5.14 DITHIANON (028)

TOXICOLOGY

Dithianon was evaluated by JMPR in 2010, when an ADI of 0–0.01 mg/kg bw and an ARfD of 0.1 mg/kg bw were established. During the 2013 Meeting, concerns were raised because of the presence of degradation products of dithianon: Reg. No. 4110904 and Reg. No. 31062. Genotoxicity studies were made available during the meeting for these two degradation products.

Reg. No. 31062 gave negative results in the Ames test and in the in vivo micronucleus assay in mice.

Reg. No. 4110904 gave negative results in the Ames test, the in vitro gene mutation (*HRPT* locus) test in Chinese hamster ovary cells and a test for chromosomal aberration in human lymphocytes. It gave positive results in a test for chromosomal aberration in V79 cells. However, the in vivo micronucleus assay in mice and the comet assay in liver and duodenum in rats gave negative results.

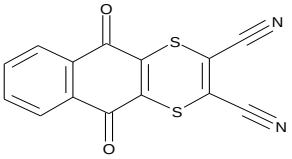
The Meeting concluded that these degradates of dithianon are unlikely to be genotoxic in vivo.

Conservative estimates of exposure were 0.08 µg/kg bw per day for chronic exposure and 1.92 µg/kg bw for acute exposure for both Reg. No. 31062 and Reg. No. 4110904. All estimates of exposure were below the threshold of toxicological concern for compounds with no evidence of genotoxicity (for Cramer class III, 1.5 µg/kg bw per day for chronic exposure; 5 µg/kg bw for acute exposure). The Meeting concluded that there is no concern for dietary exposure to these degradates.

An addendum to the toxicological monograph was prepared.

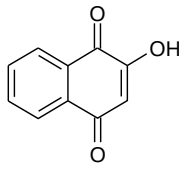
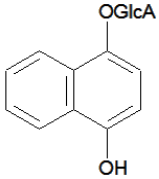
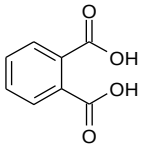
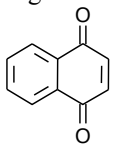
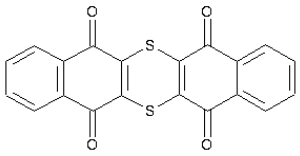
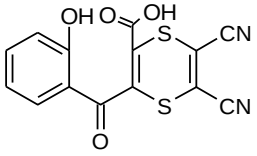
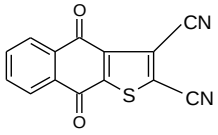
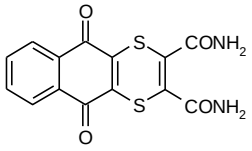
RESIDUE AND ANALYTICAL ASPECTS

The fungicide dithianon (5,10-dihydro-5,10-dioxonaphtho-[2,3-beta]-1,4-dithiine-2,3-dicarbonitrile) has been evaluated by the JMPR for the first time in 1992 (T, R). The compound was evaluated for toxicology by the 2010 JMPR where an ADI of 0.01 mg/kg bw and an ARfD of 0.1 mg/kg was allocated. The periodic review for residues was scheduled at the 39th session of the CCPR for the 2012 JMPR but postponed to evaluate in 2013.



The Meeting received information from the manufacturer on physical and chemical properties, metabolism studies on plants and animals, analytical methods, supervised residue trials data, processing studies as well as use pattern.

The metabolism and distribution of dithianon in plants and animals as well as the nature of the residue under simulated processing conditions, was investigated using the [5,6,9,10-]^{14}C-labelled compound or, in some studies, a [5,6,9,10-]^{13}C/^{14}C-labelled compound. The following abbreviations are used for the metabolites or degradation products discussed below.

CL 231509	M216F020	Reg. No. 4005234	Reg. No. 4107273
			
2-Hydroxy-1,4-napthoquinone	Glucuronic acid conjugate of 1,4-dihydroxy-naphthalene	Phthalic acid	1,4-Naphthoquinone
Reg. No. 31062	Reg. No. 4110904	Reg. No- 4110933	Reg. No. 4110934
			
Dibenzo-[*b*,*i*]-thianthrene-5,7,12,14-tetrone	5,6-Dicyano-3-(2-hydroxybenzoyl)-1,4-dithiine-2-carboxylic acid	4,9-Dihydro-4,9-dioxonaphtho[2,3–*b*]-thiophene-2,3-dicarbonitrile	5,10-Dihydro-5,10,dioxo-naphtho[2,3-*b*]-1,4-dithiin-2,3-dicarboxylic acid diamide

Animal metabolism

Metabolism studies on rats reviewed by the 2010 JMPR show that at tested doses of 10 and 50 mg/kg bw orally administered dithianon was about 40–50% absorbed in rats. The majority of the administered dose was recovered in faeces (64–72%) and in urine (27–31%). Dithianon was extensively metabolized according to the following key transformation steps: oxidation of the sulphur atoms, cleavage of the dithiine ring, reduction of the 1,4-naphthoquinone moiety and further glucuronidation, as well as substitution of the carbonitrile moieties by amino and carboxy groups. The only metabolite in rat urine at a level greater than 2% was M216F020.

Two studies were submitted on the metabolism of dithianon in lactating goats. In the first study, one lactating goat each was dosed by capsule at a daily nominal rate of 6 mg (equiv. to 2.5 ppm in the feed) and 60 mg [^{14}C] dithianon (equiv. to 28 ppm) for five days. The highest radioactive residues (TRR) of the high dose group were detected in kidney (0.49 mg/kg as dithianon equivalents) and in liver (0.17 mg/kg equiv.). Lowest TRR were found in fat (0.013 mg/kg equiv.), in milk (0.018 mg/kg equiv.) and muscle (0.013 mg/kg equiv.). Most of the [^{14}C] residue was rapidly and constantly excreted via faeces and urine—almost 80% of the applied dose was eliminated at the end of the study.

Further investigation on the nature of radioactive residues was carried out with the high dose (60 mg/day) samples. The TRR (calculated as dithianon equivalents) in muscle and fat were very low (0.013–0.014 mg/kg equiv.), and no further characterization was possible. For milk and edible tissues, the extracted radioactive residues ranged from 49% of TRR (0.08 mg/kg equiv.) in liver to 77% (0.018 mg/kg equiv.) in milk. The radioactivity in post extraction solids (PES) ranged from 20% (0.005 mg/kg equiv.) in milk to 74% (0.36 mg/kg equiv.) in kidney. Several radioactive components were detected in the extracts but not further identified. Parent dithianon was identified in liver (0.96% of TRR), kidney (2.3% of TRR) and milk (8.2% of TRR).

In the second goat study, after five consecutive daily administrations of [^{13}C/^{14}C] dithianon at a dose of 60 mg/animal and day (equivalent to 25 ppm in the feed), the highest TRR were detected in kidney (0.48 mg/kg equiv.) and in liver (0.16 mg/kg equiv.). Lower radioactive residues were found in muscle (0.013 mg/kg), in milk (0.018 mg/kg) and fat (subcutaneous 0.074 mg/kg equiv., renal 0.009 mg/kg equiv.). The major route of excretion of radioactivity was via faeces, accounting for

47% of the total administered dose. A further 18% of the total administered radioactivity was excreted via urine.

With the exception of milk, most of the radioactive residues could not be extracted. The PES in liver, kidney, muscle and fat ranged from 59.4% in kidney to 80% in muscle. Neither parent nor any corresponding metabolite was identified. However, in liver, kidney, urine and bile a very complex metabolite profile was noted. More than 20 components were found in the organic phase and at least six components were detected in the aqueous phase at low absolute residue levels (< 0.05 mg/kg) in tissues. In milk, the extracted radioactivity accounted for 78.3% of TRR (0.012 mg/kg equiv.).

The reactivity of dithianon with nucleophiles (commonly thiols in the form of proteins and peptides such as gluthathione) was demonstrated *in vitro*. Glutathione and N-acetylcysteine react very quickly with dithianon when incubated in pH 6.5 buffers at 37 °C. It was indicated that the reaction of dithianon with glutathione and protein thiol groups *in vivo* should be virtually instantaneous.

Two groups of laying hens, five hens per group, were treated orally once daily for 5 consecutive days with gelatin capsules containing dithianon. The actual doses of dithianon administered were 0.4 mg/day and 4 mg/day, equivalent to 3.6 ppm and 39 ppm in the feed, respectively.

Over the dosing period, a rapid absorption and excretion of radioactivity occurred. About 90% of the total radioactivity administered was eliminated in excreta by 6 hours after the last dose. There was no indication of accumulation of [^{14}C] dithianon in poultry tissues and eggs.

The highest TRR (in mg/kg as dithianon equiv.) were found in the kidney (0.042 and 0.34–0.38 mg/kg low and high dose, respectively), liver (0.017 and 0.17–0.19 mg/kg), skin with fat (0.005 and 0.039–0.041 mg/kg) and GI Tract (0.14 and 1.5 mg/kg). The lowest concentrations were found in muscle (0.002 and 0.022 mg/kg) and abdominal fat (< 0.002 and 0.014 mg/kg). The highest TRR in egg yolks were 0.005 and 0.075 mg/kg at the end of the study.

Solvent extraction was performed on the high dose group samples and released about of 68% of TRR in muscle (0.015 mg/kg equiv.), 76% of TRR in skin with fat (0.031 mg/kg equiv.), 72% of TRR in liver (0.13 mg/kg equiv.), 74% of TRR in kidney (0.28 mg/kg equiv.) and 47% of the TRR egg yolks (0.037 mg/kg equiv.). The majority of the extracted radioactivity was aqueous/methanol-soluble (35% in egg yolk to 67% of TRR in kidney). The chloroform-soluble radioactivity, containing less polar components, accounted for 6.6% in kidney to 16% of the TRR in liver. Radioactivity in the PES accounted for 25% in liver to 54% of the TRR in egg yolk.

Parent dithianon, detected in minor amounts in the excreta only (1.5% of TRR), was extensively metabolized to yield numerous minor metabolites. The metabolites were profiled by HPLC but were not identified as low concentrations prevented isolation. The organo-soluble metabolites accounted for ≤ 0.003 mg/kg equiv. each in the kidney and liver. One major polar component found in the aqueous/methanol extract accounted for 19% TRR (0.035 mg/kg equiv.) in liver, 11% TRR (0.042 mg/kg equiv.) in kidney, 36% TRR (0.015 mg/kg equiv.) in skin and fat, and 5.7% TRR (0.004 mg/kg equiv.) in egg yolk.

Metabolism studies performed on rats, goats and hens have shown that dithianon is rapidly and intensively metabolized by a number of degradation processes; it was only detected in trace amounts in tissues and/or excreta. As key degradation steps oxidation/reduction and reaction with nucleophiles, commonly R-SH in the form of proteins and peptides such a glutathione are assumed. These reactions result in a huge number of individual metabolites, but also incorporation into natural products. No individual metabolites had been identified; all of them were present in very minor amounts.

Plant metabolism

The metabolism of dithianon has been studied with [^{14}C] dithianon on citrus trees, apple trees, spinach and wheat. The study designs of the plant up-take parts reflect the intended use pattern with several foliar post emergence applications.

Following foliar applications, there was no translocation from the part being directly treated to other parts of the plant. When applied to fruit crops, the dithianon residues remained predominantly associated with the peel. Most of the radioactivity present (> 50% TRR) could be washed of by a surface rinse using acetonitrile/HCl. Neither parent nor any metabolite was translocated to a significant degree into flesh or pulp. Dithianon was identified as the major component of the TRR and ranged from 50.9% in wheat grain up to 96% in spinach leaves.

The parent compound is further metabolized to a large number of polar components. With the exception of spinach, these components could not be identified. None of these metabolites was found in amounts exceeding 5% of the TRR. In spinach, metabolite 4110934, a dicarboxylic acid diamide derivative, 2-hydroxynapthoquinone (CL 231509) and phthalic acid were found, indicating that the absorbed dithianon was completely metabolized by the plants. All of the individual components of the extracted residues in spinach were between 0.1 and 0.5% of the TRR (0.13–0.8 mg/kg equiv.).

The different functional groups on the dithianon molecule provide multiple sites for chemical and enzymatic attacks resulting in cleavage of the dithiine as well as the quinone ring. The primary products formed are very reactive and could be the target of quite a number of further metabolism and conjugation reactions (e.g. hydroxylation, sulphur oxidation, and reactions with naturally occurring plant constituents), but also incorporation into plant constituents. The Meeting considered parent as the only relevant residue occurring after foliar treatment of plants with dithianon.

Environmental fate

For dithianon, supervised residue trials data were received for foliar spray on permanent crops such as citrus fruits, tree nuts, pome fruits, stone fruits, grapes and hops. Therefore, neither environmental fate nor rotational crops studies are necessary.

Dithianon is not stable in aqueous media. A hydrolysis study showed DT_{50} values of 10.7 days at pH 5, 0.6 days at pH 7 and ca. 10 minutes at pH 9. The photochemical degradation at 20 °C in sterile pH 4 buffer resulted in a DT_{50} value lower than 0.05 days.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of dithianon in plant and animal commodities. Residue analytical methods for dithianon rely on HPLC with UV-detection or LC-MS/MS for plants and HPLC with electrochemical detection or LC-MS/MS for animal matrices. Typical LOQs achieved for plant and animal commodities fall in the range of 0.01–0.05 mg/kg (except hops, dried, 1 mg/kg). Methods have been subjected to independent laboratory validation.

Descriptions and validation data for analytical methods for residues of the degradation product 4110904 in citrus fruit, apples, grapes, plums and grape wine were received. The analytical methods rely on LC-MS/MS. Typical LOQs achieved for plants commodities were 0.01 mg/kg.

Stability of residues in stored analytical samples

Information was received on the freezer storage stability of dithianon and 4110904 residues in plant commodities.

Older studies from 1992–1994 show that dithianon residues were not stable in spiked samples for a period longer than two months. Newer studies with incurred residues in apples (testing period 2 years) and wine grapes (testing period 14 months) show that dithianon residues were

apparently stable at freezer temperature for the intervals tested. Residues of dithianon were not stable in wine, declining on average by 86% of the original fortification after 26 weeks of frozen storage.

The storage stability studies with 4110904 demonstrate that the compound is stable under freezer conditions in plant matrices for about two years in apples, plums and wine. Residues of 4110904 were not stable in grapes, declining by ca. 65% of the fortification level after 3 months, and in lemons, declining by ca. 55% after a week.

Definition of the residue

Animal metabolism studies were performed in lactating goats and laying hens. The parent compound dithianon is rapidly and intensively metabolized and was only detected in trace amounts in tissues and excreta. There was no bioaccumulation in tissues, milk and eggs. No individual metabolites had been identified; all of them were present in very minor amounts (< 0.05 mg/kg and also < 10% TRR).

Dithianon has a log P_{OW} of 3.2. In animal metabolism studies, the TRR in muscle and fat were comparable (dithianon *per se* could not be detected). The Meeting decided that the residue of dithianon is not fat-soluble.

In plant metabolism studies performed on fruits (oranges, apples), leafy crops (spinach) and cereals (wheat) the same metabolic behaviour was observed. The parent compound dithianon is the dominant component of the residue in plant commodities and ranged from 50.9% of the TRR in wheat grain up to 96% of the TRR in spinach leaves. No individual metabolite occur at relative amounts > 10% of TRR and of absolute concentrations of > 0.05 mg/kg in the same matrix.

Therefore, from the metabolism studies on plants and animals presented, the proposed definition of the residue is parent dithianon only.

The Meeting took into account the possibility of the formation of two hydrolysis products (Reg. No. 31062 and 4110904) in significant concentrations during industrial or household processing of dithianon treated fruits. Based on their dietary risk assessment, the Meeting concluded that there is no need to include both degradates in the residue definition for estimation of the dietary intake.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for plant and animal commodities*: Dithianon.*

The residue is not fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised residue trials data for citrus fruits, apple, pear, cherries, peaches, plums, grapes, currants, almonds and hops. If two field samples were taken or results of two replicate plots were submitted, the mean value was calculated. For HR estimation, the highest single value of the trials according to GAP was used. From two or more trials carried out side-by-side the higher residue was chosen.

Citrus fruits

In Japan, dithianon is registered for foliar spray use on citrus fruits at a maximum application rate of 3 × 2.9 kg ai/ha with a PHI of 30 days. Supervised trials with 3 × 2.0–4.27 kg ai/ha with a PHI of 28–30 days were available from Japan: four on mandarins (four for whole fruit, six for pulp), two on pomelo, as well as one each on the small citrus fruits sudachi and kabosu (*Citrus sphaerocarpa*).

The Meeting noted that only four residue trials on mandarin, two on pomelo and two on the small citrus varieties (sudachi/kabosu) are insufficient to estimate a maximum residue level for the whole group of citrus fruits.

The Meeting considered that six residue trials were available for mandarin. It was noted that in four trials data for whole fruit and in six trials pulp data were submitted. The Meeting agreed that only four trials on mandarin (whole fruit) are insufficient to estimate a maximum residue level for the subgroup mandarins. The previous recommendations of 3 mg/kg for mandarin, shaddocks or pomelos should be withdrawn.

Pome fruits

Dithianon is registered for foliar spray treatment on pome fruit in Germany with 12 treatments per season of 0.035 kg ai/hL and 0.18 kg ai/ha per m crown height (equivalent to 0.54 kg ai/ha for 3 m crown height) and a PHI of 21 days.

During the years 1975–2000, 21 trials on apples were conducted in Germany (12), France (3), Greece (1), Italy (3) and Spain (2). Foliar applications were made from 12 to 14 times to apple trees at application rates of 0.51–0.63 kg ai/ha. At a PHI of 21 days, the residues were < 0.03, < 0.05, 0.12, 0.13, 0.20, 0.24, 0.36, 0.38, 0.43, 0.48, 0.48, 0.59, 0.62, 0.76, 0.86, 1.0, 1.3, 1.5, 1.7, 1.7 and 1.7 mg/kg.

Four trials on pears were conducted in 2004 in Germany, The Netherlands, Northern France and Denmark with foliar spray by 12 × 0.53 kg ai/ha. The dithianon residues were at a PHI of 21–22 days 0.19, 0.37, 0.39 and 0.87 mg/kg.

The rank order of the combined dithianon residues on apple and pear were (n=25): < 0.03, < 0.05, 0.12, 0.13, 0.19, 0.20, 0.24, 0.36, 0.37, 0.38, 0.39, 0.43, 0.48, 0.48, 0.59, 0.62, 0.76, 0.86, 0.87, 1.0, 1.3, 1.5, 1.7, 1.7 and 1.7 mg/kg.

The Meeting noted that the ARfD of 0.1 mg/kg bw is exceeded for apple by the IESTI for children (120% of ARfD) using 1.7 mg/kg as HR and decided that the dataset is not appropriate to estimate a maximum residue level for pome fruit.

An alternative GAP is an Italian use of 4 × 0.3 kg ai/ha on apple and of 3 × 0.3 kg ai/ha on pear with a PHI of 35 days. In Macedonia, dithianon is registered in apples with 4 × 0.24–0.30 kg ai/ha and in pear with 4 × 0.32–0.4 kg ai/ha. The PHI is 35 days also.

Five apple trials were conducted in 2003 with 4 × 0.3–0.35 kg ai/ha. The dithianon residues were 34–35 days after treatment 0.11, 0.14, 0.35, 0.39 and 0.43 mg/kg.

Eleven apples trials were carried out in 2010 in Germany (1), the UK (1), Belgium (1), the Netherlands (1), France (2), Greece (1), Italy (2) and Spain (2) with 4 × 0.36 kg ai/ha. The dithianon residues were after a PHI of 35 days < 0.01, 0.02, 0.02, 0.06, 0.10, 0.14, 0.16, 0.21, 0.27, 0.34 and 0.65 mg/kg.

The combined dithianon residue data after application of 4 × 0.3–0.36 kg ai/ha from 2003 and 2010 were (n=16): < 0.01, 0.02, 0.02, 0.06, 0.10, 0.11, 0.14, 0.14, 0.16, 0.21, 0.27, 0.34, 0.35, 0.39, 0.43 and 0.65 mg/kg.

The Meeting agreed to extrapolate from apple to the whole group and estimated a maximum residue level of 1 mg/kg for dithianon residues in pome fruits to replace the previous recommendation (5 mg/kg). An STMR and an HR value of 0.15 mg/kg and 0.65 mg/kg were estimated.

Stone fruits

The GAP for stone fruits in Hungary is 2–3 times foliar spray treatment of 0.053–0.066 kg ai/hL, 0.53 kg ai/ha and a PHI of 21 days. Supervised trials were available for cherries, peaches and plums.

On cherries, sour, seven trials were carried out in Germany from 1985 to 1995 by an application of 3 × 0.53 kg ai/ha and a PHI of 21 days. The dithianon residues were 0.17, 0.26, 0.28, 0.34, 0.41, 0.49 and 0.80 mg/kg.

Further trials on cherries (sweet and sour) were conducted in 2009/2010 in the UK (2), France (3), Germany (2), Greece (2), Italy (3), The Netherlands (2) and Spain (1) with 3 × 0.53 kg ai/ha and a PHI of 20–21 days. The dithianon residues were 0.04, 0.09, 0.19, 0.19, 0.21, 0.38, 0.43, 0.45, 0.50, 0.57, 0.59, 0.69, 0.82, 0.90 and 1.0 mg/kg.

The Meeting concluded to combine the dithianon residues on cherries from both datasets. The dithianon residues on cherries were in rank order (n=22): 0.04, 0.09, 0.17, 0.19, 0.19, 0.21, 0.26, 0.28, 0.34, 0.38, 0.41, 0.43, 0.45, 0.49, 0.50, 0.57, 0.59, 0.69, 0.80, 0.82, 0.90 and 1.0 mg/kg.

On plums, twelve trials were conducted in 2009/2010 in France (3), Belgium (1), Germany (4), Italy (2) and Spain (2) with 3 × 0.53 kg ai/ha and a PHI of 20–22 days. The dithianon residues were 0.04, 0.05, 0.06, 0.10, 0.10, 0.18, 0.21, 0.25, 0.27, 0.32, 0.40 and 0.45 mg/kg.

On peaches, twelve trials were conducted in 2009/2010 in France (4), Germany (2), Greece (2), Italy (2) and Spain (2) with 3 × 0.53 kg ai/ha and a PHI of 20–21 days. The dithianon residues were 0.17, 0.18, 0.24, 0.36, 0.38, 0.43, 0.44, 0.45, 0.56, 0.60, 1.0 and 1.6 mg/kg.

The Meeting noted that the Hungarian GAP is for the stone fruit group, and considered a group maximum residue level. To consider a group maximum residue level, residues in individual commodities should be similar (e.g., medians should not differ by more than five times). The Meeting agreed to estimate a maximum residue level for the group stone fruit.

In deciding whether to combine the datasets for the different crops for use in the statistical calculator or to only utilize the data from the commodity with the highest residues, the Meeting recognized the similarity of the datasets of cherries and peaches (confirmed by the Mann-Whitney U-test). The Meeting agreed to combine these datasets for the purposes of determining a group maximum residue level for stone fruit.

The rank order of the combined dataset of cherries and peaches is (n=34): 0.04, 0.09, 0.17, 0.17, 0.18, 0.19, 0.19, 0.21, 0.24, 0.26, 0.28, 0.34, 0.36, 0.38, 0.38, 0.41, 0.43, 0.43, 0.44, 0.45, 0.45, 0.49, 0.50, 0.56, 0.57, 0.59, 0.60, 0.69, 0.80, 0.82, 0.90, 1.0, 1.0 and 1.6 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg, an STMR of 0.43 mg/kg and an HR of 1.6 mg/kg for dithianon residues in stone fruits. The previous recommendation of 5 mg/kg for dithianon in cherries was withdrawn.

Grapes

Dithianon is registered for foliar spray treatment on grapes in Slovenia with 1–8 × 0.35 kg ai/ha and a PHI of 42 days.

Trials on grapes were available from Germany (24). The plants were treated eight times during the growing season with 0.23–0.68 kg ai/ha; the last applications were in a range of 0.44–0.68 kg ai/ha. The Meeting agreed to use the proportionality approach to scale the residues of a PHI of 41–43 days according an application rate of 0.35 kg ai/ha. The rank order of scaled residues was (n=24): 0.15, 0.19, 0.29, 0.34, 0.36, 0.43, 0.44, 0.44, 0.48, 0.50, 0.54, 0.60, 0.61, 0.72, 0.75, 0.76, 0.80, 0.92, 1.0, 1.05, 1.2, 1.2, 1.4 and 2.5 mg/kg.

Further trials were conducted in France (3), Germany (1), Greece (1), Italy (4) and Spain (4). Grapes were treated with 8 × 0.56 kg ai/ha. The PHI was 41–42 days. The rank order of the scaled dithianon residues on the application rate of 0.35 kg ai/ha were (n=13): 0.21, 0.28, 0.33, 0.37, 0.63, 0.69, 0.69, 0.81, 0.81, 0.88, 0.94, 2.1 and 4.6 mg/kg.

The rank order of the combined scaled residue data was (n=37): 0.15, 0.19, 0.21, 0.28, 0.29, 0.33, 0.34, 0.36, 0.37, 0.43, 0.44, 0.44, 0.48, 0.50, 0.54, 0.60, 0.61, 0.63, 0.69, 0.69, 0.72, 0.75, 0.76, 0.80, 0.81, 0.81, 0.88, 0.92, 0.94, 1.0, 1.05, 1.2, 1.2, 1.4, 2.1, 2.5 and 4.6 mg/kg.

The Meeting estimated a maximum residue level of 5 mg/kg for dithianon residues in grapes. Because the ARfD of 0.1 mg/kg bw is exceeded by the IESTI of dithianon for grapes using 4.6 mg/kg

as HR (310% for children, 150% for general population), the Meeting decided that the maximum residue level of 5 mg/kg is not suitable for table grapes and should be apply to wine grapes only. For calculation of residues in processed commodities (juice, wine), a median residue level of 0.69 mg/kg was estimated.

The Meeting agreed to search for an alternative GAP to estimate a maximum residue level, an STMR and an HR for table grapes.

Another registration exists in Serbia of 3 × 0.35 kg ai/ha and a PHI of 35 days for grapes. Trials on grapes treated with 3 × 0.53 kg ai/ha and a PHI of 35 days from Germany (4), France (7), Spain (2), Italy (1) and Greece (1) were submitted. The Meeting agreed to use the proportionality approach to estimate a separate maximum residue level, an STMR and HR for table grapes. The scaled residue values according to Serbian application rate were (n=15): 0.29, 0.39, 0.48, 0.50, 0.56, 0.57, 0.59, 0.63, 0.64, 0.73, 0.86, 0.99, 1.1, 1.2 and 1.3 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg for dithianon residues in table grapes. The Meetin agreed to withdraw the recommendation for grapes of 3 mg/kg. An STMR of 0.63 mg/kg and an HR of 1.3 mg/kg were estimated.

Currants

In France, dithianon may be used as foliar spray on currants with an application rate of 2 × 0.49 kg ai/ha and a PHI of 14 days.

Six trials on black currants according to the French GAP (2 × 0.53 kg ai/ha, PHI 14 days) were submitted. The dithianon residues were < 0.05, < 0.05, < 0.1, 0.11, 0.61 and 0.89 mg/kg.

The Meeting agreed to extrapolate from black currants to currants, black, red, white and estimated a maximum residue level of 2 mg/kg, an STMR of 0.105 mg/kg and an HR of 0.89 mg/kg for dithianon residues in currants.

Almonds

The registered use of dithianon in almonds in France is foliar spray treatment of 2 × 0.35 kg ai/ha and a PHI of 58 days. Four French trials in line with French GAP were available. The dithianon residues were in almonds (without shell) < 0.05 mg/kg (4).

The Meeting considered four trials as sufficient for the estimation of a maximum residue level in almonds because dithianon is located on the surface of the shell and no residues are to be expected in the nutmeat and estimated a maximum residue level of 0.05* mg/kg, and an STMR and an HR of 0 mg/kg.

Hops, dry

In Austria and Germany, dithianon is registered for use on hops at 10 × 0.63–1.4 kg ai/ha (depending from growth stage) and a PHI of 14 days. German trials in line with GAP (10–12 × 0.3–1.5 kg ai/ha, PHI 14 days) were submitted. The residues were in dried cones 4.1, 16, 17, 21, 22, 32, 58, 70, 82, 88, 89, 94, 96 and 242 mg/kg.

The Meeting estimated for dithianon residues in hops, dry a maximum residue level of 300 mg/kg and an STMR of 64 mg/kg. The previous recommendation of 100 mg/kg should be replaced.

Fate of residues during processing

Nature of residues

Three studies on the nature of the residue under simulated processing conditions, performed with [^{14}C] dithianon at higher temperatures, were received.

In the first study, hydrolysis was conducted in buffers solutions whereas in the second study, [^{14}C] dithianon was incubated in apple juice under the conditions of pasteurization (pH 4, incubation for 20 minutes at 90 °C). In both studies, at pH 4, the parent molecule formed the major part of the radioactivity. In addition, a multiple number of unknown degradation products was formed; each of them < 10% of the total applied radioactivity (TAR). At high temperature conditions and pH 5 (simulated processing conditions of baking, brewing and boiling) or pH 6 (simulated processing conditions of sterilization) the hydrolytic degradation of dithianon was fast and resulted in many degradation products. The degradation product 4110904 was found at pH 5 and pH 6 in concentrations exceeding the level of 10% the total applied radioactivity (TAR) accounting for 46–57% of TRR at pH 5 and for about 20% of TRR at pH 6.

A third hydrolysis study on the degradation of dithianon in apple juice at 90 °C, 100 °C and 120 °C was conducted for further characterization of the components formed. The initial high temperature hydrolysis tests with [^{14}C] dithianon in apple juice resulted in the rapid disappearance of dithianon. Between 44 and 47% of the TAR remained as dithianon after hydrolysis at 90 °C for 20 minutes, 0.9–1% of the TAR remained as dithianon after hydrolysis at 100 °C for 60 minutes and less than 1% of the TAR remained as parent after hydrolysis at 120 °C for 20 minutes. The results of the identification of the degradation products are as follows:

- The initial high temperature hydrolysis tests resulted in the formation of naphthoquinone (4107273) at greater than 10% of the TAR upon 20 minutes of hydrolysis at 120 °C. Formation of 4107273 was not observed in the lower temperature hydrolysis samples. 4107273 was also no longer found after refrigerated storage (21 days/33 days) of the apple juice sample hydrolysed at 120 °C. The compound was only found immediately after hydrolysis.
- Phthalic acid (4005234) and compound 4110933 were both observed in hydrolysed apple juice, but always at less than 5% of the TAR.
- Compounds 4110904 and 31062 were formed at 9.4% and 10.5% of TAR, respectively, upon 60 minutes of hydrolysis at 100 °C. At 20 minutes of hydrolysis at 120 °C, 4110904 was formed at 5.8% and 31062 at 10% of TAR. Both compounds appear to be stable in hydrolysed apple juice stored refrigerated.

Level of residues

The Meeting received information on the fate of dithianon residues during the processing of oranges to juice, oil and dry pulp, of apples to juice, sauce, dried apple and wet pomace, of cherries to juice, canned cherries and jam, of plums to puree and dried prunes, of grapes to juice, must, wine, raisins and wet pomace and of hops to beer.

The processing factors obtained in the processing studies and estimated STMR-P and HR-P values are summarized below.

Raw agricultural commodity (RAC)			Processed commodity			
Name	STMR (mg/kg)	HR (mg/kg)	Name	Processing factor (median or best estimate)	STMR-P (mg/kg)	HR-P (mg/kg)
Apples	0.15		Juice	< 0.03 (median)	0.0045	
			Sauce	< 0.03 (median)	0.0045	
			Syrup	< 0.04 (median)	0.006	
			Canned apple	< 0.06 (median)	0.009	
			Dried apple	0.1 (median)	0.015	

Raw agricultural commodity (RAC)			Processed commodity			
Name	STMR (mg/kg)	HR (mg/kg)	Name	Processing factor (median or best estimate)	STMR-P (mg/kg)	HR-P (mg/kg)
			Wet pomace	2.2 (median)	0.33	
Cherries	0.43		Juice	< 0.055 (median)	0.024	
			Canned cherries	< 0.055 (median)	0.024	
			Jam	< 0.055 (median)	0.024	
Plums	0.43		Puree	0.035 (median)	0.015	
			Dried prunes	0.515 (median)	0.22	
Wine-grapes	0.69		Juice	< 0.0025 (median)	0.002	
			Must	0.024 (median)	0.017	
			Wine	< 0.003 (median)	0.002	
			Wet pomace	0.93 (median)	0.64	
Table-grapes	0.63	1.3	Raisins	1.64 (median)	1.03	2.13
Hops	64		Beer	< 0.0003 (median)	0.019	

The Meeting noted that dithianon concentrated during processing in apple pomace, wet and in raisins. Because apple pomace is not a commodity in trade, no maximum residue level is estimated.

Based on the recommended MRL of 2 mg/kg for dithianon residues in table grapes and the processing factor of 1.64, the Meeting estimated a maximum residue level of 3.5 mg/kg for dried grapes (2 × 1.64 = 3.28). An STMR-P of 1.03 mg/kg and an HR-P of 2.13 mg/kg were estimated for raisins.

The Meeting discussed the relevance of the hydrolysis products 411094 and 31062 for the residue definition for industrial or household preparations of dithianon treated fruits and made the following assumptions to estimate their dietary intake:

According to the results of the hydrolysis studies, both degradation products accounted for about 10% of the TAR.

In addition to dithianon, the degradation product 4110904 was investigated in the processing studies for dithianon on apples, cherries, plums and grapes. No residues of 4110904 above the LOQ of 0.01 mg/kg were detected in the RAC. The degradate was not detected in must, wine and juice, but in raisins where the residues were lower than 1% of the dithianon residue. The Meeting agreed to use the LOQ for must, wine and juice or the highest real measured value for raisins to estimate the dietary intake of 4110904. For hops, because no data for 4110904 were available, 10% of the STMR for dithianon in hops adjusted by the molecular weight of 4110904 (330.3) was used.

Because no residue data for the degradate 31062 in RAC and the related processed products were submitted, the estimated dietary intake is based on 10% of the STMR of parent dithianon. The Meeting noted that 31062 was formed by dimerization, resulting in the doubling of the radioactivity per molecule. Therefore the stoichiometric factor to extrapolate from dithianon to 31062 residues is 0.635 [376.1 ÷ (2 × 296.3)]. The 31062 concentrations are calculated as follows:

$RESIDUE_{31062} = STMR_{Dithianon} \times 0.635 \div 10$.

The following concentrations of the degradates 4110904 and 31062 were estimated for chronic and acute dietary intake purposes:

Name	Name	4110904, mg/kg	Basis	31062, mg/kg	Basis
Apples,	Juice	0.01	$LOQ_{4110904}$	0.0095	$STMR_{Dithianon}$
Pears	Sauce	0.01	$LOQ_{4110904}$	0.0095	$STMR_{Dithianon}$
	Canned	0.01	$LOQ_{4110904}$	0.0095	$STMR_{Dithianon}$
	Dried	0.01	$LOQ_{4110904}$	0.0095	$STMR_{Dithianon}$
Currants	Juice	0.012	$STMR_{Dithianon}$	0.007	$STMR_{Dithianon}$
Stone fruits	Juice	0.01	$LOQ_{4110904}$	0.0273	$STMR_{Dithianon}$
	Canned	0.01	$LOQ_{4110904}$	0.0273	$STMR_{Dithianon}$

Name	Name	4110904, mg/kg	Basis	31062, mg/kg	Basis
	Jam	0.01	$LOQ_{4110904}$	0.0273	$STMR_{Dithianon}$
	Plum puree	0.01	$LOQ_{4110904}$	0.0273	$STMR_{Dithianon}$
	Dried prunes	0.01	$LOQ_{4110904}$	0.052	$HR_{Dithianon}$
Wine-grapes	Juice	0.01	$LOQ_{4110904}$	0.044	$STMR_{Dithianon}$
	Must	0.01	$LOQ_{4110904}$	0.044	$STMR_{Dithianon}$
	Wine	0.01	$LOQ_{4110904}$	0.044	$STMR_{Dithianon}$
Table-grapes	Raisins	0.11	4110904 measured value	0.135	$HR_{Dithianon}$
Hops	Beer	7.1	$STMR_{Dithianon}$	4.06	$STMR_{Dithianon}$

Conservative estimates of long-term exposure of the degradation products Reg. No. 31062 and Reg. No. 4110904 after industrial or household processing were calculated for the 13 GEMS/Food cluster diets using residue concentrations estimated above. The maximum long-term daily intake was 4.7 μg per person (0.00008 mg/kg bw). Applying this intake to the TTC approach (threshold value 0.0015 mg/kg bw, Cramer Class III), the calculated exposures were up to 5% of the TTC.

Conservative estimates of short-term exposure of the degradation products Reg. No. 31062 and Reg. No. 4110904 were calculated using the residue concentrations estimated above. The maximum short-term daily intake was 115 μg per person (0.00192 mg/kg bw). Applying this intake to the TTC approach (threshold value 0.005 mg/kg bw, Cramer Class III), the maximum calculated exposure was 40% of the TTC.

The Meeting concluded that the long-term and short-term intake of residues of Reg. No. 31062 and Reg. No. 4110904 arising of dithianon, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.

Farm animal dietary burden

The 2013 JMPR evaluated residues of dithianon in apple pomace wet and grape pomace wet which are listed under by-products in the OECD feeding table for beef and dairy cattle but not for poultry.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations based on the feed items evaluated for beef cattle and dairy cattle as presented in Annex 6. The calculations were made according to the livestock diets from Australia, the EU, Japan and US-Canada in the OECD Table. Because the calculation based on the STMR-P values of the processed by-products, the maximum and mean burden is identical. The table below shows the values calculated.

Because apple pomace wet and grape pomace wet are no feed items for poultry, the livestock dietary burden for broiler and layer is zero.

	Livestock dietary burden, dithianon, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	0	0	0.165	0.165	0.853 a	0.853 a	0	0
Dairy cattle	0.083	0.083	0.090	0.090	0.853 a	0.853 a	0	0
Poultry-broiler	0	0	0	0	0	0	0	0
Poultry-layer	0	0	0	0	0	0	0	0

[a] Highest mean and maximum beef or dairy cattle dietary burden suitable for MRL and STMR estimates for mammalian meat, edible offal and milk.

Farm animal feeding and metabolism studies

No animal feeding studies of dithianon were submitted. The Meeting agreed to extrapolate the residue levels to be expected in ruminant tissues and milk from the goat metabolism studies.

The metabolism studies in lactating goats were performed at actual dose levels of 2.5 and 28 ppm in the first study and of 25 ppm in the feed of the second study. The overdosing factors are calculated as about 2.9 (2.5 ppm ÷ 0.853 ppm), 33 (28 ppm ÷ 0.853 ppm) and 29 (25 ppm ÷ 0.853 ppm), respectively.

Animal commodity maximum residue levels

The expected total residues in milk and edible tissues of ruminants can be extrapolated from the highest TRR found in the goat metabolism studies as follows:

Commodity	Feeding level, ppm	TRR from metabolism study, mg/kg	TRR extrapolated from actual dietary burden, mg/kg
Milk	2.5	< 0.01	< 0.003
Liver		0.07	0.024
Kidney		0.04	0.014
Muscle		Not detected	–
Fat		< 0.01	< 0.003
Milk	28	0.030	0.0009
Liver		0.174	0.0053
Kidney		0.489	0.0149
Muscle		0.013	0.0004
Fat		0.014	0.0004
Milk	25	0.016	0.0006
Liver		0.157	0.0054
Kidney		0.475	0.0162
Muscle		0.014	0.0005
Fat		0.074	0.0025

The extrapolated TRR are for milk, muscle and fat are lower than the LOQ of 0.01 of dithianon in animal products. In case of liver and kidney, the extrapolated TRR range from 0.005–0.02 mg/kg and 0.01–0.02 mg/kg, respectively.

The Meeting noted that the results from metabolism studies on rats, goats and hens show that dithianon is intensively metabolized. In the goat, parent dithianon was detected at low levels (≤ 0.01mg/kg) and no single metabolite in the extracts was detected > 0.05 mg/kg. Therefore, it is not expected that the calculated TRR in cattle tissues and milk arising from a burden of 0.853 ppm would account for 100% of dithianon or a related metabolite. In case of poultry, the dietary burdens for broiler and layer are zero. The Meeting concluded that the contribution of dithianon arising residues in animal products to the dietary intake is negligible.

The Meeting estimated maximum residue levels of 0.01* mg/kg for meat of mammals, other than marine mammals, edible offal (mammalian), milk, poultry meat, poultry edible offal and eggs. The STMR for milk and the STMR/HR values for mammalian and poultry meat, mammalian and poultry edible offal as well as for eggs are zero.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for plant and animal commodities: *Dithianon*.

The residue is not fat-soluble.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of dithianon were calculated for the 13 GEMS/Food cluster diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.01 mg/kg bw and the calculated IEDIs were 1–7% of the maximum ADI. The Meeting concluded that the long-term intake of residues of dithianon resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) for dithianon was calculated for food commodities and their processed fractions for which maximum residue levels were estimated and for which consumption data were available. The results are shown in Annex 4.

The Meeting noted that for apples and grapes the IESTI calculated according to the maximum GAP exceeded the ARfD of 0.1 mg/kg bw and used an alternative GAP.

For the commodities considered by the JMPR, the IESTI represented 0–40% of the ARfD for the general population and 0–90% of the ARfD for children. The Meeting concluded that the short-term intake of residues of dithianon, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.