CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance thiram

European Food Safety Authority (EFSA)

Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State France and co-rapporteur Member State Belgium for the pesticide active substance thiram are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of thiram as a fungicide on apple, pear, cherry, strawberry, peach and maize. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: thiram, peer review, risk assessment, pesticide, fungicide

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Thiram is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), France, and co-rapporteur Member State (co-RMS), Belgium, received an application from the Thiram Task Force TTF for the renewal of approval of the active substance thiram. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Belgium), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on thiram in the renewal assessment report (RAR), which was received by EFSA on 20 January 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, the Thiram Task Force TTF, for comments on 15 March 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 17 May 2016.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether thiram can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of thiram as a fungicide on apple, pear, cherry, strawberry, peach and maize, as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the uses of thiram according to the representative uses proposed result in a sufficient fungicidal efficacy against the target organisms.

A data gap was identified for a search of the scientific peer-reviewed open literature on relevant metabolites in the residue section, published within 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance.

Data gaps were identified in the area of analytical methods for the determination of the extraction efficiency of the method used for monitoring in plant and animal matrices, for a monitoring method in body fluids and tissues and analytical methods for the determination of the additives in the technical material.

Four data gaps were identified in the area of mammalian toxicology: for comparative *in vitro* metabolism studies, for a female pubertal assay (to clarify potential ED properties), for a 90-day rat study with the groundwater metabolite DMCS, and for further toxicological assessment of the metabolites M1, M2, M4, M7 and M8. The exposure estimates were predicted to be above the acceptable operator exposure level (AOEL) for re-entry workers after application on orchards in fields and application on strawberries in greenhouse.

In the residue Section, data gaps were identified to address the toxicity of M1, M2, M4, M7 and M8, to provide field residue trials analysing thiram (specific) and M1 in primary crops, the magnitude of M2, M3, M4, M7 and M8 in fruit processed commodities, the processing behaviour of M1 under standard hydrolysis conditions and finally confined rotational crops metabolism data addressing, respectively, the fate of thiram and DMCS residues. The consumer risk assessment through dietary intake cannot be finalised for the products of plant origin considering the outstanding data to finalise the residue definitions in primary and rotational crops and in processed commodities. Furthermore and considering the agreed toxicological reference values for thiram and the complete residue data sets on thiram for apple, pear and strawberry, an acute dietary intake concern for the consumers was identified for these representative uses (international estimated short-term intake (IESTI) accounted for 1,003% of the acute reference dose (ARfD) for apple, 933% of the ARfD for pear and 442% of the ARfD for strawberry).

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at the European Union (EU) level for the representative uses, with the notable exception that the applicant has indicated that; when surface water or groundwater are abstracted for drinking water purposes, residues of thiram and DMCS that are potentially present in surface water, or DMCS that has the potential to be present in groundwater, could, following the water treatment processes of chlorination or ozonation, result in the hazardous *N*,*N*-dimethylnitrous amide (NDMA) being present in drinking water. A transparent evaluation of this potential was not evaluated by the RMS, leading to a data gap and the consumer risk assessment from the consumption of drinking water being not finalised, for all the representative uses. The potential for shallow vulnerable groundwater exposure above the parametric drinking water limit of 0.1 μg/L by the toxicologically relevant metabolite DMCS was predicted to be high over the geoclimatic conditions represented by all the FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use) groundwater scenarios for the representative spray uses assessed. This is a concern for the uses on apple, pear, cherry, strawberry and peach. This concern also applies for half the FOCUS groundwater scenarios (4/8) for the seed treatment use on maize.

A number of data gaps were identified in the field of ecotoxicology in relation to dietary risk to birds and mammals, acute and chronic risk to aquatic organisms, the risk to earthworms and the dietary risk to bees from the exposure to thiram. Additionally, data gaps were identified in relation to metabolite M1 (dietary risk to birds and mammals) and metabolite DMCS (aquatic organisms and soil microorganisms). Also, a data gap was identified for further information to address the risk to sublethal effects on bees and the risk from potential metabolites occurring in pollen and nectar. The dietary risk to birds and mammal was indicated as a critical area of concern since it was related to all the representative uses.

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[2]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS France and co-RMS Belgium received an application from the Thiram Task Force TTF for the renewal of approval of the active substance thiram. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Belgium) the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on thiram in the RAR, which was received by EFSA on 20 January 2016 (France, 2016a). The RAR included a proposal to set maximum residue levels (MRLs), submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, the Thiram Task Force TTF, for consultation and comments on 15 March 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 17 May 2016. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the co-RMS Belgium on 28 June 2016. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicants and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in December 2016–January 2017.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

of thiram as a fungicide on apple, pear, cherry, strawberry, peach and maize, as proposed by the applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2017), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (28 June 2016);
- the evaluation table (6 January 2017);
- the reports of the scientific consultation with Member State experts;
- the comments received on the assessment of the additional information;
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (France, 2016b), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Thiram is the ISO common name for tetramethylthiuram disulfide or bis(dimethylthiocarbamoyl) disulfide (IUPAC).

The representative formulated products for the evaluation were 'Thiram 80 WG', a water-dispersible granule (WG) containing 800 g/kg thiram and 'Thiraflo' (UBI 6898-00), a flowable concentrate for seed treatment (FS) containing 400 g/L thiram.

The representative uses evaluated were foliar spray applications for the control of fungal diseases in apple, pear, peach, cherry and strawberry and seed treatment in maize against seedling diseases. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of thiram according to the representative uses proposed at the EU level result in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

A data gap has been identified for a search of the scientific peer-reviewed open literature on relevant metabolites in the residue Section published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b), SANCO/825/00-rev. 8.1 (European Commission, 2010).

Thiram is manufactured as a technical material containing additives. The reference specification for the first approval was updated. It should be noted that the reference specification is the specification for thiram technical not containing the additives (TC). The proposed specification is based on batch data from industrial scale production. The minimum purity of the active substance before the addition of the additives is 985 g/kg, the minimum purity of the material as manufactured is 980 g/kg. The manufactured TC is meeting the requirements of the existing FAO specification under the old procedure (AGP: CP/82, FAO, 24/1/S/18, 1979).

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of thiram or the representative formulations. The main data regarding the identity of thiram and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment and for the determination of thiram in the technical material and in the representative formulations. A data gap was identified for validated analytical methods for the determination of the additives in the manufactured technical material.

Residues of thiram in food and feed of plant origin can be monitored by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with a limit of quantification (LOQ) of 0.01 mg/kg in dry commodities and a LOQ of 0.05 mg/kg in the other plant matrices. Adequate LC–MS/MS method with a LOQ of 0.01 mg/kg exists for the determination of thiram in food and feed of animal origin (meat, liver, kidney, fat, milk and egg). Data gaps were, however, identified for the determination of the extraction efficiency of the thiram specific method in plants and in food of animal origin.

Monitoring residues of thiram in soil can be done by LC–MS/MS with a LOQ of 0.01 mg/kg. Determination of the compounds of the residue definition for surface water and drinking water can be determined by LC–MS/MS with LOQs of 0.1 μg/L for both thiram and DMCS. The LC–MS/MS method with a LOQ of 2.6 $\mu g/m^3$ is used for the monitoring of thiram in the air.

A data gap was identified for a monitoring method in body fluids and tissues.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003a), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012) and Guidance on non-dietary exposure (EFSA, 2014).

Thiram was discussed by the experts during the Pesticides Peer Review Meeting 148 in October 2016.

In the new technical specification (TC), there is no toxicologically relevant impurity. As a consequence, even though the batches used in the toxicity studies have not been demonstrated to be representative of the specification, no further concern is raised with regard to the toxicological profile of the new technical specification.

In the available studies on absorption, distribution, metabolism and excretion, thiram was demonstrated to be extensively absorbed after oral administration, widely distributed and excreted mainly via urine and faeces, and by exhalation. A data gap was identified for comparative *in vitro* metabolism studies, performed on animal species used in pivotal studies (rat and dog) and on human material (microsomes or intact cell systems) including, if possible, further identification of the fraction P3 (data gap). With regard to acute toxicity, thiram has a harmonised classification[3] as Acute Tox 4 (Harmful if swallowed and harmful if inhaled), skin and eye irritant (category 2), and skin sensitiser.

In the repeat dose studies with dogs, the lowest no observed adverse effect level (NOAEL) was 0.84 mg/kg body weight (bw) per day based on increased liver weight and clinical chemistry changes in the 1-year study. In the short-term studies with rats and mice, higher NOAELs were identified. Based on the available regulatory genotoxicity tests (negative) and on the limited evidence from published studies, thiram is considered unlikely to be genotoxic.

In the 2-year rat study, the systemic NOAEL was 1.5 mg/kg bw per day based on decreased body weight (gain), C-cell hyperplasia in females, and pancreatic steatosis. The carcinogenic NOAEL is 1.5 mg/kg bw per day based on hepatocellular adenomas (and C-cell adenoma at the high dose). All the experts agreed that a proposal should be presented for classification[4] as **Carcinogen category 2 H351** on the basis of hepatocellular adenoma and C-cell adenoma, considering that the CLP criteria also recommend taking into account benign tumours. It is noted that this 2-year rat study was part of the data supporting the discussions on classification and labelling in ECB (1999–2001); however, different criteria were applied for the assessment of tumours, giving less weight to benign tumours, and no classification for carcinogenicity was proposed at that time. In the 98-week mouse study, the systemic NOAEL was 3.1 mg/kg bw per day based on decreased body weight, anaemia, eye lesions, non-glandular stomach and urinary bladder effects, and dermal necrosis. No treatment-related neoplastic lesions were observed in the mice. Thiram has also a harmonised classification for specific target organ toxicity after repeated exposure (**STOT RE 2**).

In the multigeneration study, no adverse effect was observed on the fertility parameters. The parental NOAEL was 1.5 mg/kg bw per day, whereas the offspring NOAEL was 3 mg/kg bw per day, both based on reduced body weight. Adverse findings in literature studies possibly related to testicular toxicity were not confirmed in good laboratory practice (GLP) studies. The atrophy of testes observed in the 90-day rat study was considered secondary to systemic toxicity (and correlated with high mortality at all doses). Taking into account the limitations of the literature studies, no concern was raised for specific testicular toxicity. For the rat developmental toxicity study, the maternal NOAEL is lower than 7.5 mg/kg bw per day, based on decreased body weight gain over the whole treatment period in all dose groups; and the developmental NOAEL is 7.5 mg/kg bw per day based on decreased fetal weight and developmental delay. For the two rabbit developmental toxicity studies, the relevant maternal NOAEL is 10 mg/kg bw per day (highest dose tested); and the developmental NOAEL is 5 mg/kg bw per day based on an increased incidence of greater presacral vertebra.

During the peer review, thiram was proposed to be classified Carcinogen category 2 but not as reproductive toxicant, in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met.

[3] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

[4] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

On the basis of the available data and current knowledge (EFSA Scientific Committee, 2013), the endocrine disrupting potential of thiram could not be concluded and a data gap was identified for a female pubertal assay (including more than two doses and measurements of thyroid hormones).

For the assessment of the toxicity to the nervous system, some clinical signs of neurotoxicity were observed in all studies (acute, 90-day and developmental neurotoxicity), with brain weight changes in the 90-day and developmental studies, in the presence of systemic and maternal toxicity. On this basis, a neurotoxic potential of thiram cannot be excluded but is not severe enough to trigger specific classification. The relevant neurotoxic NOAELs were 5.9 and 1.6 mg/kg bw per day in the 90-day and developmental studies, respectively.

Several metabolites of thiram were discussed during the Pesticides Peer Review Meeting 148. For the metabolite **M3**, also major rat metabolite, it can be considered covered by the parent. For the other metabolites (M1, M2, M4, M7 and M8), the concept of threshold of toxicological concern (TTC) was considered a valid approach by the experts; however, it cannot be concluded that there is no concern due to the lack of exposure data (see data gaps in Section 3). Some toxicological data were provided for these metabolites: **M1** was negative in genotoxicity studies, **M2** had limited mutagenicity data available and showed alerts in QSAR analysis, no data on the genotoxic potential of DMA (**M4**) were available, and the limited information on **M7** and **M8** did not allow concluding on their toxicological profile and possible reference values (data gap).

For the groundwater metabolite **DMCS**, based on the proposed classification and labelling for carcinogenicity of thiram, it is considered toxicologically relevant according to the guidance document (European Commission, 2003a). Insufficient data are available to conclude on reference values; however, a 90-day toxicity study with rats is under progress and should be finalised in 2017 (data gap). For the drinking water treatment (see Section 4), it has been identified that *N*,*N*-dimethylnitrous amide (NDMA) can be formed from residues of thiram and DMCS. This compound is considered of potential concern since it is acutely toxic if swallowed and if inhaled, carcinogenic category 1B and causing damage to organs through prolonged or repeated exposure (STOT RE 1).

For thiram, the **acceptable daily intake** (ADI) is 0.01 mg/kg bw per day based on the 1-year dog and 2-year rat studies (applying an UF of 100). The first peer review (European Commission, 2003b) had agreed on the same value. The acute reference dose (ARfD) is 0.025 mg/kg bw based on the rat developmental study, and applying an uncertainty factor (UF) of 300 considering the use of a lowest observable adverse effect level (LOAEL) (reduced body weight). The first peer review had agreed on an ARfD of 0.6 mg/kg bw based on the acute neurotoxicity study. The acceptable operator exposure level (AOEL) is 0.02 mg/kg bw per day based on the developmental neurotoxicity study supported by the 90 day dog study and rat multigeneration study. The first peer review had agreed on the same value. The acute acceptable operator exposure level (AAOEL) is 0.025 mg/kg bw based on the rat developmental study, and applying an UF of 300 (increased UF based on the use of a LOAEL).

For the formulation **Thiram 80 WG**, the dermal absorption values are 13% for the dilution and 3% for the slurry formulation. For the formulation **Thiraflo**, the dermal absorption values are 1% for the undiluted formulation (400 g/L) and 3% for the highest dilution (80 g/L).

For Thiraflo, the exposure estimates for operators and workers (with Seedtropex, French model) were below the AOEL. Non-dietary exposure of workers, residents and bystanders was considered unlikely for the seed treatment.

For Thiram 80 WG, the operator exposure estimates for outdoor applications were calculated with the German model, UK Predictive Operator Exposure Model (POEM) and Agricultural Operator Exposure Model (AOEM) (EFSA, 2014). Additionally, a field study was provided for application on pome and stone fruit (using the 75th percentile). For hand-held indoor application in strawberries, predictions were made using the German model, the Dutch model and the Southern European Glasshouse Model. For the application on pome and stone fruit, the exposure estimates were 43% of the AOEL in the EFSA model, including personal protective equipment (PPE) and closed cab: and 70% of the AOEL in the field study with PPE and closed cab, including the highly contaminated operator (outlier value). For the outdoor application on strawberries, the predicted exposure is below the AOEL with the German and EFSA models with the use of PPE; whereas for the indoor application, the estimates are only below the AOEL with the Southern European Glasshouse Model. EFSA notes that the Southern European Glasshouse Model might not be relied upon because the underlying data are not publically available.

During spraying in orchards, the bystander exposure estimates according to Martin et al. (2008) were below the AOEL at a distance of 10 m, but not at 5 m or 3 m, whereas the **residential** exposure was below the AOEL at 10 and 5 m (for both adults and children). It was noted that spraying at an early crop stage would lead to exposures exceeding the AOEL at all distances, but

additional nozzle drift reduction schemes would be sufficient to mitigate the risk. During outdoor spraying on strawberries, both bystander and resident have predicted exposures below the AOEL for all distances.

The worker exposure estimates, taking into account data on residue decline (study on dislodgeable foliar residue (DFR)) and the use of PPE, were below the AOEL only for the outdoor use on strawberries (using EUROPOEM).

3. Residues

The assessment in the residue Section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on MRL calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2016) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Thiram was discussed at the Pesticides Peer Review Meeting TC 142 in November 2016.

Metabolism of thiram in primary crops was investigated upon foliar application on fruit (apples, grapes) and following seed treatment on root (sugar beet), cereals (wheat) and pulse/oilseed (soya bean) crop groups using ^{14}C thiram. The metabolic patterns in the different crops were considered similar. In all plant parts, thiram was never detected except in the surface wash fractions of apple and grapes at early sampling intervals (85–98% of total radioactive residue (TRR)) and was shown to be extensively degraded into polar compounds with further incorporation of the radioactive residues into natural constituents of the plant. In foliar-treated apples and grapes, only the **dimethyldithiocarbamate glucoside (DDC-glucoside)** was identified in grape juice but not further quantified while from the residue trials on apple, apricot and strawberry and performed in compliance with the respective representative uses, significant amounts of **M1** compound were observed in fruits (0.05–0.13 mg/kg). Following seed treatment, the major part of the radioactivity was incorporated into natural constituents in sugar beet root while in wheat and soya bean, **M1** was identified, representing 32% TRR and 7% TRR in wheat straw and grain, respectively and 11% TRR in soya bean seeds. The **DDC-glucoside** compound was also identified in wheat forage (26.5% TRR) while it was recovered at a very low proportion (< 1% TRR) in all soya bean plant parts. It is noted that the exact structure of the metabolite DDC-glucoside was not reported in the RAR. A data gap was therefore identified to provide clarification on the exact structure of this compound and the way it is formed in plants (data gap). Although a limited rate of metabolites' identification was observed in all plant matrices, the experts were of the opinion that sufficient data are available to depict a metabolic pathway of thiram for the representative uses. The residue definition for monitoring is proposed as thiram only. Based on these studies, the following risk assessment residue definition was proposed in the RAR (France, 2016a): *Thiram and its metabolites containing the CS_2 moiety, expressed as thiram*. However, considering that the identified major metabolite M1 does not contain the common CS_2 moiety and the toxicological reference values of the parent compound cannot apply to this compound, EFSA proposes that for risk assessment and considering the significant residue levels of thiram and M1 recovered in fruit crops, the residue is defined as (1) Thiram and (2) M1 compound. The way the residue definition for risk assessment will be expressed is pending upon the requested information on the toxicity profile of M1 (see data gap in Section 2). Having regard to the low to moderate persistence of thiram in soil (lab DT_{90}: 9–150 days, 20°C) and the low to medium persistence of **DMCS** compound in soil (max lab DT_{90}: 190 days, 20°C) and considering the representative use on strawberry, confined rotational crops metabolism studies addressing the fate of thiram and DMCS, respectively, in leafy crops, small grains crops and root crops are required (data gap).

A sufficient number of residue field trials conducted according to the GAPs are available for apple/pear and strawberry that determine, respectively, thiram (specific) and M1. Three additional residue trials on apricot and four residue trials on peach compliant with the SEU GAP that determine, respectively, thiram (specific) and M1 are required (data gap). A complete residue data set compliant with the NEU GAP on cherry and two additional residue trials compliant with the SEU GAP that determine thiram only are requested while complete residue data sets on cherry, respectively, for NEU and SEU and that determine M1 are requested (data gap). All the requested residue trials on apricot, peach and cherry should be analysed within storage time period where acceptable storage stability for thiram (specific) and M1 is demonstrated. The available residue data are supported by storage stability studies where thiram (specific) and M1 were concluded to be stable up to 1 year in cherry, pear, apricot, in high acid (strawberry, grapes) content commodities, in pear processed commodities and in

grape wine. It is noted that a significant degradation of residues of thiram and its metabolites containing the CS_2 moiety (CS_2 moiety method) was observed in lettuce after ca 2 months, suggesting that thiram (specific) might not be stable for 1 year for the whole high water content commodity crop group. Acceptable residues storage stability in high starch (maize grain) content commodities, maize forage and barley straw was demonstrated for up to 5 months for M1 while significant thiram (specific) residues degradation (> 30% of applied radioactivity) was observed in maize commodities (forage, grain and straw) within 2 weeks of freezer storage. Clarification is therefore requested on the observed significant residue degradation of thiram (specific) and M1 in maize commodities under frozen storage conditions (data gap). Meanwhile and since thiram (specific) residue analysis on maize were not covered by the available storage stability data on this compound, the available residue trials on maize and analysing for thiram (specific) cannot be considered as valid and sufficient NEU and SEU GAP-compliant residue trials on maize for the determination of thiram (specific) are requested provided that the residue samples are analysed immediately after sampling (data gap).

Under standard hydrolysis conditions, thiram was shown to be degraded into numerous metabolites, i.e. **M1**, **M2**, **M3**, **M7** and **M8** that accounted for 0.2–5.1% of the applied radioactivity (AR) and **M4** that was recovered as the predominant compound of total residues with 14.4% AR under pasteurisation to 72.6% of AR under sterilisation. With respect to the significant residue levels of thiram (specific) observed in the residue trials on fruit crops, it cannot be excluded that these metabolites may also occur at significant levels in processed commodities. Only residue trials addressing the magnitude of M1 residues in apple, pear and strawberry processed commodities were submitted. Furthermore, insufficient data are available to conclude on the toxicological profile of M1, M2, M4, M7 and M8 metabolites while M3 is a major rat metabolite and therefore considered as covered by the toxicological reference values set for the parent compound (see Section 2). Currently, an overall consumer exposure assessment with regard to the residues in processed commodities cannot be conducted and data gaps were identified to investigate the magnitude of M2, M3, M4, M7 and M8 residues in apple/pear, peach, cherry, strawberry processed commodities (data gap) and to address the respective toxicity of M2, M4, M7 and M8 having regard to the classification of thiram as carcinogenic category 2 (see data gap in Section 2). Moreover, in view of the significant residue levels of M1 recovered in the GAP-compliant field residue trials on apricot and strawberry (0.1 and 0.14 mg/kg, respectively), the experts were of the opinion that the fate of M1 under the standard processing conditions should also be further investigated. Since the stability of M1 under processing could not be established based on the fruit processing residue trials analysing for M1 residues, a hydrolysis study simulating the standard processing conditions for M1 compound is requested (data gap). Meanwhile and considering the outstanding data on the fate of M1 compound under the standard hydrolysis conditions, the magnitude of M2, M3, M4, M7 and M8 residues in fruit processed commodities and the toxicity of these compounds, the residue definition for processed commodities cannot be concluded on.

Assuming that thiram (specific) is the relevant residue for livestock exposure from the representative uses on apple and maize, the livestock dietary burden calculation does not trigger investigation of residues in livestock. Metabolism of thiram in laying hens and lactating goats was, however, investigated with ^{14}C thiram only over four consecutive days and the transfer of total residues was insignificant in poultry and ruminants' matrices (< 0.01 mg/kg). Both in poultry and ruminants, thiram was extensively excreted in urine, faeces and through volatile compounds and less than 10% of the administered radioactivity was recovered in tissues, milk and eggs. The parent compound was also extensively degraded and was never detected in any animal matrix. The major part of the radioactive residues was found to be incorporated into natural compounds (amino acids, proteins, fatty acids, lactose). Although these studies were not conducted in accordance with the current guidance recommendations in terms of dosing period and low rate of metabolites' identification in eggs and ruminants' kidney and muscle mainly, the experts considered that the metabolism of thiram in livestock was sufficiently depicted and the proposed residue definition for monitoring and risk assessment was proposed by default as thiram only. Based on the metabolism of thiram in feed items, animals are expected to be mainly exposed to M1 that was not recovered in any animal matrix and is a minor rat metabolite. It is therefore not possible to conclude whether this compound may undergo further degradation in livestock. However, calculated dietary intakes with regard to M1 residues in apple wet pomace was shown to be negligible (≤ 0.001 mg/kg bw per day for all livestock species) and did not trigger further metabolism data conducted with M1, assuming no degradation of M1 in apple pomace. Having regard to the estimated animal dietary burdens to, respectively, thiram (specific) and M1 and considering the representative uses, MRLs are not required for animal products. Nevertheless, a full assessment of the livestock exposure should be revisited with the potential

inclusion of M1 in the livestock risk assessment residue definition in case further uses with feed items are envisaged and considering also the outstanding data on maize field trials, the processing behaviour of M1 in apple wet pomace being the major contributor to the animal dietary burden and its toxicological properties. Fish metabolism data were not provided and are not required as thiram is considered as not fat soluble and residue levels of M1 in maize grain are < 0.01 mg/kg.

Residue data in pollen and bee products were not provided. Since the representative uses on fruit orchards, strawberry and maize show attractiveness to bees for pollen and/or nectar collection and treatment on fruit crops can take place at flowering, significant residues of thiram and its relevant metabolites in pollen and bee products cannot be excluded and further information is requested (data gap).

For the time being, a consumer risk assessment through dietary intake cannot be conducted for the products of plant origin considering the outstanding data to finalise the residue definitions in primary and rotational crops and in processed commodities. An acute dietary intake calculation was, however, performed using the EFSA PRIMo rev.2 model with regard to thiram residues only in apple, pear and strawberry considering the complete residue data sets for thiram on these crops and the agreed toxicological reference values on thiram. An acute intake concern was identified for these representative uses based on the calculated international estimated short-term intake (IESTI) that accounted for 1,003% of the ARfD for apple, 933% of the ARfD for pear and 442% of the ARfD for strawberry. Having regard to the representative uses and since MRLs for animal matrices are not required, a consumer risk assessment for the products of animal origin is not needed.

A consumer risk assessment has not been conducted for DMCS metabolite occurring in groundwater potentially used as drinking water, since this compound was considered a relevant groundwater metabolite in the light of the toxicological assessment (Section 2).

An MRL application was included in the RAR to modify the existing MRLs, respectively, for total CS_2 residues and for thiram (specific) in maize and products of animal origin. Currently and considering the outstanding data to finalise the overall consumer exposure assessment, an MRL for thiram (specific) on maize cannot be proposed. Having regard to the intended use on maize, MRLs are not required for animal products.

4. Environmental fate and behaviour

Thiram was discussed at the Pesticides Peer Review Meeting TC 141 in October 2016.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, thiram exhibited low to moderate persistence, forming the major (> 10% AR) metabolite DMCS (max. 10.5% AR), which exhibited low to medium persistence. Mineralisation of the thionyl ^{14}C radiolabel to carbon dioxide accounted for 59–75% AR after 120–205 days. The formation of unextractable residues (not sequentially extracted by: chloroform, acetonitrile then acetonitrile/water or acetonitrile then acetonitrile/water) for this radiolabel accounted for 20–48% AR after 8–45 days. In an anaerobic soil incubation, thiram exhibited low persistence forming the major metabolites DMCS and DMTSA (both max. 16% AR). In a laboratory soil photolysis investigation, thiram also exhibited low persistence with no major transformation products being formed. Thiram exhibited slight mobility or was immobile in soil. DMCS exhibited very high soil mobility. It was concluded that the adsorption of thiram and DMCS was not pH dependent.

In laboratory incubations in dark aerobic natural sediment water systems, thiram exhibited very low to low persistence, forming the major metabolite DMCS (max. 59% AR primarily in water). The unextractable sediment fraction (not extracted by sequential use of acetonitrile, acetonitrile/water then acetone) was the major sink for the thionyl ^{14}C radiolabel, accounting for 45–56% AR at study end (60 days). Mineralisation of this radiolabel accounted for 24–32% AR at the end of the study. In a laboratory sterile aqueous photolysis experiment, thiram exhibited very low persistence. A data gap was identified for satisfactory characterisation and or identification of photolysis transformation products (see Section 7). The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolite DMCS and for the representative uses as maize seed treatment for the active substance thiram, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance thiram for non-seed treatment uses, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[5] The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007, 2008) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 58.5–92.5% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in runoff by 80% and erosion runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 3.0) was appropriately used to implement these mitigation measures in the simulations. For the representative uses on apple, pear and peach, the available calculations did not use soil degradation parameters incorporating all the available reliable aerobic soil incubations. The provision of such calculations was therefore identified as a data gap (see Section 7). However, the risk characterisation has been completed for these representative uses using the available PEC calculations, despite the fact that the available PEC for apple, pear and peach underestimate the aquatic exposure that would be predicted when using all the available reliable soil degradation data (for further discussion on this risk characterisation see Section 5).

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2009) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3[5] for the active substance thiram and soil metabolite DMCS. The potential for groundwater exposure from the representative uses by thiram above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios. For the metabolite DMCS, 80th percentile annual average recharge concentrations moving below the top 1 m were calculated to be above 0.1 μg/L in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios for all the representative uses assessed except the use as a seed treatment on maize where this was the case for half (4 out of 8) FOCUS groundwater scenarios. With the available toxicological data, groundwater metabolite DMCS is considered relevant (see Section 2). From the representative uses on apple, pears and peaches where the available calculations did not use soil degradation parameters incorporating all the available aerobic reliable soil incubations, the predicted DMCS concentrations might be marginally overestimated (the provision of updated calculations was identified as a data gap, see Section 7). However, as the predicted concentrations available for apple, pears and peaches are at least an order of magnitude above 0.1 μg/L (7.42–74.38 μg/L), additional calculations are not considered essential to conclude, in the light of the conclusion in Section 2 that

[5] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

DMCS is considered a relevant groundwater metabolite. For the representative uses on cherry and strawberry, the DMCS PEC groundwater were in the range 0.21–42.22 μg/L. This therefore leads to a concern regarding groundwater exposure by the relevant metabolite DMCS for the representative uses on apple, pear, cherry, strawberry and peach. For the representative uses on maize as a seed treatment, groundwater exposure is predicted to be below 0.1 μg/L in geoclimatic situations represented by the Piacenza, Porto, Sevilla and Thiva FOCUS scenarios, with the concentration range in the other four scenarios being 0.14–0.36 μg/L. There is therefore a concern regarding groundwater exposure by the relevant metabolite DMCS in geoclimatic situation represented by the Chateaudun, Hamburg, Kremsmunster and Okehampton scenarios for the seed treatment use on maize.

The applicant provided some information to address the effect of water treatments processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. The conclusion of the applicant in this consideration was, that under the conditions of ozonation and chlorination DMCS (and thiram) might be expected to form the transformation product DMA (M4) which under these same water treatment process conditions is known to produce NDMA which is known to be hazardous (see Section 2). The RMS did not provide a detailed transparent independent assessment of this information on NDMA formation. Therefore, this was identified as a data gap (see Section 7) and leads to an assessment not finalised.

The PEC in soil, surface water, sediment, and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No 283/2013[6], data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002a), the risk to adult honeybees from chronic toxicity and the risk to bee brood, could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

Thiram was discussed at the Pesticides Peer Review Meeting 149 in October 2016.

The first tier risk assessment to **birds** and **mammals** indicated a high risk for all the representative uses. Therefore, several higher tier studies were submitted and considered in a refined risk assessment. The higher tier studies focused on the selection of relevant focal species and ecological parameters, proportion of diet obtained in the treated area (PT) and proportion of different food types (PD). Moreover, studies were available investigating avoidance/repellent effect of thiram, dehusking behaviour of some mammalian species, residue level and residue decline in feed matrices. The data and assessments available for tier 2 refined risk assessments and the endpoint to be used in long-term risk assessment for mammals were discussed at the Pesticides Peer Review Meeting 149. After the meeting, the RMS updated the risk assessments in line with the experts' discussion. As a result, the acute dietary risk to birds and mammals was concluded as low for the representative uses in strawberry and maize. However, the long-term risk for strawberry and maize was assessed as high for several focal species. Additionally, both the acute and long-term risk was indicated as high for the representative uses in orchards (for a number of specific focal species). Population modelling and field effect studies for small mammals were also available. Moreover, for the seed treatment use on maize, an estimation of the critical forage area was made (field area from which an animal must collect all the food each day in order to achieve the relevant toxicological endpoint divided by the assessment factor (AF)). However, even by considering this information alongside the available quantitative risk assessment, the expert at the meeting agreed that a low risk for the representative uses cannot be concluded. Therefore, a data gap was identified to further address the risk to birds and mammals. It is noted that, for the seed treatment use on maize, the RMS has proposed some risk mitigation measures which may be considered at Member State level.

[6] Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 93, 3.4.2013, p. 85–152.

The risk from secondary poisoning and via consumption of contaminated water was assessed as low.

No quantitative risk assessment was available for the metabolite M1 (relevant only for the spray uses). It was considered that risk for metabolite M1 would be covered by the risk assessment of the parent. Since the risk for thiram was assessed as high, a high risk from the exposure to metabolite M1 cannot be excluded (data gap).

For **aquatic organisms**, toxicity data were available on fish, aquatic invertebrates and algae both with the active substance and the representative formulation Thiram 80 WG. For the representative formulation Thiraflo and the pertinent metabolite DMCS, only an acute toxicity study on aquatic invertebrates was available.

Based on the available data, high risk (acute and chronic) to fish and aquatic invertebrates was identified for the representative uses on apple (early and late application), pear (early and late application), peach (early and late application) and cherry using the available FOCUS Step 3&4 PEC_{sw}. For the representative uses (field and greenhouse) on strawberry, low acute risk was identified for fish and invertebrates except for the FOCUS scenario R4 (for the field use) and R3 and R4 (for the glasshouse use), when mitigation measures up to 20 m no-spray buffer zone and 20 m vegetated buffer strip are applied. High chronic risk was identified both for fish and invertebrates also for the representative uses on strawberry (field and greenhouse).

For algae, low risk was identified for the representative uses on apple (early and late application), pear (early and late application), cherry, strawberry (field and greenhouse) using PEC_{sw} Step 3&4. For the representative uses on peach, high risk on algae was also identified for all the relevant exposure scenarios using Step 3 PEC_{sw}. Low risk to all the aquatic organisms was concluded for the representative use on maize.

To refine the acute risk to fish a species sensitivity distribution (SSD) was proposed since enough data were available allowing such type of refinement. However, the data fit well the curve, only when also data on ziram were combined in the SSD. This approach, however, was not accepted since more than five toxicity data are available for thiram, and therefore, the use of endpoints from other active substances is not justified.

For aquatic invertebrates, four higher tier studies were available to refine the acute and chronic risk. The experts at the Peer review Experts' meeting 149, agreed that the two oldest micro/mesocosm studies (Memmert, 2000 and Hommen, 2008; in France, 2016a) are not reliable due to the analytical method (high LOQ of = 1 μg/L) and the uncertainties linked to the exposure of the tested organisms in the system. In the two newer mesocosms, 3 and 4 applications were tested. From the first one (3 applications), a reliable no observed effect concentration (NOEC) could not be derived because of the low abundance of the most sensitive species *Polyarthra* sp.

Due to the effects observed on the most sensitive species *Polyarthra* sp. and *Synchaeta* sp. only a no observed ecologically adverse effect concentration (NOEAEC) (5 μg/L) could be derived from the mesocosms with 4 applications. Based on the MDD (Minimal Detectable Difference) (> 90%) for the most sensitive species and the uncertainties linked to the exposure in the test system, the experts agreed to apply an AF of 4 to the relevant endpoint (NOEAEC = 5 μg/L).

Since the endpoint is based on the recovery of the most sensitive species within 8 weeks, it was only appropriate to use it for refining the chronic risk to aquatic invertebrates but it was not considered to address the acute risk identified. However, when using that endpoint with the agreed AF, high risk was still identified for all the representative spray uses (apple, pear, cherry, peach and strawberry). It has also to be noted that exposure profiles were only submitted for the representative uses on cherry and strawberry. Therefore, it has to be further checked at a Member State level whether the exposure profile in the mesocosm is still considered worst-case/comparable to the predicted exposure for the other representative uses.

A screening assessment for the metabolite DMCS was presented in the RAR where the metabolite was assumed as toxic as the parent compound. However, considering all the available evidence, the approach is not considered appropriate, since for fungicides the identification of the toxophore is not always straightforward given that the toxicity to all the groups of aquatic organisms is very similar. Therefore, a screening assessment considering the metabolite as 10 times more toxic was conducted, except for the aquatic invertebrates for which an acute toxicity study was available. A high risk to aquatic organisms was identified for the all the representative uses of thiram, with the exception of a low acute risk to aquatic invertebrates.

Acute contact and oral toxicity studies on honeybees performed with the active substance and one of the representative formulations, and a chronic laboratory study with the active substance were

available. Considering these data, the RMS has concluded a low acute risk using European Commission (2002a) (HQ approach, trigger of 50). EFSA has performed tier 1 assessments in accordance with EFSA (2013). These assessments indicated a low contact and oral dietary risk for honeybees for the use on maize as seed treatment. As regards the spray uses, a low contact risk was concluded; however, the risk from the dietary exposure was assessed as high. For higher tier risk assessment, a semifield test (single spray application) and a brood feeding test were available. In the brood feeding test, a statistically significant increase in brood termination rate (for eggs) was observed. It is noted that from some aspects, this study may be considered as worst case (i.e. high concentration was used). In the semifield study, no apparent effects on the colonies were observed. On the other hand, both studies had several shortcomings compared to the recommendations of EFSA (2013). Therefore, no firm conclusion can be drawn from these studies and a data gap was identified to further address the dietary risk to bees (for the spray uses).

The acute and chronic risk through exposure via residues in guttation fluid and via surface water was assessed as low in pertinent lower tier risk assessments according to EFSA (2013). No specific assessment was performed for the puddle scenario. Nevertheless, considering all the available data and assessments, a low risk to honeybees (including potential effects on brood development) was concluded from exposure to contaminated water.

Insufficient information was available to perform a risk assessment for sublethal effects (i.e. hypopharygeal glands (HPG), data gap), accumulative effects and metabolites occurring in pollen and nectar (data gap). Data to perform a risk assessment for bumble bees and solitary bees were not available.

As regards non-target arthropods, laboratory studies were available with the standard tier 1 indicator species and with a number of additional species with two formulations. On the basis of a risk assessment with the standard tier 1 indicator species, a high in-field and off-field risk to non-target arthropods was indicated for the representative spray uses (with the exception of the off-field risk for the strawberry uses). A number of higher tier studies (extended laboratory and aged residue studies) with a number of different species were available. These studies confirmed that a high initial in-field risk cannot be excluded. On the other hand, a potential in-field population recovery was demonstrated for all the representative spray uses. On the basis of the available data and assessments, a low risk to non-target arthropods was concluded for the representative use on seed treatment.

For earthworms, high risk was identified for all the spray representative uses (apple, pear, cherry, strawberry, peach, including the use in greenhouse (strawberry) (data gap). Low risk was identified for the representative use on maize and for the metabolite DMCS.

Low risk was identified to soil macroorganisms other than earthworms for all the representative uses when exposed to thiram and the metabolite DMCS.

Low risk was identified for soil microorganisms for all the representative uses of thiram. However, no data are available with the metabolite DMCS.

Low risk was identified for non-target terrestrial plants and organisms involved in biological methods for sewage treatment.

Regarding the potential for endocrine disruption of thiram, all the available information was discussed by the experts at the Pesticides Peer Review Experts' Meeting 149. In the available full fish life cycle, test parameters like vitellogenin and/or sex ratio were not investigated. However, the experts agreed that the endpoint (NOEC) derived from that study can be considered robust enough since the only effects attributable to a potential for endocrine disruption (eggs production and spawning) were only observed at higher concentration than the NOEC, i.e. the available risk assessment using the NOEC covers the potential risk from endocrine mediated effects. Some effects were also observed in birds, i.e. reduced fertility; however, the available data were not fully reliable. Overall, the experts agreed that pending on the data gap identified in Section 2, additional data may be required to draw a firm conclusion on the potential for endocrine disruption of thiram on birds and amphibians.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Thiram	Low to moderate persistence Single first-order and biphasic kinetics DT_{50} 1.8–45.1 days (DT_{90} 9–150 days, 20°C 45% MWHC or pF2)	High risk to earthworms for all the representative uses except maize (data gap)
DMCS	Low to medium persistence Single first-order DT_{50} 10–66 days (20°C 45% MWHC or pF2)	Low risk to soil macroorganisms

DT_{50}: period required for 50% dissipation; DT_{90}: period required for 90% dissipation; MWHC: maximum water-holding capacity.

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Thiram	Slight mobility to immobile K_{Foc} 2,245–24,526 mL/g	No	Yes	Yes
DMCS	Very high mobility K_{Foc} 1.7–2.7 mL/g	Yes Apples and pears 7.93–74.38 µg/L Peach 7.42–53.83 µg/L Cherry 2.59–42.22 µg/L Strawberry 0.21–28.92 µg/L Maize 4 of 8 FOCUS scenarios 0.14–0.36 µg/L	No	Yes, based on the peer review proposed classification Carc Cat 2 for thiram

K_{Foc}: Freundlich organic carbon adsorption coefficient.
(a): At least one FOCUS scenario or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Thiram	High risk for all the relevant exposure scenarios for all the representative uses except for maize
DMCS	High risk for all the relevant exposure scenarios for all the representative uses*

*: High risk could not be excluded based on a screening assessment.

Table 4: Air

Compound (name and/or code)	Toxicology
Thiram	Acute Tox 4 H332 Harmful if inhaled LC_{50} 3.46 mg/L female

LC_{50}: lethal concentration, median.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- A search of the scientific peer-reviewed open literature on the relevant metabolites in the residue Section published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011; relevant for all representative uses evaluated; submission date proposed by the applicant: unknown).
- Validated analytical methods for the determination of the additives in the manufactured technical material (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, see Section 1).
- Determination of the extraction efficiency of the thiram specific method in plants and in food of animal origin (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, see Section 1).
- Monitoring method in body fluids and tissues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, see Section 1).
- Comparative *in vitro* metabolism studies on animal species used in pivotal studies (at least rat and dog) and on human material (microsomes or intact cell systems) including, if possible, further identification of the metabolite fraction P3 (relevant for all representative uses, submission date proposed by the applicant: first quarter 2017, see Section 2).
- During the peer review, thiram was proposed to be classified Carcinogen category 2 but not as reproductive toxicant, in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met. However, a female pubertal assay (including more than two doses and measurements of thyroid hormones) should be provided to clarify the potential endocrine disrupting properties of thiram (relevant for all representative uses, submission data proposed by the applicant: unknown, see Section 2).
- Ninety-day toxicity study with rats for the metabolite DMCS for further assessment of the derivation of reference values for the consumer risk assessment (relevant for all representative uses, submission date proposed by the applicant: 2017, see Section 2).
- Further toxicological assessment (with robust data, including literature search) should be provided for the metabolites M1, M2, M4, M7 and M8 in order to better define their toxicological profile and address the derivation of reference values (relevant for all representative uses, submission date proposed by the applicant: unknown, see Section 2).
- Clarification on the exact structure of dimethyldithiocarbamate glucoside (DDC-glucoside) and the way this compound is formed in plants (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, see Section 3).
- Confined rotational crops metabolism studies addressing the fate of thiram and DMCS, respectively, in leafy crops, small grains crops and root crops (relevant for representative uses evaluated on strawberry, maize; submission date proposed by the applicant: unknown, see Section 3).
- Three residue trials on apricot and four residue trials on peach compliant with the SEU GAP on peach that determine, respectively, thiram (specific) and M1 (relevant for representative use evaluated on peach; submission date proposed by the applicant: unknown, see Section 3).
- A complete residue data set compliant with the NEU GAP on cherry and two additional residue trials compliant with the SEU GAP that determine thiram only, complete residue data sets on cherry, respectively, for NEU and SEU and that determine M1 (relevant for representative use evaluated on cherry; submission date proposed by the applicant: unknown, see Section 3).
- Clarification on the observed significant residue degradation of thiram (specific) and M1 in maize commodities under frozen storage conditions (relevant for representative use evaluated on maize; submission date proposed by the applicant: unknown, see Section 3).

- Sufficient NEU and SEU GAP-compliant residue trials on maize for the determination of thiram (specific) are requested provided that the residue samples are analysed immediately after sampling (relevant for representative use evaluated on maize; submission date proposed by the applicant: unknown, see Section 3).
- The magnitude of M2, M3, M4, M7 and M8 residues in apple/pear, peach, cherry, strawberry processed commodities (relevant for representative use evaluated on apple, pear, peach, cherry, strawberry; submission date proposed by the applicant: unknown, see Section 3).
- A hydrolysis study simulating the standard processing conditions for M1 compound (relevant for representative use evaluated on apple, pear, peach, cherry, strawberry; submission date proposed by the applicant: unknown, see Section 3).
- Residue data in pollen and bee products for thiram and its relevant metabolites (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown, see Section 3).
- PEC in surface water, sediment and groundwater using the final agreed soil DT_{50} were not available except for the representative uses on cherries, strawberries and maize (relevant for the representative uses in apple, pear and peach; submission date proposed by the applicant: unknown see Section 4).
- The applicant provided a position paper on the effect of water treatment processes on the nature of residues present in surface water and groundwater when surface water or groundwater are abstracted for drinking water. A transparent evaluation by the RMS of the information provided was not available (relevant for all representative uses evaluated; see Section 4).
- Data to clearly establish the route of degradation of thiram under aqueous photolysis conditions where all chromatographically resolved fractions > 10% AR were identified, were not available (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to address the dietary risk to birds and mammals for thiram (relevant for all representative uses evaluated) and for M1 (relevant for all representative spray uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the acute risk to aquatic organisms (in particular fish and invertebrates) (relevant for the representative uses on apple (early and late application), pear (early and late application), cherry, peach (early and late application), submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the acute risk to aquatic invertebrates in situation represented by the R4 FOCUS scenario (relevant for the field representative uses on strawberry, submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the chronic risk to aquatic organisms (in particular fish and invertebrates) (relevant for the representative uses on apple (early and late application), pear (early and late application), cherry, peach (early and late application), strawberry (field and greenhouse); submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to algae (relevant for the representative uses on peach, submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the acute risk to fish and the chronic risk to all aquatic organisms when exposed to the metabolite DMCS (relevant for all the representative uses, submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to earthworms when exposed to thiram (relevant for all representative uses evaluated, except maize; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the dietary risk to bees should be provided (relevant for all representative uses evaluated, except maize; submission date proposed by the applicant: unknown; see Section 5)
- Further information to address the risk to sublethal effects on bees (i.e. HPG) should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5)
- Further information to address the risk from potential metabolites occurring in pollen and nectar should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5)

8. Particular conditions proposed to be taken into account to manage the risk(s) identified

- Use of closed cabin and PPE during application in pome and stone fruit in order to have an exposure estimate below the AOEL (see Section 2).
- Use of PPE by operators during outdoor application in strawberry in order to have an exposure estimate below the AOEL (see Section 2).
- Use of PPE by workers re-entering strawberry fields (outdoor) in order to have exposure estimates below the AOEL (see Section 2).
- Use of a 10 m buffer zone for the use in pome and stone fruit in order to have bystander exposure estimate below the AOEL (see Section 2).
- No-spray buffer strips up to 20 m and vegetated buffer strips up to 20 m wide are necessary to conclude low acute risk to fish and invertebrates) for the representative uses on strawberry and to conclude low risk to algae for all the representative uses of thiram except peach (early and late application) (see Section 5).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[7] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) The consumer risk assessment through dietary intake cannot be finalised for the products of plant origin considering the outstanding data to finalise the residue definitions in primary and rotational crops and in processed commodities. Furthermore and considering the agreed toxicological reference values for thiram and the complete residue datasets on thiram for apple, pear and strawberry, an acute dietary intake concern for the consumers was identified for these representative uses (see Sections 2 and 3).
2) The consumer risk assessment from the consumption of drinking water could not be finalised, while a complete evaluation of the information to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water was not available, noting that the applicant has indicated that the hazardous compound NDMA has the potential to be formed if thiram or DMCS are present in the raw water treated (see Sections 2 and 4).
3) During the pesticides peer review, the experts proposed the classification for thiram as Carcinogen category 2 but not as reproductive toxicant, in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met. However, on the basis of the available data and current knowledge (EFSA Scientific Committee, 2013), the endocrine disrupting potential of thiram could not be concluded (see Section 2 and 5).

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it

[7] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

4) A high dietary risk was identified for birds and mammals (see Section 5).

9.3. Overview of the concerns identified for each representative use considered

If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.

Table 5: Overview of concerns

Representative use		Apple	Pear	Cherry	Peach	Field strawberry	Protected strawberry	Maize
Operator risk	Risk identified						X	
	Assessment not finalised							
Worker risk	Risk identified	X	X	X	X		X	
	Assessment not finalised							
Resident/ bystander risk	Risk identified							
	Assessment not finalised							
Consumer risk	Risk identified	X	X			X	X	
	Assessment not finalised	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
	Assessment not finalised							
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X	X	X	X	X	X	
	Assessment not finalised							
Risk to aquatic organisms	Risk identified	X	X	X	X	X	X	
	Assessment not finalised							
Groundwater exposure to active substance	Legal parametric value breached							
	Assessment not finalised							
Groundwater exposure to metabolites	Legal parametric value breached[(a)]	X	X	X	X	X	X	4/8 FOCUS scenarios
	Parametric value of 10 µg/L breached							
	Assessment not finalised							

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2 Where there is no superscript number, see Sections 2–6 for further information.

(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

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Abbreviations

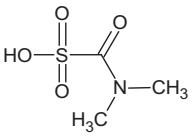
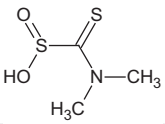
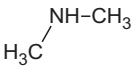
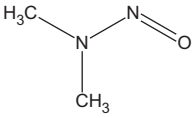
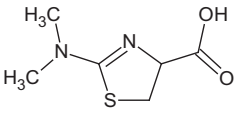
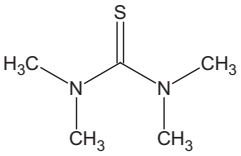
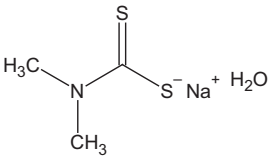
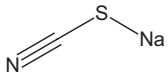
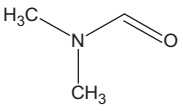
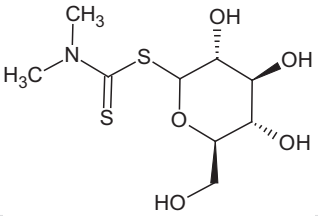
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AOEM	Agricultural Operator Exposure Model
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
CLP	classification, labelling and packaging
DDC	dimethyldithiocarbamate
DFR	dislodgeable foliar residue
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
ECHA	European Chemicals Agency
EEC	European Economic Community
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FS	flowable concentrate for seed treatment
GAP	Good Agricultural Practice
GLP	good laboratory practice
HPG	hypopharygeal glands
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MDD	minimal detectable difference
MRL	maximum residue level

MWHC	maximum water-holding capacity
NMDA	*N*,*N*-dimethylnitrous amide
NOAEL	no observed adverse effect level
NOEAEC	no observed ecologically adverse effect concentration
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
POEM	Predictive Operator Exposure Model
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAR	renewal assessment report
RMS	rapporteur Member State
SFO	single first-order
SMILES	simplified molecular-input line-entry system
SSD	species sensitivity distribution
TRR	total radioactive residue
TTC	threshold of toxicological concern
UF	uncertainty factor
WG	water-dispersible granule
WHO	World Health Organization

Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2017.4700

Appendix B – Used compound codes

Code/trivial name[(a)]	Chemical name/SMILES notation	Structural formula
DMCS	(Dimethylamino)(oxo)methanesulfonic acid CN(C)C(=O)S(=O)(=O)O	
DMTSA	(dimethylamino)(thioxo)methanesulfinic acid CN(C)C(=S)S(=O)O	
DMA (M4)	*N*-Methylmethanamine CNC	
NDMA	*N*,*N*-dimethylnitrous amide CN(C)N=O	
M1	2-(Dimethylamino)-4,5-dihydro-1,3-thiazole-4-carboxylic acid CN(C)C1=NC(CS1)C(O)=O	
M2	1,1,3,3-Tetramethylthiourea CN(C)C(=S)N(C)C	
M3	Sodium dimethylcarbamodithioate hydrate [Na+].O.CN(C)C([S-])=S	
M7	sodium thiocyanate N#CS[Na]	
M8	*N*,*N*-Dimethylformamide CN(C)C=O	
DDC-glucoside	1-*S*-(Dimethylcarbamothioyl)-1-thio-D-glucopyranose S=C(SC1O[C@H](CO)[C@@H](O)[C@H](O)[C@H]1O)N(C)C	

SMILES: simplified molecular-input line-entry system.
(a): The compound name in bold is the name used in the conclusion.