guideline Number	**Study Type/ *Classification***	**MRID Number**	**Doses**	**Results**
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/guideline*	44092622 44092623	**(1)** 10 or 50 mg/kg radiolabeled, single dose by oral gavage. **(2)** 10 mg/kg/day unlabeled, 14 days by oral gavage, PLUS 10 mg/kg radiolabeled, single dose by oral gavage. **(3)** 10 mg/kg/day radiolabeled, 7 days by oral gavage.	**Absorption:** Rapid. Dithianon was detected in plasma within 15 min. As measured in urine and bile, 31-43% was absorbed after a single dose of 10 or 50 mg/kg (23.5-33% in urine; 7.2-11.6% in bile). Not dose-dependent. **Distribution:** Besides the GI tract, highest levels in kidneys. Also detected in liver, plasma, and whole blood. Not detected in brain or spinal cord. No sex-related differences. **Metabolism:** Rapidly and completely degraded to many, mostly polar, compounds. 15 fractions isolated from urine, >25 fractions from feces, many from kidneys and liver. Only 1 fraction was >5% of the radioactivity from the single administered dose; that was a glucuronic acid conjugate found in the 8-24 hr urine sample. No sex-related differences. **Excretion:** No bioaccumulation. Within 120 hours after repeated exposure to 10 mg/kg/day for 14 days (unlabeled) plus 10 mg/kg (labeled) for 1 day, the radioactivity recovered was 64-72% of the administered dose in feces, 27-31% in urine, <0.7% cage wash, <0.2% in carcass, 0% in exhaled air. Biliary excretion was not measured in the repeated exposure study, although 7.2-11.6% of the radioactivity was recovered following a single dose. Therefore, % recovery for the repeated exposure study was not expressed in terms of absorbed dose. The terminal half-life was 46-57 hrs. No sex- or dose-related differences were noted.

13544

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