Evaluation Report for Category A, Subcategory 1.3 Application

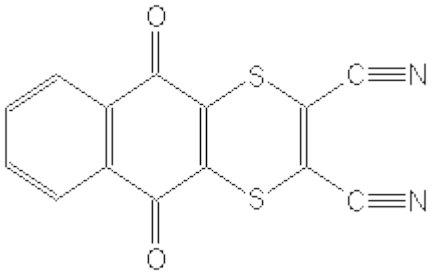
Application Number: 2015-0222
Application: New active ingredient – Maximum residue limits (MRLs) only
Product: Dithianon Technical
Registration Number: #####
Active ingredient (a.i.): Dithianon
PMRA Document Number : 2761500

Purpose of Application

The purpose of this application was to establish maximum residue limits (MRLs) for the active ingredient dithianon on several imported commodities.

1.0 Chemistry Assessment

1.1 Identity of the Active Ingredient

Active substance	Dithianon
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	5,10-dioxo-5,10-dihydronaphtho[2,3-*b*][1,4]dithiine-2,3-dicarbonitrile
2. Chemical Abstracts Service (CAS)	5,10-dihydro-5,10-dioxonaphtho[2,3-*b*]-1,4-dithiin-2,3-dicarbonitrile
CAS number	3347-22-6
Molecular formula	$C_{14}H_4N_2O_2S_2$
Molecular weight	296.3
Structural formula	
Purity of the active ingredient	96.2% nominal

1.2 Physical and Chemical Properties of the Active Ingredient

Dithianon Technical

Property	Result
Colour and physical state	Brown solid
Odour	Faint musty
Melting range	221.6ºC
Boiling point or range	N/A
Density	1.514 g/cm^3
Vapour pressure at 20°C	5.8×10^{-12} Pa (extrapolated)
Ultraviolet (UV)-visible spectrum	pH λ_{max} (nm) ε ($M^{-1}cm^{-1}$) 6.2 250 15110 1.3 237 9820 12.8 270 23196
Solubility in water at 20°C	pH=4 0.26 mg/L pH=7 0.20 mg/L pH=9 0.21 mg/L In demineralized water: 0.19 mg/L
Solubility in organic solvents at 20°C	Solvent Solubility (g/100mL) methanol 0.09 toluene 1.95 n-heptane 0.0015 ethyl acetate 0.88 dichloromethane 2.36 acetone 1.67
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 3.2
Dissociation constant (pK_a)	N/A. Dithianon has no chemical functionality which dissociates in water.
Stability (temperature, metal)	Stable at 54ºC for 2 weeks (slight decrease is still within certified limits), contact with metals may cause corrosion of the metal; not stable in sunlight.

2.0 Method of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

Methods for analysis of the end-use product are not required for this submission.

2.3 Methods for Residue Analysis

Several liquid- or gas-chromatography methods (HPLC-UV, GC-ECD) were developed for data generation purposes. A high performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS) was developed and proposed for enforcement purposes in plant matrices. This method fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation. Acceptable recoveries (70-120%) were obtained in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. The extraction solvents used in the metabolism studies were comparable to those in the proposed enforcement method, so the enforcement method is expected to adequately extract bioincurred residues of dithianon.

3.0 Health Assessments

3.1 Toxicology Summary

A detailed review of the toxicological database for dithianon, a quinone fungicide, was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. All required studies were carried out in accordance with Good Laboratory Practices and followed currently accepted international testing protocols or protocols that were considered acceptable at the time the studies were conducted. Specialized investigative studies were also provided in support of a proposed mode of action (MOA) for kidney tumour formation in female rats. Additionally, relevant published investigations of dithianon were included for the hazard assessment. In general, the scientific quality of the data was high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to dithianon.

The toxicokinetics and metabolism were investigated in rats. Dithianon was isotopically labelled (^{14}C or ^{13}C) at either the 5(10)-carbonyl carbon atoms of the quinone moiety, or the 2,3-cyano carbon atoms of the dithiine ring moiety. Treatments included gavage administration of single or repeated low doses or a single high dose. Regardless of the dosing regimen, absorption was rapid and dose-proportional, but incomplete. Absorption was 31-43% of the administered dose (AD) for single doses and repeated low doses. Plasma concentrations were measurable within 15 minutes and maximal at 6 hours post-administration. No dose- or sex-related differences in absorption were evident.

Once absorbed, dithianon and/or its metabolites were rapidly and widely distributed. The lowest concentrations occurred in the brain. Following administration of a single low dose, most organ/tissue concentrations were concordant with plasma kinetics and did not exceed maximum plasma concentrations. On this basis, uptake into most tissues was inferred to be passive and largely responsive to kinetics in the blood. The kidneys and male thyroid gland were exceptions, with maximum concentrations exceeding those of plasma by 2- to 4-fold. In both sexes, these targets had the slowest apparent elimination kinetics. Slower elimination kinetics were also apparent in the adrenal glands, bone marrow and whole blood in both sexes, as well as in the ovary. Comparable time-course information on early tissue concentrations was not available for single high dosing or for repeated low doses.

Metabolism of dithianon was rapid, extensive and complete. Unchanged dithianon was present at only trace levels in the feces and was not detected in the urine. Three major metabolites, (individually, 12-37% AD), and many minor metabolites (< 2-3% AD) were identified. Numerous fractions were also partially characterized. The three major metabolites were detected only in the urine. These included a glucuronide of the 1,4-dihydroxynaphthalene ring moiety (M216F020) and two dithiine ring metabolites (M216F029, M216F030). The main transformation steps in rats included oxidation of the sulfur atoms, cleavage of the dithiine ring, reduction of the 1,4-naphthoquinone moiety with further glucuronidation, as well as substitution of the carbonitrile moieties by amino and carboxy groups. The metabolic pathways were complex but the identified metabolites appeared generally similar in males and females. The chemical names of dithianon metabolites are listed in Table 1 of Appendix 1.

Elimination was rapid and complete, with no evident bioaccumulation. The majority was eliminated within 48 hours of dosing regardless of the dose level. Absorbed dithianon was eliminated primarily via the urine (24-33% AD) and to a lesser extent via the bile (7-12% AD). Only trace amounts were eliminated via expired air. Unabsorbed dithianon (57-72% AD) was completely degraded and/or metabolised within the gastrointestinal tract prior to elimination via the feces.

There was a small, toxicologically relevant, sex-dependent difference in the kinetics of dithianon elimination. Single-dosed females had slightly greater area under the curve (AUC) values, compared to males. This implies greater effective acute systemic exposure in females. At 48 hours, high-dose females had decreased elimination via the urine, increased retention in the carcass and no change in biliary elimination, compared to males. This pattern indicates delayed urinary elimination in females, which is consistent with acutely reduced kidney function. Female-specific acute cytotoxicity of the kidney tubule epithelium occurred at this dose level elsewhere in the toxicology database.

With repeated low dosing, elimination in females shifted slightly away from the urinary route and towards the fecal route compared to single-dosed females; this is consistent with an adaptive hepatobiliary response. Comparable changes were not evident in repeat low-dose males. In a published study, dithianon-treated mice exhibited sex-specific differences in the metabolic response of the liver, kidney and lungs following single and repeated oral exposures (PMRA# 2742219). This possibility was not explicitly investigated in rats.

In eukaryotic cells, dithianon reacts broadly with sulfhydryl groups (for example, glutathione) and interferes with thiol-dependent biological processes. For instance, in published studies dithianon modified the catalytically active sulfhydryl groups of key glycolytic enzymes, thereby potently inhibiting glycolysis (PMRA# 2742220, 2742221). Thus, dithianon's cytotoxic potential may be the result of perturbation of cellular redox-dependent processes. Notably, dithianon's cytotoxicity was generally reduced in bacterial and mammalian cell assays by metabolic activation using rat liver supernatant fraction nine (S9).

Dithianon had high acute oral toxicity in rats. At lethal doses, signs of toxicity were evident within 1-2 hours of dosing and included impaired and poor general state, dyspnoea, staggering, piloerection, smeared fur and diarrhea; death occurred within 1-4 days.

Following short-term dosing via the diet, mice, rats and dogs exhibited kidney toxicity, altered red blood cell parameters and thyroid hormone changes. In dogs, there was evidence of liver toxicity, but in rodents the liver-specific changes were considered primarily adaptive. At higher dose levels, all three species exhibited decreases in body weight and/or body weight gain as well as decreases in food consumption. Decreased food efficiency was also observed at higher dose levels, but only in rats. In rats and dogs, effects on body weight and food consumption were more evident in females than in males. Also, body weight and food consumption effects in mice and dogs were observed only following short-term dosing, whereas such effects persisted chronically in rats.

All three of the above test species exhibited increases in liver weight with short-term dietary dosing. In rodents, this persisted no longer than 28 days, with little evidence of concordant adverse functional and/or histopathological liver change. In female mice, iron deposition occurred in Kupffer cells at 28 days along with altered red blood cell parameters and increased kidney weight; increased liver weight manifested at a higher dose. Rodents dosed chronically exhibited no clear adverse liver effects. In contrast, liver weights in dogs, particularly in females, were increased at relatively low dose levels, and dose-concordant liver histopathology and liver-related clinical chemistry changes were observed following one year of dietary administration.

Thyroid hormone levels were perturbed at relatively low dose levels in rodents and dogs following short-term dietary dosing. In rats dosed with relatively high levels of dithianon, there was evidence that this perturbation persisted following longer dosing. Nevertheless, gross effects on the thyroid gland manifested only at higher dose levels, regardless of the species or duration of dosing. With short-term dosing in rodents, males exhibited a greater propensity for thyroid hormone perturbation and/or thyroid gland weight increase than females. Physiologically, the observed thyroid hormone changes in male rats tended to resemble hypothyroidism. Regardless, concordant increases in thyroid stimulating hormone (TSH) levels and thyroid gland weight occurred only at relatively high dose levels. The overall pattern of change suggests adequate homeostatic compensation of triiodothyronine (T_3) and thyroxine (T_4) levels at lower dose levels in rats. In dogs, thyroid hormones were only minimally investigated. Nevertheless, increased thyroid gland weight and histopathology (lymphocytic thyroiditis) occurred at high doses only, and with no obvious sex-specificity. Regardless of species or duration, concern for thyroid-related effects was minimal due to the nature of the effects and the dose levels at which they occurred.

Red blood cell (RBC) numbers and other closely related parameters were decreased with short-term dietary dosing in rodents and dogs. Such effects were evident at lower dose levels in females compared to males in all three species, but particularly so in dogs. In both sexes, RBC effects were consistently associated with kidney toxicity. Consequently, an acute decrease in the ratio of polychromatic to normochromatic erythrocytes (PCE/NCE) in female rats following a single high dose in a bone marrow micronucleus assay is consistent with acutely impaired erythropoiesis, but it may not be due to a direct toxic effect within the bone marrow. In addition, in a study published in the scientific literature, dithianon potently inhibited glycolysis in cultured mammalian cells (PMRA# 2742221). In rats dosed at relatively high dithianon levels, demonstrably achievable concentrations in the blood fall within a range that could begin to interfere with RBC glycolysis. Thus, a direct effect on mature RBC viability may be a contributing factor given their exclusive reliance on glycolysis for energy metabolism. Although

net decreases in circulating RBCs were modest with repeated dosing in rodents, evidence of compensatory increases in RBC production was evident; this manifested as decreased mean corpuscular hemoglobin (MCH) in female mice and increased reticulocytes in rats. This could have masked the absolute magnitude of RBC loss in rodents. In dogs, where RBC decreases were greatest, there was no evidence of compensatory change in erythropoiesis. In mice and dogs, the toxicological impact of short-term RBC destruction was evident in the liver as iron deposition within histiocytes/Kupffer cells.

The kidney was the primary target organ for toxicity in rodents and dogs, regardless of the duration of dosing. Kidney toxicity effects were more evident in rodents than in dogs and occurred at lower doses in females compared to males in all species tested. Overall, females exhibited a greater range and/or severity of kidney effects, or exhibited effects at lower dose levels compared to males. A critical aspect of dithianon-induced kidney toxicity that sets female rats apart from males appears to be a selectively increased cytotoxicity of the tubular epithelial cells within the transitional (S2) and straight (S3) segments of the proximal tubules. Given what is . Although the epithelium of all three segments are expected to play a critical role in eliminating and detoxifying dithianon, the segments with the greatest reliance on glycolysis appeared uniquely sensitive to dithianon and/or its metabolites. The earliest manifestation of cytotoxicity in these cells was mitochondrial degradation; this was observed within one to two days of exposure, depending on the dose level. Consequently, the cellular events causing mitochondrial damage and ensuing cell death were considered to have resulted from a single acute exposure to dithianon.

Kidney toxicity occurred for all exposure durations, from acute to chronic. In all three species, the number and severity of effects in the kidney increased as the dose level and exposure duration were increased. Observed effects appeared to be generally comparable in rodents and dogs, but the greatest observational detail was available for rats. In rats exposed acutely to high oral levels of dithianon, the most immediate adverse effect was tubular epithelial cell cytotoxicity, which consisted of mitochondrial damage, hydropic degeneration, dilated rough endoplasmic reticulum and nuclear degeneration. Acute cellular effects in rats administered a high oral dose of dithianon were accompanied by an increase in kidney weight and, based on toxicokinetic information, a slight but immediate decline in kidney function in female rats. Within one day of these acute effects in rats, there was also evidence of compensatory repair of the tubule epithelium.

The tubule repair response was investigated in dietary short-term mechanistic studies. At low dose levels the tubule cell response was evident as decreased apoptosis, increased cell proliferation, and increased expression of kidney injury molecule-one (KIM-1) protein. At higher dose levels, apoptosis was increased, rather than decreased; this suggests the existence of an exposure threshold beyond which the tubule repair response could become overwhelmed, resulting in increased cell death. This evident threshold is considered of relevance to the formation of tubule epithelial cell tumours in female rats (discussed in a later section).

Rats given repeated low dietary doses of dithianon exhibited transient increases in kidney weight and pallor, which did not persist beyond 28 days. Increased liver weight and greater apparent elimination via the biliary route also occurred within this time frame in female rats given repeated low doses. Thus, the transience of low-dose effects in the kidney likely reflects the time needed for a systemic adaptive response to manifest. At sufficiently high dose levels, increased

kidney weight persisted in rodents and dogs, regardless of the duration of exposure. This is consistent with the existence of a dose-response threshold within the kidney. At low dose levels in rats, regardless of whether kidney weight was increased concurrently, there was further evidence of ongoing kidney toxicity (increased epithelial cells, blood, and protein in the urine, as well as kidney histopathology); these effects were observed as early as 90 days but extended to chronic durations of exposure. Within the same subchronic to chronic time frame, high dose levels of dithianon resulted in elevated blood urea nitrogen levels, indicating that kidney metabolism was also adversely affected. In addition, chronic high dose levels in female rats resulted in histopathological changes in the kidney that reflect a greater severity of tubular cell damage (multifocal), involving atypical cell division (nuclear enlargement, karyomegaly), abnormal cell cycle regulation (atypical tubule hyperplasia, proliferating tubules), and the formation of tubule epithelial cell tumours. The kidney tumours had no adverse impact on survival in females. In addition, there was no evidence of a decrease in the latency of tumour formation at a dose that closely approached the maximum tolerated dose (MTD).

With chronic dietary dosing in mice, effects on the kidney and thyroid were generally consistent with those observed in the rat. As in rats, kidney tubule effects in females were more pronounced at lower dose levels compared to males, but in both sexes there was no evidence of tumour formation in the kidney or elsewhere.

Dithianon tested negative for genotoxicity in a majority of assays, including two bacterial reverse mutation assays, a mammalian cell (lung fibroblasts, V79) gene forward mutation assay, in vitro and in vivo unscheduled DNA synthesis assays in rat hepatocytes, in vivo chromosomal aberration (bone marrow) and micronucleus assays in rats and mice. It also tested negative in one of two acute in vivo comet assays using rat kidney cells, and there was minimal evidence that dithianon could bind covalently to DNA in liver and kidney tissues in rats. Conversely, in the rat kidney there was evidence of considerable non-covalent interaction between DNA and dithianon, and/or its metabolites. In addition, dithianon produced positive results using an in vitro forward mutation assay in mammalian cells (V79) with metabolic activation, and using an in vitro chromosomal aberration assay (V79) with and without metabolic activation. Both of these positive in vitro results occurred at, or very near, the threshold for in vitro cytotoxicity. One of the two in vivo single-dose comet assays using rat kidney cells was positive, but only at doses that were demonstrably cytotoxic to the proximal tubule epithelium. Thus, under in vitro and in vivo conditions at sufficiently high concentrations, dithianon exhibited mutagenic and clastogenic potential.

There were limitations in the conduct of both comet assays. However, the positive assay was considered superior in design because the cell isolation technique (perfusion with collagenase digestion) and the positive control chemical, streptozotocin (STZ), were considered more appropriate for dithianon. The respective consequences of these study features were that the total population of cells investigated was considered more likely to have included the most susceptible kidney cells, those of the proximal tubule epithelium, and that this expectation was specifically confirmed via the STZ-induced positive response. In the kidney, STZ is expected to selectively induce cytotoxicity/genotoxicity and subsequent cell death (necrosis/apoptosis) only in the proximal tubule epithelium, due to the expression of the GLUT 2 isoform of the facilitative glucose transporter in these cells (PMRA# 2742222, 2742223, 2742228, 2742229). Importantly, the results of this study clearly demonstrate that dithianon's in vivo cytotoxic and genotoxic

potential were closely associated in the kidney; at sufficiently low doses, cytotoxicity occurred without evident genotoxicity, whereas genotoxicity never manifested in the absence of cytotoxicity. Thus, the apparent genotoxicity in this study is considered threshold-dependent and secondary to dithianon's cytotoxic effects. Overall, the weight of evidence did not suggest primary genotoxic potential for dithianon.

The results from specialized mechanistic studies in rats were sufficiently robust to support cytotoxicity-dependent regenerative hyperplasia as the probable causative MOA for the observed female-specific kidney tubule epithelial cell tumours. The initiating key event, cytotoxicity-induced death, is a compensable, threshold-dependent event. Key precursor events of the proposed tumourigenic MOA were temporally-, spatially- and dose-concordant with tumour formation. Male rats also exhibited the key initiating cytotoxicity, but affected kidney cells were distributed diffusely and there were no treatment-related tumours. In females, cytotoxicity and cell death appeared to more specifically affect the epithelium of the straight proximal tubules within the inner cortex. This region is where most of the tumours appeared to have formed. The tumours appear to result from a unique confluence of sex-specific exposure circumstances within the kidney, rather than from a primary or generalized genotoxic effect of dithianon. Although the tumours manifested at a dose level that was possibly nearing the MTD, cytotoxicity-induced cell death was evident at lower doses. Overall, the data supported the use of a threshold approach for the cancer risk assessment. The kidney tumours were considered relevant to humans.

In a 28-day gavage neurotoxicity study, rats exhibited increased piloerection and decreased rearing in both sexes at the end of the study at the highest dose tested (HDT). Decreased motor activity also occurred in males at the same dose level, together with decreases in body weight and food efficiency. Females dosed at this level had decreases in body weight gain and food consumption. Although decreased rearing and motor activity are potentially related to an effect on the nervous system, they may also manifest due to more general or indirect causes. Given the high level of dosing and lack of corroborative neurohistopathological change, there was insufficient evidence to conclude that dithianon was selectively neurotoxic. Finally, no other potential signs of neurotoxicity were noted in the toxicology database.

Following in utero exposure, where maternal animals received dithianon via gavage, developmental toxicity included increased early intra-uterine deaths and/or abortions and post-implantation loss in rats and rabbits, and increased pre-implantation loss in rabbits. Consequently, there were concomitant decreases in live fetuses per maternal animal in both species. There was no evidence of treatment-related malformations. In both species, the observed developmental toxicity occurred in the presence of decreased body weight, body weight gain and food consumption in maternal animals. In rats, fetal body weight was decreased at twice the dose at which this effect was observed in maternal animals. At dose levels higher than the maternal lowest observable adverse effect level (LOAEL) in rats, there were increased mortalities in dams as well as gross pathology in the stomach and intestines, including enlarged Peyer's patches and a severely reddened mucosa. Although some limitations were identified in the rabbit developmental toxicity study, it was considered acceptable.

In a two-generation dietary reproductive toxicity study in rats, there were no treatment-related effects on reproductive performance. The primary target organs (kidney, liver) were not weighed in this study and the kidney was not examined histologically, but these were adequately

investigated at comparable dose levels in other studies. Systemic toxicity observed in parental animals was consistent with those reported in other repeated-dose dietary studies in rats and included reductions in body weight, body weight gain and food consumption. No treatment-related effects were observed in the offspring of either generation.

Results of the toxicology studies conducted on laboratory animals with dithianon are summarized in Table 2 of Appendix I. The toxicology reference values for use in the human health risk assessment are summarized in Table 3 of Appendix I.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Diathianon is not registered for use in Canada or the United States. As such, there are no incident reports on file with the PMRA.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* (PCPA) requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies were available for risk assessment including gavage developmental toxicity studies in rats and rabbits and a dietary reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental/maternal animals in the dietary reproductive and gavage developmental toxicity studies. In the dietary reproductive toxicity study, parental animals exhibited bodyweight and food consumption effects at the HDT. At the same dose level, there were no evident effects in the offspring. In the developmental toxicity studies, there were increased early intra-uterine deaths and/or abortions and post-implantation loss in rats and rabbits, and increased pre-implantation loss in rabbits. In both species, these serious effects occurred in the presence of more generalized maternal effects (decreased body weight, body weight gain and food consumption); the maternal/developmental no observable adverse effect level (NOAEL) was lowest in rats. Thus, in both species a serious endpoint (increased fetal loss) was demonstrated in the presence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. There was a low level of concern for sensitivity of the young and effects on the young are well characterized. Although increased fetal loss in the developmental toxicity studies was considered a serious endpoint, concern for this finding was tempered by the fact that maternal toxicity was evident at the same dose level. Accordingly, the 10-fold PCPA factor was reduced to 3-fold for exposure scenarios using the toxicological endpoint from the rat developmental toxicity study. For all other exposure scenarios, the PCPA factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

Females 13-49 Years of Age

To estimate acute dietary risk, the developmental toxicity study in the rat with a maternal/developmental NOAEL of 20 mg/kg bw/day was selected. At the LOAEL of 50 mg/kg bw/day, an increase in early resorptions was observed, and maternal animals also appeared thin, had reduced body weights and food consumption. The possibility that the fetal loss could be the result of a single exposure could not be ruled out; this endpoint is therefore considered relevant to an acute risk assessment. An increase in early resorptions was also observed in the developmental toxicity study in the rabbit, but the NOAEL established in the rat study was lower. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. **Thus, the composite assessment factor (CAF) is 300.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (females 13-49)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{20 mg/kg bw/day}}{300} = 0.07 \text{ mg/kg bw}$$

General Population (excluding females 13-49 years of age)

To estimate acute dietary risk, the 7-day nephrotoxicity study in the rat with a NOAEL of 12 mg/kg bw/day was selected for risk assessment. At the LOAEL of 60 mg/kg bw/day, kidney tubule cellular damage was observed. These effects were evident as early as two days following dosing, and are therefore relevant to an acute risk assessment. Comparable cellular and subcellular damage, or immunohistological evidence of such damage, occurred in three single-dose studies at doses above the NOAEL established in the nephrotoxicity study. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. **Thus, the CAF is 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (general population)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{12 mg/kg bw/day}}{100} = 0.1 \text{ mg/kg bw}$$

3.3 Determination of Acceptable Daily Intake

To estimate risk from repeat dietary exposure to dithianon, the chronic dietary toxicity/oncogenicity study in the rat with a NOAEL of 1 mg/kg bw/day was selected for risk assessment. At the LOAEL of 6 mg/kg bw/day, evidence of kidney damage was observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. **Thus, the CAF is 100.**

The ADI is calculated according to the following formula:

$$ADI = \frac{NOAEL}{CAF} = \frac{1 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day}$$

The ADI provides respective margins of 600 and 2000 to the NOAELs for renal epithelial tumours and early resorptions observed in female rats.

Cancer Assessment

Kidney tubule epithelial cell tumours were observed in female rats administered a high dose of dithianon following chronic dosing. The proposed MOA for tumour formation was deemed plausible and was adequately supported by the data provided; dose and temporal concordance, as well as spatial concordance within the kidney, were considered adequately characterized and coherent. Although there was adequate evidence to support a threshold-based approach to risk assessment for the renal epithelial tumours in female rats, the human relevance of these tumours could not be discounted. The established toxicology reference values provide a sufficient margin to this tumour.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant commodities is dithianon. The data gathering/enforcement analytical methods are valid for the quantitation of dithianon residues in crop matrices. The residues of dithianon are stable in apples, pears, cherries and plums for 24 months, grapes for 21 months, and hops for 6 months when stored in a freezer at ≤-15°C. Therefore, adequate storage stability data are available to support the storage conditions and intervals in the field and processing trials. The raw agricultural commodities of apples, cherries, plums, grapes and dried hops were processed, and dithianon residues concentrated in raisins only (1.6x). Crop field trials conducted in Germany, France, Australia, the Netherlands, UK, Italy, Spain, Denmark, Belgium, and Greece using end-use products containing dithianon (at approved or exaggerated rates) in or on apples, pears, cherries (sweet and tart), plums, grapes and dried hops are sufficient to support the proposed MRLs.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 4.02, 05-10-c), which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey for the years 2005-2010 available through CDC's National Center for Health Statistics (NCHS).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the intermediate chronic analysis for dithianon: 100% crop treated, default and experimental processing factors (when available), and residues of the petitioned crops based on supervised trial median residue (STMdR) values. The intermediate chronic dietary exposure from all supported dithianon food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 15% of the ADI. The highest exposure and risk estimate is for children 1-2 years old at 45% (0.004446 mg/kg bw/day) of the ADI, which is not of health concern.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the intermediate acute analysis for dithianon: 100% crop treated, default and experimental processing factors (when available), and residues of the petitioned crops based on maximum residue values. The intermediate acute dietary exposure for all supported dithianon imported commodities was estimated to be 16% (0.011093 mg/kg bw/day) of the ARfD for females 13-49 years old (95th percentile, deterministic), and 9-62% of the ARfD for all other population subgroups (95th percentile, deterministic), which is considered acceptable.

3.5.3 Maximum Residue Limits

The recommendation for MRLs for dithianon was based upon the submitted field trial data from the exporting countries, and the guidance provided in the OECD MRL Calculator. MRLs to cover residues of dithianon in/on crops and processed commodities are proposed as shown in Table 3.1. Residues in processed commodities not listed in Table 3.1 are covered under the proposed MRLs for the raw agricultural commodities (RACs).

Table 3.1. Summary of Field Trial and Processing Data Used to Support Maximum Residue Limits (MRLs)

Commodity	Application Method/ Total Application Rate (kg a.i./ha)	PHI (days)	Residues (ppm)		Experimental Processing Factor	Recommended MRL (ppm)
			LAFT	HAFT		
Apples	Foliar broadcast/ 5.6-7.4	21	0.11	1.90	-	5
Pears	Foliar broadcast/ 13.6-22.3	21	1.71	3.67	-	8
Cherries (sweet and tart)	Foliar broadcast/ 1.5-1.6	13-14	0.08	1.50	-	3
Plums	Foliar broadcast/ 0.63-0.70	14-15	<0.02	0.13	-	0.5
Grapes	Foliar broadcast/ 3.5-4.5	41-43	0.25	7.36	Raisins (1.6x)	8 (RAC) 12 (Raisins)
Hops (dried)	Foliar broadcast/ 10.0-12.1	14	4.1	95.5	-	300

LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial

4.0 Environmental and Value Assessments

Environmental and value assessments were not required for this application.

5.0 Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided in support of this application.

The toxicology database submitted for dithianon is adequate to define the majority of toxic effects that may result from exposure. In short- and long-term studies with adult animals, the targets of toxicity were the kidney, liver, thyroid gland and red blood cells. There was no evidence of disregulation of the immune system, and no evidence that dithianon was selectively neurotoxic. In the rat reproductive toxicity study and in the developmental toxicity studies in rats and rabbits, there was no evidence of increased sensitivity of the young. In the developmental toxicity studies, increased fetal loss, considered a serious endpoint, was observed in the presence of maternal toxicity. There was no evidence of carcinogenicity in mice after longer-term dosing. Chronic dosing with dithianon resulted in kidney tumours in female rats. Based on the mechanistic data provided, a proposed MOA for kidney tumours in rats was considered plausible and was supported by the data. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residues in plants is adequately understood. The residue definition for enforcement is dithianon in plant products. The proposed use of dithianon on apples, pears, cherries (sweet and tart), plums, grapes and dried hops does not constitute a risk of concern for chronic or acute dietary exposure (food alone) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs on imported commodities. The PMRA recommends that the following MRLs be specified for residues of dithianon.

Commodity	**Recommended MRL (ppm)**
Hops (dried)	300
Raisins	12
Grapes, pears	8
Apples	5
Sweet cherries, tart cherries	3
Plums	0.5

List of Abbreviations

↑	increase
↓	decrease
♀	female
♂	male
#	number
∞	infinity
µg	micrograms
abs	absolute
AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ALT	alanine aminotransferase
ALK	alkaline phosphatase
ARfD	acute reference dose
AST	aspartate aminotransferase
AUC	area under the curve
BrdU	bromodeoxyuridine
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC/NCHS	Centers for Disease Control and Prevention/National Center for Health Statistics
CI	confidence interval
cm	centimetre(s)
CYP	cytochrome P-450 enzyme
DEEM-FCID	Dietary Exposure Evaluation Model-Food Commodity Intake Database
DNA	deoxyribonucleic acid
EAC	Ehrlich acites carcinoma cells
EM	electron microscopy
EMS	ethyl methanesulfonate
F_1	first generation
fc	food consumption
fe	food efficiency
g	gram(s)
G6PDH	glucose-6-phosphate dehydrogenase enzyme
GAPDH	glyceraldehyde-3-phosphate dehydrogenase enzyme
GC-ECD	gas chromatography with electron capture detection
gen	generation
GGT	gamma-glutamyl transferase
h	hour(s)
ha	hectare(s)
HAFT	Highest Average Field Trial
HCT	hematocrit
HDT	highest dose tested
HGB	hemoglobin

HK	hexokinase enzyme
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
i.p.	intraperitoneal
kg	kilogram(s)
KIM-1	kidney injury molecule-1
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LAFT	Lowest Average Field Trial
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
mg	milligram(s)
mL	millilitre(s)
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MOA	mode of action
MRL	maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
NCE	normochromatic erythrocytes
NHANES/WWEIA	National Health and Nutritional Exam Survey/What We Eat in America
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OSOM	outer stripe of the outer medulla of the kidney
P	parental generation
Pa	Pascal(s)
PC	positive control
PCE	polychromatic erythrocytes
PCPA	*Pest Control Products Act*
PCV	packed cell volume
PHI	preharvest interval
p*K*a	dissociation constant
PLT	platelet cell count
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RAC	raw agricultural commodity
RBC	red blood cell
rel	relative
RER	rough endoplasmic reticulum
Rf	retention factor (relative migration distance using TLC)
RQ	respiratory quotient
S1	segment 1 (convoluted) of kidney proximal tubule
S2	segment 2 (transitional) of kidney proximal tubule
S3	segment 3 (straight, pars recta) of kidney proximal tubule
S9	supernatant fraction nine (metabolic activator agent)
STMdR	supervised trial median residue

STZ	streptozotocin
T_3	tri-iodothyronine
T_4	thyroxine
TH	testosterone hydroxylase
TLC	thin layer chromatography
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
UV	ultraviolet
WBC	white blood cell
wc	water consumption
wk	week
wt	weight

Appendix I Tables and Figures

Table 1 Metabolite Identification

Metabolite Identifier	Chemical name
M216F004	partially saturated thiazine-derivative of parent compound
M216F008	partially saturated, carboxy substituted, thiazine-derivative of parent compound
M216F012	2-amino-(1,4)-naphthoquinone
M216F013	2-sulfonato-3-acetoamido-1,4-dihydroxynaphthalene
M216F020	glucuronide of 1,4-dihydroxynaphthalene
M216F026	glucuronide of the hydroquinone of parent compound
M216F028	glucuronide of the hydroquinone of parent compound
M216F029	maleonitrile sulfonic acid
M216F030	S-methyl-dimercaptomaleonitrile
M216F031	S-methyl-dimercaptofumaronitrile (E-isomer of M216F030)
M216F036	isomeric glucuronide of 2-acetoamido-1,4-dihydronaphthalene
M216F037	isomeric glucuronide of 2-acetoamido-1,4-dihydronaphthalene
M216F038	glucuronide of the hydroquinone of parent compound
M216F039	1-sulfato-4-hydroxynaphthalene

Table 2 Toxicity Profile of Technical Dithianon

[Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects observed above the LOAEL(s) as well as non-adverse effects observed below the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.]

Study Type/ Animal/ PMRA#	Study Results

Study Type/ Animal/ PMRA#	Study Results
Excretion, metabolism (gavage, preliminary, 2007) Rat, Sprague-Dawley PMRA# 2493485	Rats were administered a single oral dose of 50 mg/kg bw (high dose) of quinone-labelled dithianon (5(10)-label; ^{14}C and ^{13}C). Excretion: Excretion was rapid and nearly complete within 48-72 h (>95% AD at 72 h). It occurred primarily via the feces (~69% AD), and to a lesser extent via the urine (~28% AD), regardless of the sex. Metabolism: Dithianon degrades rapidly and was not detected in the excreta. In the feces, most likely due to alkaline hydrolytic instability/reactivity of dithianon and its metabolites, there were a very large number of minor metabolites/degradates. In the urine, there was a single main transformation product (>15% AD, a glucuronic acid metabolite, identified as M216F020 in PMRA# 2493486). Except for M216F20 in the urine, metabolites/degradates were less than 5% AD, regardless of the sex and sampling interval. The major transformation reactions included: 1) ring cleavage, 2) oxidation/reduction, 3) reaction with nucleophiles, 4) subsequent conjugation. Supplemental

Study Type/ Animal/ PMRA#	Study Results
Distribution, excretion, metabolism (gavage, 2009) Rat, Sprague-Dawley PMRA# 2493486	Rats were administered a single oral dose of 10 mg/kg bw (low dose) or 50 mg/kg bw (high dose) of quinone-labelled dithianon (5(10)-label; ^{14}C and ^{13}C). No major differences were observed in absorption, excretion (kinetics and recoveries), or metabolism (metabolite patterns and pathway) according to the sex or the dose level, where such comparisons could be made. Absorption: Not assessed quantitatively, but apparently rapid and estimated to be ~40% AD. Distribution: The TRR at 6 h was quantified in the liver (~0.1-0.3% AD, 0.82-2.0 mg/kg TRR), kidneys (~0.1-0.4% AD, 5.7-8.4 mg/kg TRR), plasma (~0.03-0.1% AD, 1.4-3.4 mg/kg TRR); comparatively low TRR occurred in bone marrow. There were no major dose- or sex-related differences in the reported TRRs. Excretion: Excretion was rapid and nearly complete within 48-72 h (>95% AD at 72 h). It occurred primarily via the feces (~69% AD), and to a lesser extent via the urine (~28% AD), regardless of the sex. Metabolism: Dithianon was extensively metabolized, likely as a consequence of its reactive structure. Key transformation steps were thought to include 1) oxidation of the sulphur atoms, 2) cleavage of the dithiine ring, 3) reduction of the 1,4-naphthoquinone moiety and further glucuronidation, as well as 4) substitution of the carbonitrile moieties by amino and carboxy groups. Identified metabolites were from fractions extracted using acetonitrile. In the urine, the most predominant metabolite was M216F020 (9-10% AD, a glucuronic acid derivative of the (1,4)-dihydroxylated naphthalene moiety). Another 18 minor to negligible metabolites, of varying polarity, were identified in urine (<1-2% AD). A majority lacked the dithiine ring moiety of dithianon. In the feces, five metabolites dominated (of ~30 total extracted), but all were quantitatively minor (<1% AD). Nine other quantitatively negligible metabolites were identified, but many others were not identified; most were characterized as being polar to semi-polar. The most predominant feces metabolite was M216F012 (0.4-0.6% AD, 2- amino-(1,4)-naphthoquinone). A significant fraction of total radioactivity appeared tightly bound in the feces, as it was difficult to extract using various additional methods. A huge number of metabolites, with a broad range of polarity, were detected among the extracted radioactivity, but no unchanged parent was detected. In the liver, numerous metabolites occurred (8 identified) but none predominated; there was a qualitative overlap with metabolites identified in feces. In the kidney, there were numerous metabolites (8 identified) but

Study Type/ Animal/ PMRA#	Study Results
Excretion kinetics and radioactive residue levels in blood plasma and bone marrow (gavage, 2009) Rat, Sprague-Dawley PMRA# 2493487	♀ rats were administered a single oral dose of 9.8 mg/kg bw (low dose) or 8.3 mg/kg bw (low dose) of quinone-labelled (5(10)-label; ^{14}C) or dithiine-labelled (2,3-cyano-label; ^{14}C) dithianon, respectively. Absorption: Rapid Excretion: Rate and extent of excretion via urine was greater for 2,3-cyano label than 5(10) label. For the 5(10) label 59% AD was excreted within 24 h (34% AD urine, 26% AD feces). For the 2,3-cyano label 84% AD was excreted within 24 h (63% AD urine, 21% AD feces). At 24 h, the TRR levels were low in blood plasma (≤ 0.05% AD) and bone marrow (≤ 0.0004% AD) regardless of the label. Samples obtained in this study were investigated further in a metabolism study (PMRA# 2633539) and in a DNA binding study (PMRA# 2493484)

Study Type/ Animal/ PMRA#	Study Results
Metabolism (gavage, 2010) Rat, Sprague-Dawley PMRA# 2633539	♀ rats were administered a single oral dose of 9.8 mg/kg bw (low dose) or 8.3 mg/kg bw (low dose) of quinone-labelled (5(10)-label; ^{14}C) or dithiine-labelled (2,3-cyano-label; ^{14}C) dithianon, respectively. Metabolism: Extensive, with very few major metabolites, many minor metabolites, and fractions which were partially characterized according to polarity. In the urine (0-24h) there were three predominant metabolites, M216F020 (14% AD, 5(10)-label), M216F030 (37% AD, 2,3-cyano label) and M216F029 (12% AD, 2,3-cyano label) with individual remaining metabolites generally accounting for ≤ 3% AD, regardless of the label. Identification of 5(10) and 2,3-cyano labelled metabolites was 20% and 54% AD, respectively. Partial characterization of 5(10) and 2,3-cyano-labelled metabolites was 14% (mostly semi-polar substances) and 8% AD (mostly polar), respectively. The only metabolite common to the 5(10) and 2,3-cyano labels was M216F038 (0.9% AD and 0.4% AD, respectively). In the feces (0-24 h) there were many 5(10)-labelled metabolites (46 as HPLC peaks, each < 2% AD), with the two most predominant peaks identified as M216F004 (1.2% AD) and M216F008 (0.8% AD). There were also many unidentified 2,3-cyano-labelled metabolites (44 as HPLC peaks, each < 0.6% AD, wide range of polarity), with one predominant peak (2.6% AD, not identified). Only trace amounts of unchanged dithianon were identified. Identification of 5(10)- and 2,3-cyano-labelled metabolites was 2% and 0% AD, respectively. Characterization of 5(10)- and 2,3-cyano-labelled metabolites was 12% (mostly semi-polar to non-polar substances) and 12% AD (mostly non-polar), respectively. Overall, for the 0-24 h urine and feces combined, identification of labelled metabolites was 76% AD and all but 13% of this was accounted for by the three main urine metabolites. In the plasma, none of the metabolites at 24 h post-dose was quantitatively significant in terms of % AD. The main transformations included 1) cleavage of dithiine ring to dimercaptomaleonitrile followed by 2) S-methylation (M216F030 and E-isomer, M216F031, trace), or 3) thiol oxidation to maleonitrile sulfonic acid (M216F029, dithiine ring degradate), 4) reduction of the naphthoquinone moiety and subsequent glucuronidation (M216F020) or sulfation (M216F039, trace). Minor transformation products of the 1,4-dihydroxynaphthalene moiety, bearing an acetamido group, were identified; they include two isomeric glucuronides (M216F036 and M216F037) and the sulphonate of 3-acetamido-1,4-dihydroxynaphtalene (M216F013). A partially saturated carboxy-substituted thiazine-derivative of the parent (M216F008), and a corresponding decarboxylated metabolite (M216F004) were also identified as minor metabolites. In addition, reduction and glucuronidation of the naphthoquinone moiety of uncleaved dithianon (M216F026);

Study Type/ Animal/ PMRA#	Study Results
Absorption, metabolism, distribution, excretion (gavage, 1989) Rat, Sprague-Dawley PMRA# 2493491, 2493490	Rats were administered a single oral dose of 10 mg/kg bw (low dose) or 50 mg/kg bw (high dose), or repeated (14 days) oral doses of 10 mg/kg bw of quinone labelled (5,6,9,10-label; ^{14}C) dithianon. Absorption: Absorption was rapid, but incomplete. Based on biliary excretion information ~57 to 72% of total fecal excretion was inferred to be unabsorbed dithanon and/or its transformation products. After single oral doses, mean peak plasma concentrations occurred at 6 h in both sexes and declined thereafter, regardless of the dose. Mean terminal half-lives were 55.8/56.8 h (♂/♀, low dose) and 46.4/ 56.7 h (♂/♀, high dose). The $AUC_{0-\infty}$ values were 24 to 35% greater in ♀ compared to ♂, regardless of the dose level. This indicates that the effective systemic dose likely was slightly greater in ♀ than in ♂. Excretion: Elimination was rapid and complete. Essentially, no radioactivity was eliminated via expired air (<0.05% AD). In general, after a single oral dose at 10 or 50 mg/kg bw, broadly similar proportions of radioactivity was excreted via the urine (~31% AD) and feces (~66% AD), regardless of the sex; elimination was approximately 97% complete within 48 h for both routes. An exception to this occurred in high dose canulated animals, in which there was diminished urinary excretion in ♀ compared to ♂ (33/24% AD, ♂/♀). Generally, after a single oral dose, biliary excretion was approx. 7-12% AD in ♂ and ♀. The pattern of excretion in ♂ for single and repeated low doses was essentially the same. In contrast, with repeated dosing, ♀ exhibited slightly greater reliance on fecal elimination (~72% AD) and a correspondingly diminished reliance on urine elimination (~27% AD); likely this reflects enhanced reliance on adaptive hepatic elimination via the biliary route, rather than diminished absorption. Distribution: After a single oral low dose, the highest absolute tissue concentrations (µg equivalents/g or mL) of radioactivity occurred at 6 h post-dose (gastrointestinal tract: 97/110, ♂/♀; kidneys: 2.7/2.0, ♂/♀; plasma: 0.76/0.75, ♂/♀); the kidney in both sexes, and the thyroid gland in ♂, were the only organs/tissues which had maximum concentrations of absorbed radioactivity that exceeded peak levels in the blood plasma. Concentrations of radioactivity in most tissues and organs diminished rapidly with time and generally according to blood plasma kinetics. Exceptions to this general pattern of elimination included the kidneys, thyroid gland, bone marrow, adrenal glands and whole blood in both sexes, as well as the ovary; these organs and tissues exhibited slower tissue-specific elimination kinetics compared with that of the blood plasma. At 120 h after a single high dose, retention in the kidneys and thyroid gland was approximately 4-fold and 8-fold higher, respectively, compared to the low dose results. Nevertheless, radioactivity at 168 h after a single low dose of dithianon was below the limit of detection in most organs and

Study Type/ Animal/ PMRA#	Study Results
Metabolism, excretion (gavage, 1994) Rat, Sprague-Dawley PMRA# 2493488, 2493489 (amendment)	Rats were administered a single oral dose of 50 mg/kg bw (high dose) of quinone labelled (5,6,9,10-label; ^{14}C and ^{13}C) dithianon. Clinical signs: diarrhea (0 - 24 h) Excretion: Most of the urinary radioactivity was excreted between 6-24 h post-dose (15/12% AD ♂/♀); 0-24 h post-dose fecal amounts represented 49/27% AD ♂/♀. Recoveries (86/70% AD ♂/♀) were lower than the precedent study due to diarrhea from 0-24 h. Metabolism: Dithianon degradation was rapid and complete. There were large numbers of minor, mostly polar, degradates. A small number were identified, including 2-amino-1,4-naphthoquinone and 4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-2,3-dicarbonitrile, and a penta-fluorobenzyl conjugate of 2-hydroxy-3-mercapto-1, 4-naphthoquinone. The proposed metabolic steps included cleavage of the dithiine ring between positions 3 and 4, 4 and 4' and their symmetrical counterparts by nucleophilic agents, possible hydroxylation in different positions of the phenyl ring and the different degrees of oxidation of the sulfur atoms, resulting in a variety of reactive polar products. As there were apparently no preferential pathways, a plurality of products were formed which all appear to occur in trace amounts only. There were no apparent sex-related differences in metabolism or excretion.
Acute oral (gavage, 2005) Rat, Wistar PMRA# 2493416	LD_{50} (♀) = 300 mg/kg bw High toxicity ≥300 mg/kg: impaired and poor general state, dyspnoea, staggering, piloerection, smeared fur and diarrhea observed from 1 h post-dose until study day 6 after administration (♀)
Acute oral (gavage, 1987) Rat, Wistar PMRA# 2493418, 2493417 (amendment)	LD_{50} (♂/♀) = 702 mg/kg bw (95% CI: 528-1015 mg/kg bw) LD_{50} (♂) = 720 mg/kg bw (95% CI: 597-893 mg/kg bw) LD_{50} (♀) = 678 mg/kg bw/day (95% CI: 557-1171 mg/kg bw) Moderate toxicity ≥600 mg/kg bw: bw, sedation and ruffled fur with increased incidence, dyspnea, curved body position, diarrhea, emaciation

Study Type/ Animal/ PMRA#	Study Results
28-day oral (dietary, range-finding, 1987) Mouse, CD-1 PMRA# 2493438	NOAEL and LOAEL were not established as study was considered supplemental. ≥75 mg/kg bw/day: ↓ T_3; ↓ T_4 (♂); ↓ HGB, PCV, ↑ kidney wt, ↑ iron deposition in Kupffer cells of liver (♀) 150 mg/kg bw/day: ↓ bw, bwg (wk 0-1), fc (wk 1), HGB, PCV, MCH; ↓ T_4, ↑ liver wt, kidney wt (rel. only) (♀) Study was considered supplemental as several parameters were not evaluated.
28-day oral (dietary, range-finding, 1966) Rat, Sprague-Dawley PMRA# 2493439	NOAEL and LOAEL were not established as study was considered supplemental. ≥125 mg/kg bw/day: inappetence, growth suppression, empty alimentary canals, lung congestion 500 mg/kg bw/day: mortality, clinical signs (piloerection, alopecia, dyspnea, torpor, ptosis) Study was considered supplemental as several parameters were not evaluated.
90-day oral (dietary, 1987) Rat, Sprague-Dawley PMRA# 2493432, 2493430, 2493431, 2493440	NOAEL = 15/3.0 mg/kg bw/day (♂/♀) LOAEL = 87/16 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, bwg, terminal bw, ↓ RBC, HCT, HGB, ↑ reticulocytes, WBC, ↓ T_3, T_4 , ↑ TSH, blood urea, total protein, albumin, globulin, α1-globulin, adrenal wt, thyroid wt (♂); ↑ kidney wt (♀) Effects that persisted following a 4-week recovery period: ↓ RBC; ↓T_4 (♂); ↑ kidney wt, adrenal wt (♀)
90-day oral (dietary, 1989) Dog, Beagle PMRA# 2493436, 2493434, 2493435, 2493437	NOAEL = 3.0 mg/kg bw/day LOAEL = 13 mg/kg bw/day Effects at the LOAEL: ↓ glucose, ↑ ALK, liver wt, kidney wt, ↓ thymus wt; ↓ bw, fc, ↑ T_4 (♀)

Study Type/ Animal/ PMRA#	Study Results
52-week oral (dietary, 1987) Dog, Beagle PMRA# 2493433	NOAEL (♂) = 5.2 mg/kg bw/day LOAEL (♂) = 27 mg/kg bw/day Effects at the ♂ LOAEL: ↓ fc, ↓ RBC, HGB, PCV, ↑ PLT, codocytes, ALK, AST, ALT, ↑ liver wt, thyroid wt, kidney wt, hepatocellular hypertrophy (clear or lacey cytoplasm), intranuclear eosinophilic inclusions and sinusoidal foci of pigmented histiocytes in liver (iron-positive), severity of proximal tubular cell pigment (fine brown granules) in kidney, ↑ thyroid wt with lymphocytic thyroiditis NOAEL (♀) = 1.9 mg/kg bw/day LOAEL (♀) = 9.6 mg/kg bw/day Effects at the ♀ LOAEL: ↓ RBC, HGB, PCV, ↑ blood in urine, ↓ urine specific gravity, ↑ liver wt, kidney wt, ↑ hepatocellular hypertrophy (clear or lacey cytoplasm), ↑ proximal tubular cell pigment (fine brown granules) in kidney
80-week oral (dietary, oncogenicity, 1990) Mouse, CD-1 PMRA# 2493442	NOAEL (♂) = 15 mg/kg bw/day LOAEL (♂) = 75 mg/kg bw/day Effects at the ♂ LOAEL: ↓ survival, ↑ fur staining, water consumption, kidney wt, rel thyroid wt, kidney cortical cysts, kidney infarcts, chronic nephrosis of cortical tubules of kidneys (dilated tubules with flocculent material) NOAEL (♀) = 3 mg/kg bw/day LOAEL (♀) = 15 mg/kg bw/day Effects at the ♀ LOAEL: ↑ kidney wt, chronic nephrosis of cortical tubules of kidneys (dilated tubules with flocculent material) No evidence of oncogenicity.
104-week oral (dietary, combined chronic toxicity/oncogenicity, 1991) Rat, Sprague-Dawley PMRA# 2493441	NOAEL ~1 mg/kg bw/day LOAEL ~6 mg/kg bw/day Effects at the LOAEL: ↑ proteinuria, blood in urine; ↑ GGT (♂); ↑ eosinophilic inclusions (degraded renal tubule epithelial cells), epithelial cells in urine, tubular nephrosis, basophilic tubules, atypical tubule hyperplasia, glomerulonephropathy (♀) Evidence of oncogenicity (renal epithelial tumours in ♀ at the HDT of 30 mg/kg bw/day, which was approaching but did not exceed the MTD.)

Study Type/ Animal/ PMRA#	Study Results
Two-generation reproductive toxicity (dietary, 1991) Rat, Sprague-Dawley PMRA# 2633528	Parental NOAEL = 13/16 mg/kg bw/day (♂/♀) Parental LOAEL = 39/47 mg/kg bw/day (♂/♀) Effects at the parental LOAEL: ↓ bw, bwg (F_1 gen premating), fc (P, F_1 gen premating); ↓ bw, bwg, (P gen premating and mating) (♂); ↓ bwg (P gen lactation), fc (P, F_1 gen gestation) (♀) Reproductive NOAEL = 39/47 mg/kg bw/day (♂/♀) Reproductive LOAEL was not established. No treatment-related reproductive toxicity was observed. Offspring NOAEL = 47 mg/kg bw/day (♀) Offspring LOAEL was not established. No treatment-related offspring toxicity was observed.
Developmental toxicity (gavage, preliminary, 1989) Rat, Sprague-Dawley PMRA# 2493452, 2493451	NOAELs and LOAELs were not established as study was considered supplemental. Maternal effects: ≥40 mg/kg bw/day: ↓ live fetuses/dam (slight) ≥70 mg/kg bw/day: ↓ bwg (slight), ↑ post-implantation loss 100 mg/kg bw/day: ↓ bw, ↑ wc, excessive urination Developmental effects: 100 mg/kg bw/day: ↓ fetal wt Supplemental
Developmental toxicity (gavage, 1991) Rat, Sprague-Dawley PMRA# 2493453	Maternal NOAEL = 20 mg/kg bw/day Maternal LOAEL = 50 mg/kg bw/day Effects at the maternal LOAEL: thin appearance, ↓ bw, bwg, fc, ↑ post-implantation loss, early intra-uterine deaths/abortions, ↓ live fetuses/dam Developmental NOAEL = 20 mg/kg bw/day Developmental LOAEL = 50 mg/kg bw/day Effects at the developmental LOAEL: ↑ post-implantation loss, early intra-uterine deaths/abortions, ↓ live fetuses/dam Evidence of developmental toxicity / serious endpoint (fetal loss) in the presence of maternal toxicity.

Study Type/ Animal/ PMRA#	Study Results
Developmental toxicity (gavage, preliminary, 1989) Rabbit, New Zealand White PMRA# 2493455, 2493454	NOAELs and LOAELs were not established as study was considered supplemental. Maternal effects at 40 mg/kg bw/day: ↓ bw, bwg, fc, wc, ↑ abortions, total intra-uterine death, ↓ litter wt, total number live fetuses, ↑ total number intrauterine deaths, early resorptions, post-implantation loss Developmental effects at 40 mg/kg bw/day: ↑ total intra-uterine death, ↓ litter wt (due to smaller litter size), total number live fetuses, ↑ total number intrauterine deaths, early resorptions, post-implantation loss Supplemental
Developmental toxicity (gavage, 1990) Rabbit, New Zealand White PMRA# 2633538	Maternal NOAEL = 25 mg/kg bw/day Maternal LOAEL = 40 mg/kg bw/day Effects at the maternal LOAEL: ↓ bw, bwg, fc, ↑ abortions, ↑ pre- and post-implantation loss, ↓ number fetuses/doe Developmental NOAEL = 25 mg/kg bw/day Developmental LOAEL = 40 mg/kg bw/day Effects at the developmental LOAEL: ↑ post-implantation loss, ↓ number fetuses/doe Evidence of developmental toxicity / serious endpoint (fetal loss) in the presence of maternal toxicity.
28-day oral neurotoxicity (gavage, 2003) Rat, Wistar PMRA# 2493450	NOAEL = 15 mg/kg bw/day LOAEL = 30 mg/kg bw/day Effects at the LOAEL: dark discoloured urine, urine staining of anogenital region Effects at the next higher dose of 60 mg/kg bw/day: ↑ piloerection, ↓ bwg, fc, rearing; ↑ salivation, ↓ bw, fe, motor activity (♂) No evidence of selective neurotoxicity

Study Type/ Animal/ PMRA#	Study Results
7-day oral (dietary, 2009) study of kidney S-phase cell cycle histopathology and immunochemistry response in ♂ Rat, Sprague-Dawley PMRA# 2493496, 2493502	NOAEL not established as study was considered supplemental. Only ♂ investigated in this study. KIM-1 was investigated at the high dose only. ≥6.5 mg/kg bw/day: ↓ fc, ↑ basophilic tubules in renal cortex, cell proliferation (BrdU, diffuse only, OSOM region only), apoptosis (TUNEL positive, renal cortex), ↓ apoptosis (TUNEL positive, OSOM region) 33 mg/kg bw/day: ↓ bwg, cell proliferation (BrdU, cortex region), ↑ KIM-1 expression (similar extent in whole kidney, cortex and OSOM) Supplemental.
7-day oral (dietary, 2009) study of kidney S-phase cell cycle histopathology and immunochemistry response in ♀ Rat, Sprague-Dawley PMRA# 2493498, 2493500	NOAEL not established as study was considered supplemental. Only ♀ investigated in this study. KIM-1 was investigated at the high dose only. ≥8.0 mg/kg bw/day: ↓ fc, ↑ kidney wt 41 mg/kg bw/day: ↓ bwg, fe, ↑ liver wt, multifocal vacuolar degeneration (proximal tubule epithelial cells, OSOM and cortex), cell proliferation (BrdU, band-like, stripe-like or spot-like patterns, OSOM and cortex regions, OSOM > cortex), KIM-1 protein expression (cortex > whole kidney or OSOM) Supplemental.
28-day oral (dietary, 2009) study of kidney S-phase cell cycle histopathology and immunochemistry response in ♂ Rat, Sprague-Dawley PMRA# 2493495, 2493501	NOAEL not established as study was considered supplemental. Only ♂ investigated in this study. ≥6.8 mg/kg bw/day: ↑ kidney wt, basophilic tubules in renal cortex, cell proliferation (BrdU, diffuse only, OSOM region only), apoptosis (TUNEL, OSOM > cortex) 34 mg/kg bw/day: ↑ liver wt Supplemental.

Study Type/ Animal/ PMRA#	Study Results
28-day oral (dietary, 2009) study of kidney S-phase cell cycle histopathology and immunochemistry response in ♀ Rat, Sprague-Dawley PMRA# 2493497, 2493499	NOAEL not established as study was considered supplemental. Only ♀ investigated in this study. KIM-1 was investigated at the high dose only. ≥8.2 mg/kg bw/day: ↓ bwg, fc 44 mg/kg bw/day: ↓ bw, fe, terminal bw, ↑ kidney wt, multifocal vacuolar degeneration (proximal tubule epithelial cells, OSOM and cortex), cell proliferation (BrdU, diffuse and stripe-like pattern, OSOM and cortex), apoptosis (TUNEL, cortex > OSOM), KIM-1 protein expression (cortex > whole kidney or OSOM) Supplemental.
7-day oral (dietary, 1991) nephrotoxicity study of histopathology using light and electron microscopy Rat, Sprague-Dawley PMRA# 2493505	NOAEL = 12 mg/kg bw/day LOAEL = 60 mg/kg bw/day Effects at the LOAEL: ↑ kidney wt, pale/discoloured kidney, mitochondrial damage within single proximal tubule cells (small focal lesions of minimal severity, 2 days via EM only, ♀>♂), swollen mitochondria and intercellular edema (proximal cells, days 4 and 7, ♀>♂), hydropic degeneration in proximal tubular cells (days 4 and 7, ♀>♂), foci of basophilic tubules (day 7, ♀>♂); ↑ dilated RER and some nuclear degeneration (days 4 and 7), 'lipofuscin' type granules (proximal tubule cells, day 4), lysosomes with inclusions of osmiophilic material (proximal tubule cells, day 7) (♀)
28-day oral (dietary, 1993) study of renal cell proliferation in ♀ Rat, Sprague-Dawley PMRA# 2493504	NOAEL not established as study was considered supplemental. Only ♀ investigated in this study. ≥2 mg/kg bw/day: ↑ kidney discolouration (as combined incidences, 7 to 28 days) ≥12 mg/kg bw/day: ↑ kidney wt (rel day 7; day 14), cell proliferation (BrdU), hydropic degeneration (swollen cells, pyknotic nuclei, S2 segment of proximal tubules) 60 mg/kg bw/day: ↑ kidney wt (abs day 7 and 28), basophilic tubules (combined incidences, 7 to 28 days) Supplemental.

Study Type/ Animal/ PMRA#	Study Results
Acute oral (gavage, 2011) study of kidney cytotoxicity and histopathology Rat, Sprague-Dawley PMRA# 2493481	NOAEL not established as study was considered supplemental. ≥50 mg/kg bw: ↑ KIM-1 expression in OSOM and whole kidney (♀ > ♂) ≥100 mg/kg bw: piloerection, lethargy ≥200 mg/kg bw: ↑ diarrhea, bw loss, minimal-moderate tubular degeneration in kidneys; ↓ bw (♂) 300 mg/kg bw: 1 mortality/sex, ↑ KIM-1 expression in cortex of kidney (♀ > ♂); ↓ bw (♀) Supplemental.
Acute oral (gavage, 2009) study of the potential for DNA binding in the liver and kidney in ♀ Rat, Sprague-Dawley PMRA# 2493484	NOAEL not established as study was considered supplemental. ♀ rats were administered a single oral dose of 9.8 mg/kg bw or 8.3 mg/kg bw (low doses) of quinone-labelled (5(10)-label; ^{14}C) or dithiine-labelled (2,3-cyano-label; ^{14}C) dithianon, respectively. (Samples from PMRA# 2493487). 8.3 or 9.8 mg/kg bw: Negative. There was minimal evidence of covalent binding to DNA in liver and kidney* tissues at the dose levels investigated. The PC (acetylaminofluorene) induced a high level of covalent binding to DNA. *Although covalent binding to DNA is unlikely based on the results of this study, there appeared to be a considerable degree of non-covalent interaction between dithianon and DNA and/or chromatin protein in the kidney. Supplemental.
Bacterial reverse mutation assay (1986) S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 PMRA# 2493458, 2493457	Negative Tested up to cytotoxic concentrations.

Study Type/ Animal/ PMRA#	Study Results
Bacterial reverse mutation assay (1987) S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 PMRA# 2493460, 2493459	Negative Tested up to cytotoxic and precipitating concentrations.
In vitro mammalian cell gene forward mutation assay in V79 lung fibroblasts (1993) Hamster, Chinese PMRA# 2493462, 2493461	Positive Tested up to cytotoxic concentrations. Without activation (-S9) in 1 of 3 experiments at 1.33 µg/mL (markedly cytotoxic concentration, relative cloning efficiency = 1%). With activation (+S9) in 2 of 4 experiments at ≥1.00 µg/mL in the absence of excessive cytotoxicity.
In vitro mammalian cell gene mutation assay in V79 lung fibroblasts (1984) Hamster, Chinese PMRA# 2493466, 2493465, 2493467	Negative Tested up to cytotoxic concentrations.
In vitro Chromosome aberration assay in V79 lung fibroblasts (1988) Hamster, Chinese PMRA# 2493469, 2493468	Positive Tested up to cytotoxic concentrations. Cytotoxicity greater in absence than in presence of S9. ±S9 (7, 18 h, non-excessive to possibly excessive cytotoxicity, based on mitotic index), +S9 (28 h fixation, non-excessive cytotoxicity, based on mitotic index).

Study Type/ Animal/ PMRA#	Study Results
In vitro unscheduled DNA synthesis assay in hepatocytes (1986) Rat, Wistar PMRA# 2493472, 2493470, 2493471	Negative Tested up to cytotoxic concentrations.
In vivo acute oral bone marrow chromosome aberration assay (gavage, 1990) Rat, Wistar PMRA# 2493475, 2493474	Negative Tested up to the MTD, as determined in a pre-test Effects at 394 mg/kg bw included a reduction of the spontaneous activity, eyelid closure and apathy (♂/♀)
In vivo acute oral unscheduled DNA synthesis assay in hepatocytes (gavage, 2009) Rat, Wistar PMRA# 2493480	Negative (♀, only) Effects at 36 mg/kg bw included clinical signs (diarrhea)
In vivo acute oral micronucleus assay in bone marrow (gavage, 2009) Rat, Wistar PMRA# 2493473	Negative Effects ≥50 mg/kg bw/day included severe clinical signs (piloerecetion, hunched posture, irregular respiration and diarrhea) within 4-6 h post-dose Effects at 75 mg/kg bw/day included ↓ PCE/NCE ratio at 6 and 24 h (♀)
In vivo acute oral micronucleus assay in bone marrow (gavage, 1984) Mouse, NMRI PMRA# 2493476	Negative Tested up to a dose resulting in clinical signs of overt toxicity. Exposure to bone marrow was not confirmed. Effects at 100 mg/kg bw included clinical signs (dyspnoea, ptosis, diarrhea, ↓ activity); ↓ bw (♂)

Study Type/ Animal/ PMRA#	Study Results
In vivo acute oral comet assay in rat kidney cells (gavage, 2009) Rat, Wistar PMRA# 2493479, 2493478, 2493483, 2733094	Positive (secondary to cytotoxicity) Genotoxicity occurred only at doses (≥50 mg/kg bw) that also produced cytotoxicity within the kidney proximal tubule epithelium. At a sufficiently low dose (25 mg/kg bw/day) cytotoxicity was evident in the absence of genotoxicity. 1st comet experiment: Effects at 50 mg/kg bw: ↑ tail intensity at 24 h, ↑ clinical signs (piloerection, hunched posture, irregular respiration) (♀) 2nd comet experiment: Effects at 50 and 75 mg/kg bw: ↑ tail intensity at 24 h, ↑ clinical signs (piloerection, hunched posture, irregular respiration) (♀) 3rd comet experiment: Effects at 75 mg/kg bw: ↑ tail intensity at 24 h (incidence > concurrent negative control) Streptozotocin (STZ) and ethyl methanesulfonate (EMS) induced positive responses. Concurrent cell pathology / cytotoxicity (EM) at 24 h: ≥25 mg/kg bw: ↑ proximal tubular epithelial cell degenerative lesions in single cells (mitochondria - slightly to moderately enlarged and swollen with a primarily involvement of inner chamber/matrix, matrix -decreased density due to matrix dilution, with cristae reduced in number, shortened, disorientated and displaced to the periphery), ↑ signs of cell organelle degradation (whorled membranous bodies with myelin figures in single tubular epithelial cells) (♀) ≥50 mg/kg bw: ↑ proximal tubular epithelial cell dilation of cytoplasmic tubular system in single cells (cytoplasmic vacuolation) 75 mg/kg bw: ↑ clinical signs (piloerection, irregular respiration, diarrhea) (♀)

Study Type/ Animal/ PMRA#	Study Results
In vivo acute oral comet assay in rat kidney cells (gavage, 2011) Rats, Sprague-Dawley PMRA# 2493482, 2733095	Negative Ethyl methanesulfonate (EMS) induced a positive response. ≥50 mg/kg bw: diarrhea, ↓ fc, urine volume; ↑ kidney wt (24 h) (♂); ↓ wc, ↑ KIM-1 expression (OSOM, 6 and 24 h) (♀) ≥100 mg/kg bw: piloerection, ↓ bw (7-8%); ↓ wc, ↑ kidney wt (6 h), ↑ KIM-1 expression (OSOM, 24 h) (♂) 200 mg/kg bw: lethargy; slight tubular degeneration in renal cortex (♀)
In vitro mechanistic, cell metabolism (1980) Ehrlich acites carcinoma cells (EAC) and yeasts (S. cerevisiae) Šturdík and Drobnica, 1980 PMRA# 2742221	Evidence that dithianon was generally reactive towards cellular thiol groups, and selectively inhibits glycolytic enzymes (HK, GAPDH, G6PDH) due to their catalytically active thiol groups. The main metabolic effects on EAC cells were inhibition of glycolysis and respiration (energy metabolism); exogenous reduced glutathione is protective against this inhibition. ≥2 µg/ml: ↓ adenine and valine incorporation (EAC cells) ≥5 µg/ml: ↓ aerobic and anaerobic glycolysis (EAC cells), ↓ glycolytic enzyme activities (HK, GAPDH, G6PDH; EAC homogenates); ↓ glucose consumption, growth, ↑ RQ (all yeasts) ≥31.25 µg/ml: ↓ total reduced thiols (66-84%; EAC homogenates) Supplemental
In vivo mechanistic study of CYP enzymes (i.p. route, 1999) Mouse, CD1 Pozzetti et al., 1999 PMRA# 2742219	Mice were administered dithianon (using corn oil) as a single i.p. dose of 3 mg/kg bw (low dose) or 6 mg/kg bw (high dose), or repeated (3 days) oral doses of 3 mg/kg bw. CYP induction/suppression assayed in microsomes via testosterone hydroxylase (TH) activities. There was evidence of complex dithianon-mediated organ-specific and sex-specific changes in induction or suppression of TH substrate-specific CYP activities in isolated microsomes from the liver, kidneys, and lungs. Overall effects: In the liver, included induction (♂>♀), suppression (♀>♂) for single dose, and suppression (♂>♀) for repeated doses. In the kidney, included induction (♂>♀), suppression (♀>♂) for single dose, and induction (♂~♀) for repeated doses. In the lung, included mixed induction and suppression for single dose, and induction (♂~♀) for repeated doses.

Table 3 Toxiclogy Reference Values for Use in Health Risk Assessment for Dithianon

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1]

Acute dietary general population	7-day nephrotoxicity dietary study in rats	NOAEL = 12 mg/kg bw/day Kidney tubular damage occurring as early as 2 days following dosing	100
	ARfD = 0.1 mg/kg bw		
Acute dietary females 13-49 years of age	Developmental toxicity gavage study in rats	NOAEL = 20 mg/kg bw/day Fetal loss	300
	ARfD = 0.07 mg/kg bw		
Repeated dietary	Chronic/carcinogenicity dietary study in rats	NOAEL = 1 mg/kg bw/day Kidney pathology, including tubular damage	100
	ADI = 0.01 mg/kg bw/day		
Cancer	A threshold-dependent mode of action for kidney epithelial cell tumours in female rats was supported by the data. The risk assessment for chronic effects is considered protective of any cancer effect.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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2493378	2010, Dithianon: Structure elucidation of [CBI removed], DACO: 2.11.4 CBI
2493379	2012, BAS 216 F (Dithianon): Discussion of formation of impurities, DACO: 2.11.4 CBI
2493380	2015, DACO 2 - Chemistry requirements for the registration of a technical grade of active ingredient (TGAI) or an integrated system product , DACO: 2.12.1 CBI
2493381	1998, Comparison of high pressure liquid chromatography method CFS M 13/1/P to UV method CIPAC 153/TC for the determination of [CBI removed] in technical grade Dithianon and revision of the Dithianon specification (Report Amendment 1), DACO: 2.13.1 CBI
2493382	2009, Analytical method APL0582/01: Determination of the impurities in BAS 216 F TGAI (technical grade active ingredient), DACO: 2.13.1 CBI
2493383	2009, Validation of analytical method APL0582/01: Determination of the impurities in BAS 216 F TGAI (technical grade active ingredient), DACO: 2.13.1 CBI
2493384	2009, Dithianon: Additional validation data to report BASF DocID 2009/1011372, DACO: 2.13.1 CBI
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2493398	1992, Dithianon: Determination of the Stability, DACO: 2.14.13 CBI
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2493404	2005, Determination of the solubility in organic solvents at 20?C of Dithianon (BAS 216 F, Reg.No. 049 638) TGAI, DACO: 2.14.8
2618298	2016, Part 2 BASF Response to PMRA Clarification request dated February 24 2016, DACO: 2.11.3,2.13.3,2.15 CBI
2629745	2016, Dithianon TGAI - Description of manufacturing process, DACO: 2.11.3 CBI
2638961	2016, BASF Response- Part 2, DACO: 2.11.3 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
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2493435	1990, Addendum No.2 to 90-Day Feeding Study of Dithianon, Batch No. 15 C/86, in Beagle Dogs, DACO: 4.3.2
2493436	1989, 90-Day Feeding Study Of Dithianon, Batch No. 15 C/86, In Beagle Dogs, DACO: 4.3.2
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2493438	1987, Dithianon: 4 week oral (dietary administration) dose range-finding study in the mouse, DACO: 4.3.3

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2493454	1993, Amendment NO. 1 to Final Report - Dithianon preliminary oral (gavage) embryotoxicity study in the rabbit, DACO: 4.5.3
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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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