KEMI
Swedish Chemicals Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Thiram

EC No 205-286-2

CAS No 137-26-8

Evaluating Member State: Sweden

Dated: 18 March 2015

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2014

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. CONCLUSION

1. CONCERN(S) SUBJECT TO EVALUATION

Thiram was originally selected for substance evaluation in order to clarify suspected risks about:

- Human health/Potential endocrine disruptor

- Exposure/Wide dispersive use, high RCR, aggregated tonnage

During the evaluation no other concerns were identified. The scope of the evaluation was limited to clarifying potential endocrine disrupting properties of thiram relevant to human health only (thus, not for the environment) and potential exposure of workers owing to high RCR.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Thiram has a harmonised classification in Annex VI to the CLP Regulation[2] covered by the index number 006-005-00-4 (see Table 8).

Thiram is approved as an active substance in plant protection products until 30 April 2017. Currently, France (Rapporteur Member State (RMS)) and Belgium (Co-Rapporteur Member State) are evaluating thiram for renewal of approval within the AIR-3 programme (Regulation (EU) No 686/2012)[3].

Thiram is also used as a biocide and is included in the review programme for existing active substances used in biocidal products. Belgium is appointed as the RMS and the time limit for submitting the assessment report is 31 December 2020 (Regulation (EU) No 1062/2014)[4].

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

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[2] 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.

[3] COMMISSION IMPLEMENTING REGULATION (EU) No 686/2012 of 26 July 2012 allocating to Member States, for the purposes of the renewal procedure, the evaluation of the active substances whose approval expires by 31 December 2018 at the latest.

[4] COMMISSION DELEGATED REGULATION (EU) No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action	✓

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Not applicable, see section 5.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN	
The concern could be removed because	**Tick box**
Clarification of hazard properties/exposure	✓
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

Thiram caused systemic toxicity in several *in vivo* studies even at low dose ranges. The available *in vitro* data shows that thiram is cytotoxic. In the light of general systemic toxicity, the available data set does not allow concluding that thiram alters function of the endocrine system and consequently causes adverse health effects.

No professional or consumer uses are identified for thiram in the registration dossier. The long-term DNELs for systemic effects for workers were derived from the lowest NOAEL observed among all the available studies. Since thiram is a skin sensitiser the registrant aims to avoid dermal exposure to workers to the extent possible.

The RCRs for all the exposure scenarios for workers are below 1. With the proposed operational conditions and risk management measures the risks to workers are under control for the identified uses of thiram.

5.2. Other actions

None proposed.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable, see section 5.

Part B. SUBSTANCE EVALUATION

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Thiram was originally selected for substance evaluation in order to clarify suspected risks about:

- Human health/Potential endocrine disruptor

- Exposure/Wide dispersive use, high RCR, aggregated tonnage

During the evaluation no other concerns were identified but it is important to emphasize that the scope of the evaluation was limited to clarifying initial grounds for concern.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Endocrine disruption – Human health	Concern not substantiated.
Risks to workers	Concern not substantiated.

7.2. Procedure

The updated Community rolling actin plan (CoRAP) was published on the ECHA website on 26 March 2014. The scope of the evaluation was limited to clarifying potential endocrine disrupting properties of thiram relevant for human health only (thus, not for the environment) and potential exposure of workers owing to high RCR.

On 17 July 2014 the eMSCA performed PubMed search for the string "thiram OR 137-26-8 OR tetramethylthiuram OR thiuram" and found 20 *in vivo* and 13 *in vitro* studies to be relevant for the current scope of evaluation.

Studies reported in the registration dossier for the endpoints toxicokinetics, repeated dose toxicity, carcinogenicity, toxicity to reproduction, and specific investigations – neurotoxicity were also reviewed. Upon request, the registrant provided the full study reports of all the studies under these endpoints on 3 September 2014. Along with these the registrant provided also the full study report of an unpublished developmental neurotoxicity (DNT) study not yet reported in the registration dossier.

Thiram was discussed at the 3rd Endocrine Disruptor Expert Group meeting[5], 11-12 November 2014.

[5] Information on the role and mandate of this group can be found on the ECHA webpage http://echa.europa.eu/en/addressing-chemicals-of-concern/substances-of-potential-concern/substance-specific-groups/endocrine-disruptor-expert-group.

Upon further request, the registrant commented on the efficiency and specification of gloves and provided an unpublished *in vitro* dermal penetration study, not yet reported in the registration dossier, on 16 January 2015.

On 16 March 2015 the registrant was reminded of its obligation to update the registration dossier with relevant new information without undue delay.

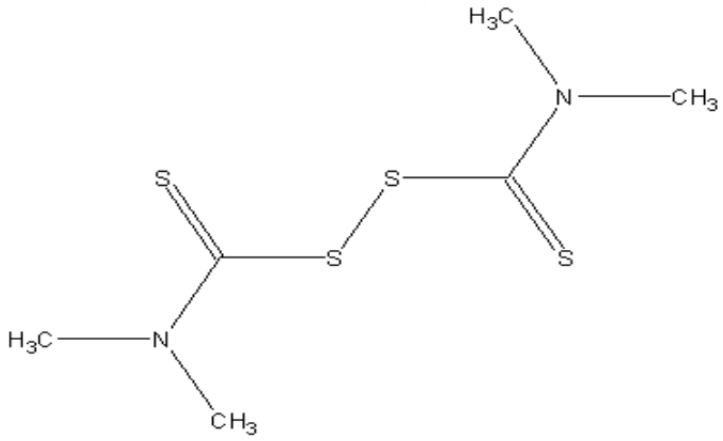
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Thiram
EC number:	205-286-2
CAS number:	137-26-8
Index number in Annex VI of the CLP Regulation:	006-005-00-4
Molecular formula:	$C_6H_{12}N_2S_4$
Molecular weight range:	240.4
Synonyms:	TMTD

Type of substance: Mono-constituent

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid
Melting/freezing point	144 - 146 °C

Vapour pressure	0.00002 Pa at 25 °C
Water solubility	0.0171 g/L at pH 7 and 20 °C
Partition coefficient n-octanol/water (Log Kow)	1.8 at pH 4 2.1 at pH 7 1.9 at pH 10
Flammability	Non flammable
Explosive properties	Non explosive
Oxidising properties	Waived
Granulometry	Particle size Percentile Mean D10 0.74 µm D50 4.31 µm D90 15.74 µm
Dissociation constant	pKa 8.19 at 25 °C

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 7

USES	
Uses as intermediate	None identified in the registration dossier
Formulation	Formulation into liquid preparations
	Formulation into solid preparations
Uses at industrial sites	Inclusion in a matrix in the general rubber goods industry
	Inclusion in a matrix in the tyre industry
Uses by professional workers	None identified in the registration dossier
Consumer Uses	None identified in the registration dossier
Article service life	Rubber articles

Thiram is also used as an active substance in plant protection products and as a biocide which are not in the scope of the REACH Regulation.

Technical function of thiram is as an accelerator in the vulcanisation of rubber (Health Council of the Netherlands, 2003).

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
006-005-00-4	Thiram (ISO) tetramethylthiuram disulphide	205-286-2	137-26-8	Acute Tox. 4* Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2 Acute Tox. 4* STOT RE 2* Aquatic Acute 1 Aquatic Chronic 1	H302 H315 H317 H319 H332 H373** H400 H410	M=10	

* The classification as obtained from Annex VII shall then substitute the minimum classification indicated in this Annex if it differs from it.
** The classification under 67/548/EEC indicating the route of exposure has been translated into the corresponding class and category according to this Regulation, but with a general hazard statement not specifying the route of exposure as the necessary information is not available.

7.6.2. Self-classification

Thiram has a harmonised classification in Annex VI to the CLP Regulation and the registrant has not proposed any self-classification.

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Two key and one supporting study performed in rats were reported under toxicokinetics in the registration dossier. The key studies were GLP-compliant and in accordance to the US EPA guideline OPP 85-1 (Metabolism and Pharmacokinetics). The study reported as supporting was a single dose experiment with an objective to identify metabolites.

An unpublished *in vitro* dermal penetration study on thiram using human skin performed with GLP-compliance and in accordance to OECD 428 and 417, not yet reported in the registration dossier, was provided by the registrant to the eMSCA during the evaluation. In this study, the dermal absorption values for thiram for the two dose levels tested, 1.46 g/L and 617 g/L, were found to be 12% and 3%, respectively.

Summary of toxicokinetics

Absorption: Oral absorption of thiram is complete and rapid. The dermal absorption values for thiram at concentrations 0.15% and 62% are 12% and 3%, respectively. The registrant used a default dermal absorption value of 10% for risk assessment.

Distribution: Tissue levels ranged from 1.2 to 3.8% of the administered dose. The highest percentage was seen in blood (0.9 – 1.99%), liver (0.4 – 1.8%), muscle (0.05 – 0.6%), bone (~ 0.5%) and kidney (0.07 – 0.16%). All other tissues, in both sexes, contained less than 0.1% of the administered dose.

Metabolism: Following five metabolites were identified: DDC (dimethyldithiocarbamate)-thiosulfenic acid, DDC-alanine, 2-thioxothiazolidine-4-carboxylic acid, DDC-glucuronide, and DDC-methyl ester.

Excretion: At least 83.7% and 89.6% of the administered dose of thiram was eliminated within four days from males and females, respectively.

7.9.2. Acute toxicity and Corrosion / Irritation

Not evaluated.

Thiram has a harmonised classification as
Acute Tox. 4; H302: Harmful if swallowed
Acute Tox. 4; H332: Harmful if inhaled
Skin Irrit. 2; H315: Causes skin irritation
Eye Irrit. 2; H319: Causes serious eye irritation

7.9.3. Sensitisation

Not evaluated. Thiram has a harmonised classification as Skin Sens. 1; H317: May cause an allergic skin reaction.

7.9.4. Repeated dose toxicity

In the following tables studies reported in the registration dossier are summarised.

Table 9: Summary of the repeated dose toxicity studies via oral route reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Repeated dose toxicity: oral.001	1/EU Method B.26 (Sub-Chronic Oral Toxicity Test: Repeated Dose 90-Day Oral Toxicity Study in Rodents)	Thiram 99.43% *Rat/Crl: CD(SD)BR/M&F*	10 Oral via feed *13 week*	Males: 0, 3.5, 38 and 67 mg/kg bw Females: 0, 4, 38 and 80 mg/kg bw	Effects at high and/or mid doses: Reduced food consumption & bd wt gain, lower absolute organ wt & higher organ-to-body wt percentages. Haemolysis including lower RBC count, Hb and Hc, as well as higher leukocyte count in females and higher MCV, MCH in both sexes. Lower albumin and higher urea nitrogen and chloride in females as well as lower total protein and glucose in both sexes. Macrosopic and microscopic findings in non-glandular stomach and mesenteric lymph nodes.	NOAEL: 4 mg/kg bw/d based on reduced bd wt. & food consumption and alterations in clinical blood chemistry at next dose level.
Exp Key Repeated dose toxicity: oral.002	1/EPA OPP 82-1 (90-Day Oral Toxicity)	Thiram 97.5% *Dog/Beagle/M&F*	4 Oral via feed *90 days*	M: 0, 1.94-2.58, 6.17-7.85, 10.55-14.69 mg/kg bw/d F: 0, 2.14-2.55, 6.67-8.01, 11.75-13.42 mg/kg bw/d	Mid and/or high dose: Reduced food consumption & bd wt gain. Reduced RBC count, increased MCV & MCH, higher platelet count. Lower total protein, albumin and higher cholesterol. Hepatocellular degeneration with granulomatous inflammation. Low dose: Reduced RBC count increased MCV values and lowered albumin in males.	NOAEL: Ca. 2 mg/kg bw/d. eMSCA remark: No NOAEL could be established in this study as at ca. 2 mg/kg bw/d haematological effects were statistically significant.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Repeated dose toxicity: oral.003	1/EPA OPP 83-1 (Chronic Toxicity)	Thiram 97.5% *Dog/Beagle/M&F*	6 Oral via feed *52 weeks*	M: 0, 0.84, 2.61, 7.35 mg/kg bw/d F: 0, 0.90, 2.54, 7.23 mg/kg bw/d	No effects on food consumption or bd wt at any dose level. High dose: Reduced RBC in males. Decreased total protein & albumin, increased cholesterol. Increased abs. (in males) & rel. liver wts. Increased liver-to-brain wt ratios in males. Mid dose: No hematological effects. Decreased total protein, increased cholesterol (in males). Increased abs. & rel. liver wts in males	NOEL: 0.84 - 2.54 mg/kg bw/d
Exp Key Repeated dose toxicity: oral.004	1/No guideline followed, range finding study for a carcinogenicity study	Thiram 97.5% *Mice/CD-1/M&F*	10 Oral via feed *4 weeks*	M: 51-58, 101-115, 177-226 mg/kg bw/d F: 59-66, 111-127, 221-281 mg/kg bw/d	Reduced food consumption (in males & females) and reduced bd wt gain, lower RBC count, Hb and Hc (in males) at all dose levels. In females, reduced RBC count at mid-dose, increased platelet count in mid & high doses, and decreased glucose at high dose.	LOAEL: 51 - 59 mg/kg bw/d based on reduced body weight and food consumption, altered haematological parameters and clinical signs
Exp Key Repeated dose toxicity: oral.005	1/No guideline followed, range finding study for a sub-chronic study	Thiram 99.43% *Dog/Beagle/M&F*	2 Oral via feed *4 weeks*	M: 4, 16 and 26-15 mg/kg bw/d F: 4, 12 and 27-21 mg/kg bw/d	Reduced bd wt gain (at mid & high doses), lower RBC & platelet counts, Hb, Hc values (in males at mid & high doses). Higher ALT, AST and AP, and hepatocellular degeneration with sinusoidal cell proliferation and pigmentation (at high dose).	NOAEL: 4 mg/kg bw/d based on reduced body weight and food consumption and alteration in clinical blood parameters at next dose level

Table 10: Summary of the repeated dose toxicity study via dermal route reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Repeated dose toxicity: dermal. 001	1/EPA OPP 82-2 (Repeated Dose Dermal Toxicity -21/28 Days)	Thiram 99% *Rabbit/ New Zealand White/ M&F*	5 Dermal *3 weeks*	0, 100, 300, 1000 mg/kg bw/d	Erythema with/without oedema in all groups with greater frequency in mid & high doses. Reduced bd wt gain & food consumption, increased liver enzymes GOT, GPT, and cholesterol levels (in females) and increased alkaline phosphatase activity in both sexes at high dose.	NOEL: 300 mg/kg bw/d based on systemic effects at next dose level No NOEL identified for dermal irritation

Summary and discussion on repeated dose toxicity

Thiram has a harmonised classification as STOT RE 2; H373: May cause damage to organs through prolonged or repeated exposure. The dog seems to be the most sensitive species among the tested ones for thiram toxicity. The **lowest NOAEL of 0.84 mg/kg bw/d** was observed in a one-year dog study (Exp Key Repeated dose toxicity: oral.003) based on increased liver weight, increased blood cholesterol and decreased total protein observed in males at the next dose level of 2.61 mg/kg bw/d. **This NOAEL was used by the registrant for the chemical safety assessment of thiram to derive long-term DNELs for systemic effects.**

7.9.5. Mutagenicity

Not evaluated.

7.9.6. Carcinogenicity

In the following table studies reported in the registration dossier are summarised.

Table 11: Summary of the carcinogenicity studies via oral route reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Carcinogenicity.001	1/EPA OPP 83-2 (Carcinogenicity)	Thiram 97.6% *Mice/CD -1/M&F*	50 Oral via feed *97 weeks*	M: 0, 3, 24, 50 mg/kg bw/d F: 0, 3, 57, 112 mg/kg bw/d	Decreased food consumption & bd wt gain in mid & high dose groups. Mid dose: Increased MCV & MCH and decreased MCHC values in males. Reduced RBC, increased WBC and platelet count, decreased mean absolute brain wt & increased splenic pigmentation (also in high dose) in females. Hyperkeratosis of non-glandular stomach in males. Retinal atrophy and microscopic effects in the urinary bladder in both sexes (also in high dose).	NOAEL carcinogenicity: 50 -112 mg/kg bw/d, highest dose

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
					High dose: Decreased MCHC values in males. Increased platelet count, and decreased RBC, Hb, and Hc values in females. Hyperkeratosis of non-glandular stomach in both sexes.	
Exp Key Carcinogenicity.002	2/EPA 83-5 (1982) [Deviations: Organ wts of adrenals, epididymides, uterus, spleen, & heart were not determined]	Thiram 97.5% *Rat/Sprague-Dawley/M&F*	60 Oral via feed *104 weeks*	M: 0, 1.46, 7.31, 14.66 mg/kg bw/d F: 0, 1.80, 8.86, 18.57 mg/kg bw/d	Low dose: Reduced food consumption in both sexes and reduced absolute kidney wt & kidney-to-brain wt ratios in males. Reduced bd wt gain & food consumption in mid & high doses. Lower RBC count, Hb, Hc and higher MCV & MCH values in females in mid & high doses. Reduced absolute kidney wt and kidney-to-brain wt ratios in males in mid and high dose. Increased relative brain wt (in both sexes), liver wt (in females) and lower right ovary wt & right ovary-to-brain wt ratios in high dose.	NOAEL carcinogenicity: 14.66 - 18.57 mg/kg bw/d, highest dose NOAEL general toxicity: 1.46 - 1.80 mg/kg bw/d based on effects on bd wt gain and anatomic pathology findings eMSCA remark: Since there were statistically significant effects at the lowest dose it should be the LOAEL.

Summary of carcinogenicity

Thiram was not carcinogenic in rats or mice. The studies on carcinogenicity are summarised to compare the adverse effects observed in different chronic studies.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

In the following tables key studies reported in the registration dossier are summarised.

Table 12: Summary of the study on fertility effects reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Toxicity to reproduction.001	1/EPA OPP 83-4 (Reproduction and Fertility Effects)	Thiram 97.84% *Rat/Charles River Crl:CD® VAF/Plus®/M&F*	26 Oral via feed *2-gen study*	F0 males: 0, 1.52, 2.94 and 8.88 mg/kg/ bw/d F0 females: 0, 2.27, 4.61 and 13.89 mg/kg bw/d F1 males: 0, 1.83, 3.82 and 11.37 mg/kg bw/d F1 females: 0, 2.39, 5.12 and 16.21 mg/kg bw/d	Reduced body weight and food consumption in F0 animals at mid & high doses. Reduced body weight in F1 and F2 animals at high dose. "Organ weight: There were no treatment-related effect on testes weight in the F0 and F1 generation males." "Necropsy: All macrosopic and microscopic changes seen in the rats were considered to be spontaneous or agonal." "Reproductive performance: No treatment-related differences in the male and female copulatory and fertility indices, the gestation index, the mean copulatory interval or the mean gestation length were observed. Sperm were present, motile and morphologically normal."	NOAEL, parental systemic toxicity: ca. 1.5 mg/kg bw/d based on body weight and food consumption reduction NOAEL, offspring systemic toxicity: ca. 3 mg/kg bw/d based on body weight reduction NOAEL, reproduction: > 9 mg/kg bw/d, highest dose in F0 males.

Table 13: Summary of the key studies on developmental toxicity reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Developmental toxicity / teratogenicity.001	1/OECD Guideline 414 (Prenatal Developmental Toxicity Study)	Thiram 98.26% *Rabbit/ New Zealand White/ F*	20 Oral gavage *GD 7-19*	0, 1, 5 and 10 mg/kg bw/d	Increase in body weight gain and food consumption which was not considered to be treatment related. Slight increase in the uterine weights which was not considered to be treatment related (control: 392.2 g, low: 470.7 g, mid: 417.8 g, and high: 478 g). No treatment related teratogenic malformations. Compared to controls, increase in no. of fetuses with 27 presacral vertebrae at high dose which was within historical control range.	NOAEL, maternal and developmental toxicity: > 10 mg/kg bw/d, highest dose
Exp Key Developmental toxicity / teratogenicity.002	1/EPA OPP 83-3 (Prenatal Developmental Toxicity Study)	Thiram 99.5% *Rabbit/ New Zealand White/ F*	15-20 Oral gavage *GD 6-19*	0, 1, 2.5 and 5 mg/kg bw/d	Reduced maternal body weight gain at high dose. No further treatment related adverse effects were reported in the results.	NOAEL, maternal: 2.5 mg/kg bw/d NOAEL, developmental: > 5 mg/kg bw/d, highest dose
Exp Key Developmental toxicity / teratogenicity.003	1/EPA OPP 83-3 (Prenatal Developmental Toxicity Study)	Thiram 99.82% *Rat/Sprague-Dawley /F*	25 Oral gavage *GD 6-15*	0, 7.5, 15, and 30 mg/kg bw/d	Reduced body weight in mid and high dose females. Lower placental weight compared to control at low, mid and high doses but the values were within historical control range. Reduced fetal body weight and slightly higher incidence of small fetuses at mid dose (compared to control but within historical control range) and at high dose groups. Increased incidences of reduced 13th ribs (but not in a dose-response manner; % incidence in control: 3.2, low dose: 6.1, mid dose: 13.1, and high dose: 9.5).	No maternal toxicity NOAEL identified; LOAEL: 7.5 mg/kg bw/d based on effects on body weight. NOAEL, fetotoxicity: 15 mg/kg bw/d based on slightly reduced foetal weight at this dose, but within historical control range.

In addition to the three key studies summarized above, the registration dossier includes two supporting studies under developmental toxicity endpoint which were range-finding studies performed in the rabbit and the rat to select dose-levels for pre-natal developmental toxicity studies. Further information on these can be found on the ECHA dissemination webpage.

Summary of toxicity to reproduction

No adverse effects that may warrant classification of thiram for this endpoint were observed in the above studies.

7.9.8. Specific investigations: Neurotoxicity

In the following table key studies reported in the registration dossier are summarised.

Table 14: Summary of the neurotoxicity studies reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/ dose Route *Duration*	Doses	Results	Effect Level
Exp Key Neurotoxicity.001	2/US-EPA FIFRA, Guideline 82-5 (with deviations)	Thiram 98.76% *Rat/Sprague-Dawley /M& F*	15 Oral via feed *90 days*	M: 0, 1.5-2.3, 5.9-10.2 and 22.8-40.2 mg/kg bw/d F: 0, 1.8-2.6, 6.9-10.1 and 21.6-43.9 mg/kg bw/d	Reduced body weight gain and food consumption in mid and high dose groups. Increased number of rears and incidence of hyperactivity during weeks 8 & 13 in high dose males and during week 8 only in low, mid, & high dose females. Lower brain weights in high dose animals. No treatment related effects on motor activity and histopathology.	NOEL, systemic toxicity: ca. 1.5 - 2.3 mg/kg bw/d (M), ca. 1.8 - 2.6 mg/kg bw/d (F) NOEL, neurotoxicity: ca. 5.6 - 10.2 mg/kg bw/d (M), ca. 6.9 - 10.1 mg/kg bw/d (F)
Exp Key Neurotoxicity.002	2/OECD Guideline 424 (Neurotoxicity Study in Rodents) (with deviations: no histopathology)	Thiram 98.7% *Rat/Alpk:APfSD (Wistar derived)/M&F*	10 Oral gavage *Single dose followed by 14 days observation period*	0, 10, 25, 60 and 150 mg/kg bw/d	Lower body weights and food consumption in 60 and 150 mg/kg bw groups. Reduced motor activity in the high dose females.	NOEL, systemic toxicity: 25 mg/kg bw/d based on effects on body weight at next dose level NOEL, neurotoxicity: 150 mg/kg bw/d (M), and 60 mg/kg bw/d in females based on effects on motor activity at next dose level.
Exp Supporting Neurotoxicity.003	2/US EPA FIFRA 81-8 (with deviations)	Thiram 98.76% *Rat/Sprague-Dawley /M&F*	15 Oral gavage *Single dose followed by 16 days observation period*	0, 5, 150 and 600 mg/kg bw/d	Decrease in body temperature, no. of rears, startle response, muscle tone and increase in grip strength in mid and high dose groups 2.5 hrs post-treatment. Most of the symptoms except body temperature disappeared at days 7 & 14. "There were no treatment-related macroscopic or microscopic pathological changes affecting the nervous system in any of the high dose animals."	NOAEL, neurotoxicity: 5 mg/kg bw/d based on effects on arousal, parasympathetic nervous system activity, body core temperature and motor activity at 150 mg/kg bw/d.

In the following table an unpublished GLP-compliant study performed according to the US EPA developmental neurotoxicity study guideline is summarized. The study is not yet reported in the registration dossier but provided by the registrant to the eMSCA during the evaluation.

Table 15: Summary of the unpublished study on neurotoxicity not yet reported in the registration dossier.

Reference	Reliability /guideline	Test material *Species/strain/Sex*	No./sex/dose Route *Duration*	Doses	Results	Effect Level
Experimental study, unpublished report	1/US EPA OPPTS 870.6300 (Developmental Neurotoxicity Study)	Thiram 99.6% *Rat/Crl: CD (SD) IGS BR/F*	24 Oral via feed *GD 3-20*	0, 1.6-4.1, 3.8-9.2, and 6.6-18 mg/kg bw/d	High dose females: Reduced body weight gain & food consumption and clinical signs of toxicity such as pale skin and/or eyes and irregular respiration. High dose pups: Reduced body weight gain. Differences in the pre-pulse inhibition of the auditory startle response of males and impaired performance of females in the Morris water maze at day 61/62. No treatment-related histopathological effects were observed.	NOAEL, maternal toxicity: 3.8-9.2 mg/kg bw/d based on effects on body weight gain, food consumption & clinical signs of toxicity at next dose level. NOAEL, functional DNT: 3.8-9.2 mg/kg bw/d based on effects on sensory function in males and learning & memory in females. NOAEL, morphological DNT: 6.6-18 mg/kg bw/d, highest dose

Discussion and conclusion on neurotoxicity

In this section studies from peer-review literature are also included, the summaries of which are in Table 17 or Table 18.

In vivo data

In a developmental neurotoxicity study in rats (unpublished and not yet reported in the registration dossier) according to the US EPA guideline (OPPTS 870.6300), thiram was administered via feed from gestation day 3 to 20 at dose levels of 1.6 – 4.1, 3.8 – 9.2, and 6.6 – 18 mg/kg bw/d. The high dose females had reduced body weight gain and food consumption, and clinical signs of toxicity such as pale skin and/or eyes and irregular respiration. The high dose pups had reduced body weight gain and differences were observed

in the pre-pulse inhibition of the auditory startle response of males and impaired performance of females in the Morris water maze test at day 61/62. No treatment-related histopathological effects were observed at any dose levels. The NOAEL for maternal toxicity was set at 3.8 – 9.2 mg/kg bw/d based on effects observed in the high dose group. The NOAEL for functional developmental neurotoxicity was also 3.8 – 9.2 mg/kg bw/d based on the effects on sensory function of males and learning and memory in females in the high dose group. No morphological effects were observed at any dose level; thus, the NOAEL for morphological developmental neurotoxicity was set at the high dose, 6.6 – 18 mg/kg bw/d (Experimental study, unpublished report).

In a sub-chronic adult neurotoxicity study in rats, thiram was given via feed at 1.5 – 2.3, 5.9 – 10.2, and 22.8 – 40.2 mg/kg bw/d in males and 1.8 – 2.6, 6.9 – 10.1, and 21.6 – 43.9 mg/kg bw/d in females. Reduced body weight gain and food consumption in mid and high dose rats and lower brain weights in high dose rats were observed. The high dose males showed increased number of rears and increased incidence of hyperactivity during weeks 8 and 13, and similar effects were observed during week 8 only in low, mid, and high dose females. No treatment related effects were observed on motor activity and histopathology (Exp Key Neurotoxicity.001).

Neurotoxic effects of thiram were also observed in two acute neurotoxicity studies in rats. 150 mg thiram/kg bw reduced motor activity in females (Exp Key Neurotoxicity.002). Two-and-half hours post-treatment with a single dose of 150 and 600 mg thiram/kg bw, rats showed decreased number of rears, startle response, muscle tone and an increased grip strength. However, these symptoms disappeared at days 7 and 14 (Exp Supporting Neurotoxicity.003).

In the chronic study by Maita et al. (1991), thiram at 13.8 mg/kg bw/d caused regressive changes of the sciatic nerve accompanied by atrophy of the calf muscle in female rats. In 1976, Lee and Peters published a study with results from two chronic experiments carried out to study the neurotoxic and behavioural effects of thiram in rats. In the first experiment, rats (male and female) were given thiram for 80 weeks at 5.3 – 6.1, 20.4 – 25.5, and 52 – 66.9 mg/kg bw/d. High dose females showed neurotoxic effects characterised by ataxia and paralysis of the hind legs. Neuropathology of two of the high dose ataxic females showed demyelination, degeneration of the axis cylinders, and presence of macrophages in the nerve bundle of the sciatic nerve; and degeneration in the ventral horn of the lower lumbar region of the spinal cord. The non-ataxic rats showed behavioural effects such as altered walking pattern of the hind legs with decreases in stride width and the angle between contralateral steps (mid and high dose females) and the high dose females required significantly more shock-motivations and cleared lower height in a jump/climb ability test. An open-field study indicated hyperactivity in the non-ataxic rats (mid and high dose) of both sexes. In the second experiment, 24 female rats were given 65.8 mg thiram/kg bw/d for 36 weeks. About 17% of the animals developed ataxia and paralysis and ca. 38% showed clasping of the hind feet when picked up by the tail. Histopathology of the ataxic rats suggested the peripheral nerve as the primary site of the lesion.

Single oral doses of thiram in male rats caused significant reduction in orientation hypermotility (240 mg/kg bw), decreased subcortical EEG activity (40 and 240 mg/kg bw), and decreased re-formation of norepinephrine (60 mg/kg bw) (Thuránszky et al., 1982). Intraperitoneal administration of thiram to male rats at 80 mg/kg bw cumulative dose after four daily doses caused mild hind limb paresis (Komulainen and Savolainen, 1985).

In vitro data

Han et al. (2003) investigated the neurotoxic mechanism of dithiocarbamates using neuronal-like PC12 (rat pheochromocytoma) cells with thiram concentrations ranging from 0.01 to 10 µM. Thiram induced dose- and time-dependent cell death with LC50 of 0.3 µM. With 1 µM thiram, determination of type of cell death showed typical apoptotic features like DNA fragmentation and an increase of subdiploid nuclei. Thiram at 0.1 – 1.5 µM concentrations induced rapid and sustained increase in intracellular Ca^{+2} ions in a dose-dependent manner which was completely blocked by flufenamic acid, a non-selective cation channel inhibitor. Thiram induced apoptotic cell death was inhibited by BAPTA-AM, an intracellular Ca^{+2} chelator.

Conclusion on neurotoxicity

Thiram caused functional developmental neurotoxicity at maternally toxic doses and adult neurotoxicity. Some histopathological data and an *in vitro* study suggest thiram causes neuronal cell death.

7.9.9. Selection of the critical DNEL(s) / DMEL(s) and / or qualitative / semi-quantitative descriptors for critical health effects

The eMSCA agrees with the registrant's selection of critical studies and the DNEL derivation (see Table 16 below) except the use of 10% default dermal absorption value. According to the ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7c) a default dermal absorption value of 10% can be used for substances with molecular mass above 500 and log P is outside the range [-1, 4]. Thiram doesn't fulfil these criteria. The dermal penetration values from an *in vitro* study with human skin are 12% and 3% for the concentrations 0.15% and 62% of thiram, respectively. Among the identified uses, the lowest concentration of thiram in use is for the industrial use 'formulation into liquid preparations'; for this concentration a dermal penetration value of more than 11% was obtained by an interpolation between 12% and 3%. Therefore, the eMSCA used 12% dermal absorption value and recalculated the DNEL for long-term dermal systemic effects.

Table 16

CRITICAL DNELS FOR WORKERS				
Exposure pattern - type of effect	**Most sensitive endpoint**	**Corrected dose descriptor**	**Registrant's DNELs**	**Justification / Remarks**
Long-term inhalation – systemic effects	Repeated dose toxicity	NOAEC = 1.475 mg/m³ Corrected from the NOAEL = 0.84 mg/kg bw/d from one-year oral study in dogs	0.118 mg/m³	Overall assessment factor = 12.5
Acute inhalation – systemic effects	Repeated dose toxicity	NOAEC = 7.05 mg/m³ Corrected from the NOAEL = 4 mg/kg bw/d from 28-day oral study in dogs	0.564 mg/m³	Overall assessment factor = 12.5

Long-term inhalation – local effects	-	-	-	No dose-response data available
Acute inhalation – local effects	-	-	-	No dose-response data available
Long-term dermal – systemic effects	Repeated dose toxicity	NOAEL = 8.4 mg/kg bw/day Corrected from the NOAEL = 0.84 mg/kg bw/d from one-year oral study in dogs	0.48 mg/kg bw/day **eMSCA's DNEL = 0.40 mg/kg bw/day**	Overall assessment factor = 17.5
Acute dermal – systemic effects	Repeaed dose toxicity	NOAEL = 750 mg/kg bw/day From a 21-day dermal study in rabbits	25 mg/kg bw/day	Overall assessment factor = 30
Long-term dermal – local effects	-	-	-	No dose-response data available
Acute dermal – local effects	Sensitisation	-	-	No dose-response data available

The registrant used default assessment factors for DNEL derivation as recommended in the ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.8).

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

The eMSCA performed PubMed search for the string "thiram OR 137-26-8 OR tetramethylthiuram OR thiuram" on 17 July 2014 and found 20 *in vivo* and 13 *in vitro* studies to be relevant for the current scope of evaluation. Following tables summarises those studies.

Table 17: Summary of relevant *in vivo* studies from peer-reviewed literature.

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Maita et al., 1991 *Chronic toxicity studies in Wistar rats and Beagle*	104 weeks *Male rats: 0, 0.1, 1.2, and 11.6 mg/kg (avg daily dose)* *Female rats: 0, 0.1, 1.4, and 13.8 mg/kg (avg daily dose)*	Rats: Retarded growth and slighly decreased food consumption in high dose group. Anemia and regressive changes of the sciatic nerve accompanied by atrophy of the calf muscle in high dose females. Dogs in the high dose group had severe toxic signs including nausea or vomiting, salivation, and	NOEL, rats: 0.1 mg/kg NOEL, dogs: 0.4 mg/kg

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
dogs Thiram 98.7% *Rats/Wistar/M&F* *Dogs/Beagle/M&F* Oral via diet (rats) Oral, gelatin capsules (dogs)	*Dogs: 0, 0.4, 4, and 40 mg/kg* 64 rats/sex/dose 4 dogs/sex/dose *Rats and dogs: Urinalysis, hematology, blood biochemistry, opthalmology, several organ weight analyses and their histopathology.*	occasional clonic convulsion and opthalmological changes such as fundal hemorrhage, miosis, and desquamation of the retina. Liver failure, kidney damage (in females), and anemia in mid and high dose dogs.	-
Mishra et al., 1993 *To investigate the effects of thiram on structural and functional changes in testes of rats.* Thiram 95% *Rats/Wistar/M* Oral gavage	30, 60, and 90 days *0, 5, 10, or 25 mg/kg* 25 per group *Serum cholesterol (in 6 animals per group), gonadosomatic index (testes weight/body weight * 100), histopathological and biochemical evaluation of testes.*	Animals exposed for 90 days had diarrhoea, salivation, nasal bleeding, mild ataxia and decreased body weight gain in a dose-dependent manner. A total of 5, 7, and 8 animals died in the groups 5, 10, and 25 mg/kg, respectively. Slight increase in gonadosomatic index at 10 mg/kg (after 60 and 90 days) and 25 mg/kg (after 30, 60, and 90 days). Animals exposed for 90 days at 25 mg/kg had degeneration of few seminiferous tubules including necrosed spermatogenic cells and inactive sperms and increase in interstital space filled with oedematous fluid. Dose-dependent increase in testicular enzyme activities like lactate dehydrogenase, alkaline phosphatase, glucose-6-phosphate dehydrogenase. Significant decrease in succinate dehydrogenase and acid phosphatase and increase in serum cholesterol and testicular free sialic acid at all dose levels.	LOAEL: 5 mg/kg *"It may be concluded that exposure of low dose of thiram (25 mg/kg/d) to male rats for 90 days is suggestive of structural and functional changes in testes."*
Mishra et al., 1998 *To investigate the effects of long-term administration of thiram on morphological and biochemical changes in testes of rats.* Thiram 98%	180 and 360 days *0, 5, 10, or 25 mg/kg* 25 per group *Serum cholesterol (in 6 animals per group),* *weights of testes, epididymis, seminal vesicle, and prostates, histopathological and biochemical evaluation of testes.*	Animals exposed for 360 days had diarrhoea, salivation, nasal bleeding, dyspnea, convulsion, ataxia and decreased body weight gain in a dose-dependent manner. **A total of 2, 6, 11, and 11 animals died in the groups 0, 5, 10, and 25 mg/kg, respectively.** Changes in relative weights of testes & epididymis (increased) and in seminal vesicles (decreased) in 10 and 25 mg/kg groups after 180 and 360 days. Decrease in relative weight of prostate after 360 days in 25 mg/kg group.	LOAEL: 5 mg/kg *"Based on the parameter studied it is suggested that thiram at dose as low as 5 mg/kg/day for 360 days produced dose dependent damaging effects on the testes of rats*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Rats/Druckery/ M Oral gavage		Dose and time dependent pathomorphological changes in testes like necrosed seminiferous tubules with large interstitium, detachment of germinal cells and accumulation of debris matter in the lumen of the tubules. Dose and time dependent changes in testicular enzymes: increased activity of lactate dehydrogenase, glucose-6-phosphate and alkaline phosphatase; decrease activity of succinate dehydrogenase, acid phosphatase, and sodium & potassium ions dependent ATPase. Also, the free sialic acid & serum cholesterol were increased and protein content was decreased in all treated groups.	*indirectly blocking the process of spermatogenesis."*
Lee and Peters, 1976 Experiment 1 *To study the neurotoxic and behavioral effects of thiram in rats.* Thiram Source and purity not specified *Rats/Charles River CD/M&F* Oral via diet	80 weeks *Males (avg daily dose): 0, 5.3, 20.4, and 52 mg/kg* *females (avg daily dose): 0, 6.1, 25.5, and 66.9 mg/kg* 24/sex/dose *Neuropathology, behavioral effects (hind leg walking gait (females), jump/climb ability test (females), open-field test (males & females)*	High dose females (~ 33%) had neurotoxic effects characterised by ataxia and paralysis of the hind legs. Neuropathology of two of the high dose ataxic females showed demyelination, degeneration of the axis cylinders, and presence of macrophages in the nerve bundle of the sciatic nerve; and degeneration in the ventral horn of the lower lumbar region of the spinal cord. The behavioral effects observed in apparently normal rats include altered walking pattern of the hind legs with decreases in stride width and the angle between contralateral steps (mid and high dose females) and the high dose females required significantly more shock-motivations and cleared lower height in a jump/climb ability test. An open-field study indicated hyperactivity in the nonataxic rats (mid and high dose) of both sexes.	NOAEL: 5.3 (M), 6.1 (F) mg/kg LOAEL: 20.4 (M), 25.5 (F) mg/kg *Neurotoxicity occurred only in high dose females. These neurotoxic effects are not believed to be sex-dependent. Though concentration was the same in the feed, due to difference in body weight and feed consumption, females had higher intake of thiram.*
Lee and Peters, 1976 Experiment 2 *To study the neurotoxic and behavioral effects of thiram*	36 weeks *0 and 65.8 mg/kg (avg daily dose)* 24 per group *Neurofunction, Neuropathology*	~ 17% of the animals developed ataxia and paralysis. ~38% showed clasping of the hind feet when picked up by the tail. Histopathology of the ataxic rats suggests the peripheral nerve as the primary site of the lesion.	LOAEL: 65.8 mg/kg -

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
in rats. Thiram Source and purity not specified *Rats/Charles River CD/F* Oral via diet			
Stoker et al., 1993 Experiment 1 *To investigate the acute effects of thiram on the hormonal control of ovulation.* Thiram 98% *Rats/Long-Evans/F ovariectomised, estrogen-primed animals* i.p.	Single dose at 11:00 hrs after a recovery period of 72 hrs *0, 6, 12, 25, 50, or 100 mg/kg* 5/6 mg/kg; 10/12 mg/kg; 8/25 mg/kg; ?/50 mg/kg; ?/100 mg/kg *LH surge was determined in the blood drawn at 13:00, 15:00, 17:00, and 19:00 hrs*	Complete suppression of estradiol-induced LH surge in all animals in 100 & 50 mg/kg groups, in 75% animals in 25 mg/kg group, in 40% animals in 12 mg/kg group.	NOEL: 6 mg/kg *"In both [ovariectomised] and intact females, administration of relatively low concentrations of the fungicide thiram during a period just prior to the anticipated appearance of the LH surge blocked the LH rise in a dose-related fashion."*
Stoker et al., 1993 Experiment 2 *To investigate the acute effects of thiram on the hormonal control of ovulation.* Thiram 98% *Rats/Long-Evans/F intact animals* i.p.	Single dose at 09:00, 11:00, 13:00, or 18:00 hrs on the day of vaginal proestrus *0, 12, 25, or 50 mg/kg* 5/12 mg/kg; 5 or 6/25 mg/kg; 5 or 6/50 mg/kg *Ovulation in the proestrous rats*	Ovulation was blocked by 25 and 50 mg/kg given at 13:00 hrs in all animals; and also by 50 mg/kg given at 11:00 hrs in 60% animals.	NOEL: 12 mg/kg *"At the relatively low doses of thiram employed in the present study, the proestrous surge of luteinizing hormone and subsequent ovulation could be consistently blocked by appropriately timed administration.*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
			"
Stoker et al., 1993 Experiment 3 *To investigate the acute effects of thiram on the hormonal control of ovulation.* Thiram 98% *Rats/Long-Evans/F intact animals* i.p.	Single dose at 1300 hrs on the day of vaginal proestrus *0, 12, 25, or 50 mg/kg* 5/group *LH surge was determined in the blood drawn at 1400, 1700, and 1900 hrs*	Complete suppression of LH surge in all animals in 50 mg/kg group and in 60% animals in 25 mg/kg group.	NOEL: 12 mg/kg *"In both [ovariectomised] and intact females, administration of relatively low concentrations of the fungicide thiram during a period just prior to the anticipated appearance of the LH surge blocked the LH rise in a dose-related fashion."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Traina et al., 1994 *"Aim of this study was to test, using sensitive testicular parameters, whether thiram directly affects germinal cells."* Thiram (CAS: 137-26-8) Technical grade 99% *Mice/B6C3F1/M* i.p.	One single dose or five daily single doses *75 mg/kg (single dose)* *25 mg/kg (five daily doses)* 6 to 8 per group *Testes weight, testicular sperm head number and activity levels of lactate-dehydrogenase-X (LDH-X), sorbitol-dehydrogenase (SDH), isocitrate-dehydrogenase (ICDH), and malate-dehydrogenase (MDH) measured at days 14, 28, 35, and 56 after acute and subacute treatment.*	29% and 15% mortality within 5 days after acute and subacute treatment, respectively. **"In spite of the high levels of toxicity registered with these treatment schedules, none of the reproductive indicators (testis weight, sperm head number, enzyme activities) measured at days 14, 28, 35, and 56 after acute and subacute treatments with thiram in oil showed significantly marked variations from control values".**	LOAEL: 25 mg/kg *"Under these conditions thiram did not cause cytotoxicity on differentiating spermatogonia and on late spermatocyte stages of mice gonads."*
Witkowska et al., 1992 *To investigate the effects of thiram on amino acids transport in rats jejunum.* Thiram Purity not specified *Rats/Wistar/M* Oral gavage	Six times a week for 28 days *0 or 26 mg/kg* 4 to 6 per group *Transport of leucine and methionine in the jejunum of rats after 1, 7, 14, and 28 days.*	Time dependent inhibition in leucine and methionine transport (19, 42, and 45% inhibition after 7, 24, and 28 days, respectively). Thiram only affected the active transport of amino acids.	LOAEL: 26 mg/kg *"On the basis of our results it can be presumed that inhibition of leucine and methionine influx by thiram might be due to impact of the pesticide on Na^+, K^+ - ATPase activity and also on protein synthesis, leading to a decrease in production of the transport proteins."*
Sadurska and Boguszewski, 1993 *To study the changes in lipoprotein*	Single dose and six times a week for 14, 30, or 90 days *0 or 290 mg/kg (single dose) and*	Single dose of thiram (290 mg/kg) decreased LPL activity in adipose tissue and increased the levels of total plasma cholesterol, triacylglycerols and the high density lipoprotein (HDL) cholesterol. Repeated exposure of thiram (29 mg/kg) decreased LPL activity after 14 and 30 days and distinctly	LOAEL: 29 mg/kg *"The changes observed in the lipoprotein lipase activity*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
lipase (LPL) activity from adipose tissue and plasma liver lipids in thiram intoxicated rats. Thiram Source and purity not specified *Rats/Wistar/M* Oral	*0 or 29 mg/kg (repeated dose)* 10 - 30 in control groups and 10 in treated groups *LPL activity from adipose tissue and lipid levels in blood plasma and liver of the rat.*	increased after 90 days. The levels of total cholesterol (after all periods) and HDL cholesterol (only after 30 days) increased accompanied by decrease in free fatty acids content and increase of hepatic triacylglycerols.	*of thiram-poisoned rats correspond to the profiles of plasma lipoproteins typical of thyroid hypofunction."*
Robens, 1969 *To study the teratogenic effects of pesticides (carbaryl, diazinon, norea, disulfiram, and thiram).* Thiram, bis(dimethylthiocarbamoyl) disulfide. Technical grade, purity not specified. *Hamster/Golden Syrian/F* Oral gavage	During organogenesis (gestation days 7 and/or 8) *Thiram in 10 ml/kg DMSO: 31, 63, 125, 250, 500, and 1000 mg/kg* *Thiram in 5 ml/kg DMSO: 125 mg/kg* *Thiram in 10 ml/kg CMC: 125, 250, 300, and 500 mg/kg* 4 to 8 per group *Fetuses: number per litter, average fetal weight, gross defects examination, viability on day 15 post-delivery, percent fetal mortality, and % terata*	Higher dose levels of thiram in 10 ml/kg DMSO was lethal with 50, 25-40, and 25% maternal deaths in the dose groups 500, 250, and 125 mg/kg, respectively. % fetal mortality (approx.): 9-24, 17, 6-29, 40-43, 59-82, 84-100, and 100% in the groups control, 125 mg/kg thiram in 5 ml/kg DMSO, 31, 63, 125, 250, and 500 mg/kg thiram in 10 ml/kg DMSO, respectively. And 2-5, 0-6, 19-35, 61-67, and 100 in the groups control, 125, 250, 300, and 500 mg/kg thiram in 10 ml/kg CMC, respectively. % terata (approx.): 2-24, 14, 23-48, 19-56, 0-88, and 0-100% in the groups controls, 125 mg/kg thiram in 5 ml/kg DMSO, 31, 63, 125, 250, 500 mg/kg thiram in 10 ml/kg DMSO, respectively. And 0.4-0.6, 2-3, 20-23, and 13-33% in the groups controls, 125, 250, 300, and 500 mg/kg thiram in 10 ml/kg CMC. The litter size in the groups with high % of fetal mortality was small and with a decrease in average individual fetal weight. Significant fetal malformations included short or curved tail, limb defects and umbilical hernia.	LOAEL: 31 mg/kg *"Thiram was clearly teratogenic when suspended in a nonteratogenic agent [CMC] as well as when dissolved in DMSO;"*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Hasegawa et al., 1988 *To examine the carcinogenic potential of thiram in F344 rats* Thiram Practical grade Purity not specified *Rats/F344/M&F* Oral via diet	104 weeks *Males: 0, 18.3, and 39.2 mg/kg (avg daily dose)* *Females: 0, 20.2, and 42.3 mg/kg (avd daily dose)* 50/sex/dose *Food consumption & body weight, clinical and pathological findings, non-neoplastic lesions, tumor incidence and distribution.*	Decreased food consumption and body weight. Higher mortality in female high dose group. High dose males showed liver dysfunction in biochemical examination of blood. No treatment related significant lesions or tumor induction were observed in any tissue except for dose-dependent reduction in spontaneous leukemia in both sexes and slightly reduced incidences of pituitary and thyroid adenomas in females.	NOAEL, carcinogenicity: 39.2 (M), 42.3 (F) mg/kg *"Under the present experimental conditions, thiram was not carcinogenic in F344 rats."*
Thuránszky et al., 1982 *To investigate the effect of dithiocarbamate -type chemicals on the nervous system of rats.* Thriam Source and purity not specified *Rats/Wistar/M* Oral	Single dose *0 or 240 mg/kg (orientation hypermotility)* *0, 40 or 240 mg/kg (subcorticol EEG)* *0 or 60 mg/kg (tissue levels of dopamine (DA), norepinephrine (NE), epinephrine E)).* 3 in each group for bioassay but not reported for other two investigations. *Orientation hypermotility, subcortical EEG, and bioassay of DA and NE, E formation from ^{3}H-tyrosine.*	Thiram caused significant reduction of orientation hypermotility 120 minutes after dosing. When measured until 3 minutes after dosing, thiram decreased subcorticol EEG activity at both 40 and 240 mg/kg dose levels. Thiram decreased the re-formation of norepinephrine which can be explained by an inhibition of dopamine-β-hydroxylase (DBH) enzyme.	LOAEL: 40 mg/kg *"The inhibition of DBH may be involved in the delayed psychosedative influence, however the short-term effects (up to 15-30 min) are probably not accounted for by the same mechanism. It might rather be due to some membrane effect or some other kind of direct influences."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Flippin et al., 2009 *To test "the hypothesis that serum T4 concentrations of rodents exposed to a mixture of both TH synthesis inhibitors (pesticides [thiram, pronamide, and mancozeb]) and stimulators of T4 clearance in the liver (polyhalogenated aromatic hydrocarbons, PHAHs [18]) could be best predicted by an integrated addition model."* Thiram (CAS: 137-26-8) 98% *Rat/Long-Evans/F* Oral gavage	Four consecutive days *6.25, 12.5, 25, 50, 100, 200, 400, and 800 mg/kg* 8 to 16 per group *Serum was collected 24 hours after the last exposure and T4 concentrations were measured by radioimmunoassay.*	Thiram caused dose-dependent decrease in the circulating levels of T4 with an ED50 (the dose which elicits a 50% decrease in T4) of ~ 250 mg/kg. Decreased body weight gain in animals exposed to ≥ 50 mg/kg thiram.	LOAEL: 50 mg/kg *"Animals exposed to highest dose of the mixture experienced a 45% decrease in serum T4. Three additivity model predictions (dose addition, effect addition, and integrated addition) were generated based on single chemical data, and the results were compared. Effect addition overestimated the effect produced by the combination of all 21 chemicals. The results of the dose- and integrated-addition models were similar, and both provided better predictions than the effect-addition model."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Stoker et al., 2003 *To test the hypothesis that the reduced litter size in thiram-delayed rats is a consequence of altered oocyte function arising from intrafollicular oocyte aging.* Thiram 98% *Rat/Long-Evans/F* i.p.	Single dose at 12:45 hrs on the day of vaginal proestrus and bred the following night. *0 or 50 mg/kg* 8 per group *Delayed oocytes, zygotes, and 2-cell embryos for evidence of fertilisation and polyspermy.* *Cortical granule distribution and analysis.*	No difference in the number or morphology of delayed oocytes. A significant increase in % of unfertilised zygotes, polyspermic zygotes and in the number of supplementary sperms within the perivitelline space. Significant increase in the no. of unfertilised oocytes among 2-cell embroys and in the % of 2-cell embryos with higher mean no. of supplementary sperm. All the polyspermic zygotes exhibited an abnormal pattern of cortical granule exudate.	LOAEL: 50 mg/kg *"In summary, the present study demonstrated that exposure to a pesticide that delays the LH surge and ovulation also indirectly alters the time course of events in the oocyte that normally prevent polyspermy. This alteration results in polyspermy and, thereby, affects the outcome of pregnancy."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Stoker et al., 1996 *To characterise pregnancy outcome following thiram-induced ovulatory delay* Thiram 98% *Rats/Long-Evans/F* i.p.	Single dose at 12:45 hrs on the day of vaginal proestrus and bred the following night (thiram-delayed group) or the same night of treatment (thiram-nondelayed group) *0 or 50 mg/kg* 7 in the thiram-delayed group and 30 in the thiram-nondelayed group *Female mating behavior.* *No. of implantation sites in the uteri of GD 7, 11 & 20 in thiram-delayed group and GD 20 in thiram-nondelayed group.* *Embroys from GD 11 in thiram-delayed group were evaluated for growth, development, and dysmorphogenesis.* *Fetuses from GD 20 thiram-delayed and -nondelayed groups were examined for gross eye defects, thorasic & abdominal visceral defects and skeletal examination.*	Reduced no. of sexually active females in the thiram-nondelayed group (3/7) compared to controls (12/12) and thiram-delayed group (24/30). No difference in the proportions of sperm-positive females in the thiram-delayed and -nondelayed groups compared to controls. The display of sexual receptivity and sperm-positive smears by the thiram-delayed females was consistent with delayed ovulation. Reduced no. of pregnant animals in the thiram-delayed group (12/26). [thiram-nondelayed group: 5/7; controls: 11/12] No significant difference in the no. of implantation sites compared to controls. Decrease in the mean no. of live embryos on GD 11. No gross abnormalities except reduced crown-rump length, head length, and somite numbers. Significant reduction in the development score. In one litter with 13 implantation sites, 3 embryos were completely resorbed, 2 were partially deteriorated, 3 were very small but with yolk sac circulation, heartbeat, & without any malformation and the remaining 5 were not remarkably different from controls. An increase in mean number of resorption sites on GD 20 in thiram-delayed group. No difference in the number of corpora lutea in either of the groups compared to controls. Significant reduction in the mean litter size of the thiram-delayed group but no effect in the thiram-nondelayed group. No gross fetal abnormalities or differences in male to female ratios in any of the group and no visceral or skeletal defects.	LOAEL: 50 mg/kg *"The current study demonstrates that a single exposure to the fungicide thiram (50 mg/kg), when administered during a critical period on the day of proestrus prior to mating, results in a decrease in the rate of fetal development, as well as a reduction in the number of live fetuses and an increase in the number of resorptions on GD 20."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Rahden-Staron et al., 2001 *To study the induction of the CYP 1A and CYP 2B monooxygenases in rat liver by some fungicides, drugs, and a plant flavonoid.* Thiram (CAS no. 137-26-8) 99.8% *Rats/Wistar/M* i.p.	Single dose *0, 80, and 100 mg/kg* 5 to 6 per group *Induction of CYP 1A and CYP 2B in the S9 (microsomal fraction) prepared from treated rat livers.*	100 mg/kg thiram caused a much more pronounced effect on the induction of CYP 1A and CYP 2B (more distinct compared to CYP 1A) than that caused by 80 mg/kg.	LOEL: 80 mg/kg -
Komulainen and Savolainen, 1985 *To study the effect of dithiocarbamate fungicides and thiurams on ^{3}H-haloperiol binding in rat brain.* Thiram Purity not specified *Rats/Wistar/M* i.p.	Four days *0 or 80 mg/kg (cumulative dose after four daily doses)* 5 to 6 per group *^{3}H-haloperiol binding to cerebral membranes*	The rats receiving thiram had mild hind limb paresis, were atactic and flaccid to handle. No effect on the specific ^{3}H-haloperidol binding in the cerebrums.	LOAEL: 80 mg/kg /4 days *"The results indicate that neither dithiocarbamates nor thiurams altered the specific binding of ^{3}H-haloperidol in the rat cerebrum after such a short-term exposure. This suggests that these agents neither affected D_2 receptors directly nor induced adaptive changes in the receptors during this time range."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Caroldi and De Paris, 1995 *To compare the effects of disulfiram and thiram on adrenal catecholamine content and plasma dopamine-β-hydroxylase (DBH) activity.* Thiram 98% pure *Rats/Wistar/M* Oral gavage	Single dose *100 mg/kg* 3 to 5 per group *Adrenal dopamine content and plasma DBH activity.*	Statistically significant increase after 4 and 24 hrs (but not after 8 days) in adrenal dopamine content (by reducing the conversion of dopamine to noradrenaline) in rats given single dose of 100 mg/kg thiram. Thiram significantly reduced plasma DBH activity after 4 and 24 hrs of single 100 mg/kg dose.	LOAEL: 100 mg/kg *Thiram affects dopamine contents in rat adrenals by reduced conversion of dopamine to noradrenaline. "The observed variations of plasma DBH activity reflect the changes of catecholamine metabolism in rat adrenals, offering a suitable marker for the biological monitoring of workers occupationally exposed to thiram."*
Dalvi et al., 1984 *To investigate hepatotoxicity of thiram.* Thiram 99% *Rats/SD/M* i.p.	Single dose *120 mg/kg* 3 in each group *24 hrs after treatment, determination of serum glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT) and acetylcholinesterase (ACE) activities.* *Determination of benzphetamine N-demethylase (BND) activity and cytochrome P-450 content of the liver microsomes and liver glutathione levels.*	Statistically significant increase in SGOT and SGPT activities and decrease in ACE activity. Significant decrease in BND activity, cytochrome P-450 content, and decrease in glutathione levels.	LOAEL: 120 mg/kg *Thiram was found to be hepatotoxic in male Sprague-Dawley rats.*
Lee et al., 1978 *To investigate the acute (rat &*	Acute: Single dose -	LD50s (in g/kg): Male rats = 4, female rats = 1.9, male mice = 4, female mice = 3.8 Most deaths occurred after 2-7 days while showing signs like ataxia and hyperactivity followed by	LD50: 1900 mg/kg (female rats)

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
mice), subchronic and chronic (rats) oral toxicity of ferbam and thiram. Thiram Practical grade Purity not specified *Rats/CD/M&F (acute and chronic tox), only M (subchronic)* *Mice/CD-1/M&F (acute tox)* Oral gavage (acute tox) or via diet (subchronic & chronic tox)	8 to 16 per group *LD50 by Lichfield and Wilcoxon method.*	inactivity, loss of muscular tone, and alopecia and also labored breathing and clonic convulsions.	-
	Subchronic: 13 weeks *0, 30, 58, and 132 mg/kg* 5 per group *Behavioural changes, body weights, feed consumption, hematologic examinations, blood chemistry analyses, weights & microscopic examination of several organs.*	Dose-dependent decrease in body weight and feed consumption. In high dose group: 5 deaths, moderate tubular degeneration of the testes with atypical spermatids in the epididymis, mild increase in serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and blood urea nitrogen (BUN). In medium dose group: mild increase in BUN.	LOAEL: 30 mg/kg -
	Chronic: 80 weeks *0, 5, 20, and 52 mg/kg (M)* *0, 6, 26, and 67 mg/kg (F)* 6 per group *Behavioural changes, body weights, feed consumption, hematologic examinations, blood chemistry analyses, weights & microscopic examination of several organs.*	Four, 9, 3, and 7 unscheduled deaths, not related to thiram, among the control, low, medium, and high-dose rats, respectively. Dose dependent decrease in body weight. One high dose female developed lower body ataxia & another showed severe curvature of the thoracic spine and atrophy of both hind legs during 20th and 69th week. Six more females showed similar signs during 39th and 80th week eventually leading to paralysis posterior to the lumbar region and atrophy of the hind legs. Alopecia observed in some ataxic and nonataxic rats of high and medium dose. "**Histopathology of central and peripheral nervous systems of the nonataxic, ataxic, or paralyzed rats did not reveal any specific lesions."** **"Peripheral blood elements and clinical blood chemistries in rats treated with various doses of thiram were not apparently altered."** Increased relative thyroid and testes weights in high dose males. Increased relative liver, spleen, kidney, thyroid, ovary, & brain weights in the high dose and increased relative spleen weight in the medium dose females. Dose-dependent increase in fatty infiltration in male pancreas. Squamous metaplasia of the thyroid in high dose male and females.	LOAEL: 5 mg/kg -

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
Short et al., 1976 *To study the effects of ferbam and thiram on reproduction in rats, organogenesis in rats and mice, and the peri- and postnatal period in rats.* "The practical grade of thiram used for these investigations had a melting point of 154-157°C." Purity not specified. *Rats/Charles River CD/M&F* *Mice/Swiss-Webster-dervied/M&F* Oral, via diet (in reproduction and peri-& postnatal study) and via gavage (in teratology study).	Reproduction in rats: 13 weeks (M) and 14 days (F) before mating. *Males: 0, 30, 58, or 132 mg/kg (avg daily dose)* *Females: 0, 30, or 96 mg/kg (avg daily dose)* 20/sex/dose *"Fertility (confirmed pregnancies/sperm positive females x 100), gestation (confirmed pregnancies with viable fetuses/confirmed pregnancies x 100), viability (pups alive at Day 4/pups alive at birth x 100), and lactation (pups alive at Day 21/pups alive at Day 4 x 100) indices were used to summarize the observations on reproduction."*	Males: Dose dependent decrease in body weight and food consumption. 70% mortality in 132 mg/kg group. Hair loss and rough coats observed in 58 and 132 mg/kg groups. 30 or 58 mg/kg had no effect on fertility. Rats in 132 mg/kg group had impaired breeding and half of them showed evidence of testicular hypoplasia, tubular degeneration, and atypical spermatids in the epididymis (unpublished data). Females: Dose dependent decrease in body weight and food consumption. 30 mg/kg group: significant reduction in no. of implants per dam and pups per dam. 96 mg/kg group: 25% mortality and only 1 of 20 was successfully mated. Prolonged diestrous phase of the estrous cycle which was reversible. No effect on fertility index, gestation index, or the ratio of viable embryo to implants in this group.	LOAEL, systemic toxicity, males & females: 30 mg/kg. NOAEL, reproduction, males: 58 mg/kg. LOAEL, reproduction, females: 30 mg/kg.
	Teratology in rats and mice: GD 6-15 (except group 200 mg/kg which were dosed at GD 6 or 7-12) in rats. GD 6-14 in mice. *Rats: 0, 40, 90, 136, 164, or 200 mg/kg* *Mice: 0, 100, or 300 mg/kg* Rats: 10 to 32 per group Mice: 27 or 28 per group *Rats and mice: % mortality, gestation & fetal body weights. The no. of live, dead, and resorbed fetuses and their examination for external, soft tissue and skeletal anomalies.*	Rats: Dose dependent decrease in gestation body weight and fetal body weight. 77% mortality in 200 mg/kg group. Significant reduction in no. of implants per dam and complete resorptions in 164 and 200 mg/kg groups. Mice: No effect on gestation or fetal body weights, litter size, or incidence of resorptions. 22% mortality in 300 mg/kg group. Following incidences of fetal anomalies were observed (compared to control) in 300 mg/kg group: hydronephrosis (12/67 vs 8/69), hydrocephalus (8/67 vs 2/69), slight (22/71 vs 6/76) or marked (6/71 vs 4/76) collapsed cranium, thick atrial wall (2/67 vs 0/69), malaligned sternabrae (10/71 vs 4/76), and the presence of fibrous material connecting lens and retina (5/67 vs 0/69).	Rats: LOAEL, systemic toxicity and teratogenicity: 40 mg/kg Mice: LOAEL, teratogenicity: 300 mg/kg *"Fungicide treatment that affected reproduction was associated with adult toxicity."*

Reference ***Aim of the study*** **Test material** ***Species/strain/Sex*** **Route**	**Duration** ***Doses*** **No./sex/dose** ***Parameters investigated***	**Results**	**Effect Level** ***Author's conclusion***
	Peri- & postnatal effects in rats: GD 16 to PND 21 *0, 17/51 mg/kg (avg before birth/avg after birth), or 26/115 mg/kg (avg before birth/avg after birth)* 10-20 per group *Feed intake in dams, dam & pup body weight on lactation days 0, 4, and 21. Viability and lactation indices.*	No effect on duration of gestation. Decreased feed intake by dams before and after birth in both groups. Decreased dam body weight on lactation day 0 in both groups. Decreased viability and lactation index in high dose group. Decreased pup body weight in both groups.	LOEL, development: 17/51 mg/kg *"Most [fetal] anomalies produced by treatment with the fungicides, however, were probably due to depression of growth, since there was no pattern of well-defined anomalies that would suggest a specific teratogenic effect."*

Table 18: Summary of relevant *in vitro* studies from peer-reviewed literature.

Reference ***Aim of the assay*** **Test material**	**Cells** ***Concentration*** **Investigations**	**Results**	**Effect level** **Author's conclusion**
Marinovich et al., 1997 *Examining the effects of the test substance on peroxidative activity in Chinese Hamster Ovary cells transfected with the human thyroid peroxidase (TPO) gene.* Thiram 97%	Chinese Hamster Ovary cells *0.1 to 50 µM* The activity of TPO was assayed by the reactions of guaiacol oxidation and iodination.	Thiram had no effect on iodination or oxidative activity of TPO.	NOEC: 50 µM "A possible interpretation of the data in view of the in vivo effects, is that all thyroid effects [of ethylenebis dithiocarbamates] result from inhibition by ETU of the TPO iodination step"

Reference ***Aim of the assay*** **Test material**	**Cells** ***Concentration*** **Investigations**	**Results**	**Effect level** **Author's conclusion**
Li et al., 2014 *To investigate whether carbamate pesticides induce apoptosis and necrosis in human natural killer cells.* Thiram Purity not specified	NK-92CI (human natural killer cells) *0.063 to 4 µM* Apoptosis and necrosis was determined by FITC-Annexin-V/PI staining. To explore the mechanism of apoptosis intracellular levels of active caspases 3 and mitochondrial cytochrome-c release were determined by flow cytometry.	Thiram induced cell death (apoptosis and necrosis) in a dose- and time-dependent manner. Thiram induced a significant increase in active caspase-3 in a dose-dependent manner, which was blocked by pre-treatment of a general caspase inhibitor, suggesting that it induced apoptosis at least partially via the caspase cascade pathway. Thiram induced a significant increase of cytochrome-c-negative cells in a dose-dependent manner, indicating that it induced mitochondrial cytochrome-c release (which is an early event during apoptosis).	LOAEC: 0.1 µM Findings in the current study suggest that thiram induces apoptosis via both the caspase-cascade and the mitochondria/cytochrome-c pathways.
Han et al., 2003 *To investigate the neurotoxic mechanism of dithiocarbamates using neuronal-like PC12 cells.* Thiram Purity not specified	PC12 cells (rat pheochromocytoma cells) *0.01 to 10 µM* Cell viability assay DNA fragmentation and subdiploid nuclei (a hallmark of apoptosis) Alteration of intracellular Ca+2 and its characterisation	Thiram induced dose- and time-dependent cell death with LC50 of 0.3 µM. With 1 µM thiram, determination of type of cell death showed typical apoptotic features like DNA fragmentation and an increase of subdiploidy nuclei. Thiram (0.1 - 1.5 µM) induced rapid and sustained increase in intracellular Ca+2 ions in a dose-dependent manner which was completely blocked by flufenamic acid, a non-selective cation channel inhibitor. Thiram induced apoptotic cell death was inhibited by BAPTA-AM, an intracellular Ca+2 chelator.	LOAEC: 0.1 µM Thiram induces apoptotic neuronal cell death by Ca+2 influx through non-selective cation channels.

Reference ***Aim of the assay*** **Test material**	**Cells** ***Concentration*** **Investigations**	**Results**	**Effect level** **Author's conclusion**
Meyer et al., 2012 *To study the species-specific differences in the inhibition of human and zebrafish 11ß-hydroxysteroid dehydrogenase 2 (HSD2) by thiram and organotins.* Thiram Purity not specified	Human embryonic kidney cells (HEK-293) Zebrafish embryonic fibroblast cells ZF-4 *1 nM, 100 nM, 10 µM, and 1000 µM* HEK-293 cells were transfected with plasmids for human wild-type HSD2 and ZF-4 cells were transfected with plasmids for zebrafish wild-type HSD2. Effect of thiram on the enzyme activity was then measured using cell lysates.	Thiram inhibited human HSD2 and zebrafish HSD2 activites with IC50s of 96 ± 17 nM and 18.3 ± 6 µM, respectively.	Human HSD2 IC50 = 96 ± 17 nM Zebrafish HSD2 IC50 = 18.3 ± 6 µM Thiram exerted only a weak inhibitory effect on zebrafish HSD2 compared to human HSD2. "The lack of cysteine in the substrate binding pocket of zebrafish [HSD2], which can form stabilizing interactions with the 3-carbonyl on the steroid substrate, provides an explanation for the loss of inhibition by thiram."
Garbrecht et al., 2006 *To study the effects of thiram, a 11-ß hydroxysteroid dehydrogenase type 2 (HSD2) inhibitor, on the reduction of glucocorticoid receptor ligand binding.* Thiram Purity not specified	Human lung epithelial cells (NCI-H441) *500 nM, 5 µM, or 50 µM* Effect on HSD2 activity in intact human cells. Modulation of effects of dexamethasone (Dex) on surfactant protein gene expression in H441 cells. Effects on ligand binding to the glucocorticoid receptor (GR). To test the hypothesis that sulfhydryl-containing amino acid residues, such as cysteine, in the ligand-binding domain of the GR were targets of Thiram modification, competitive binding assays were performed in Thiram-treated H441 cells pre-incubated with or without the thiol-reducing agent, dithiothreitol (DTT).	Treatment of intact H441 cells with Thiram reduced HSD2 oxidase activity in a dose-dependent manner, with a 50 µM concentration inhibiting HSD2 oxidase activity by ~ 46 ± 6%." Thiram did not affect the HSD2 protein levels and had no effect on cell viability, total cellular RNA or protein content, or cell morphology. Co-treatment of Dex-stimulated cells with Thiram abolished the Dex-mediated down-regulation of pulmonary surfactant protein A mRNA levels and attenuated the Dex-mediated increase in pulmonary surfactant protein B mRNA levels. Dose-dependent inhibition (72 ± 4% by 50 µM thiram) of Dex binding to the GR and a 37 ± 5% reduction in the specific binding of cortisol to the GR. Effects of thiram (50 µM) on ligand binding to the GR were completely blocked by pre-treatment of cells with 1 mM DTT.	LOEC (statistically significant): 5 µM "Taken collectively, these data demonstrate that attenuated down-stream GC signaling, via decreased binding of ligand to the GR, is a novel cellular effect of Thiram exposure in human lung epithelial cells."

Reference ***Aim of the assay*** **Test material**	**Cells** ***Concentration*** **Investigations**	**Results**	**Effect level** **Author's conclusion**
Atanasov et al., 2003 *To study the inhibition of 11ß-hydroxysteroid dehydrogenase type 2 (HSD2) by dithiocarbamates (DTCs).* Thiram Highest grade available from Sigma AG Purity not specified	HEK-293 cells *10 nM to 50 µM* Effect on HSD2 and HSD1 (11β-hydroxysteroid dehydrogenase type 1). Effects of preincubation and dithiothreitol (DTT) on thiram-induced inhibition. Role of Cys90 in HSD2 activity. Role of NAD+ in thiram-induced inhibition of HSD2 activity.	Thiram inhibited HSD2 activity (IC50 = 132 ± 12 nM) but did not affect HSD1 activity. Preincubation with 100 nM thiram abolished HSD2 activity, suggesting irreversible enzyme inhibition and the sulfhydril protecting reagent DTT blocked thiram-induced inhibition of HSD2. Cys90 in the NAD+ binding site of HSD2 was identified as the likely target of dithiocarbamates. Incubation with different concentrations of NAD+ showed that it protects against thiram-induced inhibition of HSD2 activity.	IC50 = 132 ± 12 nM (for HSD2 activity) "In conclusion, we have demonstrated that DTCs are potent inhibitors of [HSD2] and provided evidence for irreversible inhibition of the enzyme by sulfhydryl modification, whereby Cys90 seems to be the major target for modification."
Grosicka et al., 2008 *To study the changes in antioxidant defense systems induced by thiram in V79 Chinese hamster fibroblasts* Thiram (CAS no. 137-26-8) 99.8%	Chinese hamster fibroblasts V79 cells *100 and 150 µM* Catalytic activities of superoxide dismutases (SOD1 and SOD2), Se-dependent and Se-independent glutathione peroxidases (GSH-Px), glutathione reductase (GR), and catalase (CAT), as well as total glutathione/glutathione disulfide ratio (GSHtotal/GSSG).	At 150 µM thiram increased the activities of SOD1, Se-dependent GSH-Px, and GR. 100 and 150 µM thiram had no significant changes in the SOD2 activity and inhibited CAT and Se-dependent GSH-Px.	LOEC: 100 µM "This study suggests that following the changes in antioxidant defense systems thiram can act through the production of free radicals."
Grosicka et al., 2005 *To study the effects of glutathione (GSH) depletion on apoptosis induced by thiram in Chinese hamster fibroblasts.* Thiram (CAS no. 137-26-8) 99.8%	Chinese hamster fibroblasts V79 cells *50, 100, and 150 µM (and 200 µM for cell viability assay)* Cell viability assay. "The level of intracellular reduced glutathione (GSH), protein sulfhydryl (PSH) groups, protein carbonyls (PC), membrane lipid peroxidation reflected by	Dose dependent decrease in cell viability with an LC50 of 150 µM and 100% toxicity at 200 µM. 50 - 100 µM thiram induced cellular GSH depletion (by 40-50%), protein (2-fold) and membrane lipid peroxidation (1.7 fold), as well as induced apoptosis without causing necrosis through cytotoxic effects. Pretreatment of cells with a	LOEC: 50 µM "The present study is the first report that shows oxidative damage of cellular proteins produced by thiram exposure and suggests a cause-and-effect relationship between decreased GSH level and apoptosis induced by thiram."

Reference *Aim of the assay* Test material	Cells *Concentration* Investigations	Results	Effect level Author's conclusion
	enhanced thiobarbituric acid reactive substrates (TBARS) production, as well as apoptotic effect were determined." "To investigate the role of decreased GSH content in the toxicity of thiram, GSH level was modified prior to exposure."	GSH biosynthesis precursor prevented GSH decrease, PC and TBARS production, as well as caspases activation induced by thiram. Previous depletion of GSH enhanced thiram effects.	
Cereser et al., 2001 *To investigate the toxic effects of thiram in cultured human skin fibroblasts.* Thiram Purity not specified	Cultured human skin fibroblasts *0.1 to 5.0 mg/l* Cytotoxicity and cell proliferation, intracellular levels of glutathione (GSH) and glutathione reductase activity, lipid peroxidation, and effect of *N*-acetyl-L-cysteine (NAC) and L-buthionine-(S,R)-sulfoximine (BSO) pretreatment on thiram-induced cytotoxicity.	Thiram induced dose dependent cytotoxicity, depleted intracellular reduced GSH content with a concomitant increase in oxidised glutathione concentration. Alteration of glutathione levels was accompanied by a dose-dependent decrease in glutathione reductase (GR) activity. Thiram increased lipid peroxidation suggesting that GSH depletion and the lower GR activity gave rise to increased oxidative processes. Pretreatment with NAC (a GSH precursor) prevented both thiram induced lipid peroxidation and cell death. Previous depletion of GSH by BSO exacerbated thiram cytotoxicity.	LOEC: 0.1 mg/l "In summary, we have demonstrated that exposure to thiram resulted in a rapid oxidation of GSH in cultured human skin fibroblasts. Depletion of GSH led to oxidative cellular damage as reflected by increased lipid peroxidation, and finally loss of cell viability."
Elskens and Penninckx, 1995 *In vitro demonstration of the inactivation of glutathione reductase by thiram.* Thiram Purity not specified	*Saccharomyces cerevisiae* *0.052 to 0.832 mM* Kinetic characteristics of glutathione reductase inactivation by thiram.	Thiram inactivated glutathione reductase in a time-dependent manner only with enzyme in the reduced state and in the absence of glutathione.	LOEC: 0.052 mM -

Reference *Aim of the assay* Test material	Cells *Concentration* Investigations	Results	Effect level Author's conclusion
Kitagawa et al., 2002 *To characterise the thiuram toxicity to yeast cells and select biomarker candidates using DNA microarray technology.* Thiuram (CAS no. 137-26-8) Purity not specified	*Saccharomyces cerevisiae* *75 µM* Characterisation of several genes expression	Many genes involved in detoxification and stress response were highly induced. Genes concerned with folding and proteolysis were induced reflecting the protein denaturing and degradation effects of thiuram. Thiuram also induced genes involved in redox and defense against reactive oxygen species suggesting it's oxidative stress effects. "Genes classified for carbohydrate metabolism and energy were also highly induced, and these gene products may play the role of providing the energy for the detoxification mechanism." "In addition, in view of the induction of some genes involved in DNA repair, thiuram potentially causes DNA damage."	- -
Fujita et al., 2003 *To evaluate the effect of industrial chemicals on mammalian peptide hormones using the yeast pheromone signaling pathway.* *Chemicals tested: TPN (CAS: 1897-45-6), thiuram (137-26-8), captan (133-06-2), oxine-copper (10380-28-6), zineb (12122-67-7), and ziram (137-30-4).* Thiuram (bis(dimethyldithiocarbamoyl) disulfide, CAS No. 137-26-8). Purity not specified.	Yeast *Saccharomyces cerevisiae* strains W303A and 144-3A *0.1, 1, and 10 mg/L* Effect of the chemicals on shmoo formation in *a* cells (W303A and W303A with fused plasmid pSL307) incubated in growth medium with α factor (homologous to mammalian luteinizing hormone releasing hormone (LHRH)). Effect on the pheromone response pathway in the W303A strain with pSL307 fused to the *FUSI-lacZ* reporter gene using a *β*-galactosidase activity assay Effect on quantitative mating efficiency assay: *α* cells (144-3A strain) incubated with *a* cells and the conjugated diploid *a/α* cells were quantified.	Thiram caused concentration dependent decrease in efficiency of shmoo formation (Control: 70%; 0.1 mg/L: ~ 61%; 1 mg/L: ~ 43%; 10 mg/L: ~ 34%. Thiram had no effect on the *FUSI-lacZ* expression. Thiram at 10 mg/L inhibited mating efficiency.	LOEC: 0.1 µM "Analysis of the yeast pheromone signaling pathway helps to establish chemical toxicity assay models for mammalian peptide signal transduction pathways."

Reference *Aim of the assay* Test material	Cells *Concentration* Investigations	Results	Effect level Author's conclusion
Soto et al., 1995 *"The E-SCREEN assay was developed to assess the estrogenicity of environmental chemicals using the proliferative effect of estrogens on their target cells as an end point."* Thiram Source and purity not specified	Human breast cancer MCF-7 cells *10 mM* "This quantitative assay compares the cell number achieved by similar inocula of MCF-7 cells in the absence of estrogens (negative control) and in the presence of 17 *β*-estradiol (positive control) and a range of concentrations of chemicals suspected to be estrogenic."	Not estrogenic (no effect on proliferation).	- -

7.10.3. Discussion and conclusion on endocrine disrupting properties

Systemic toxicity caused by thiram is also discussed below to aid in drawing conclusions on its potential endocrine disrupting properties.

Systemic toxicity

The lowest NOAEL among all the available studies (including in the open literature) was found to mg/kg bw/d based on increased absolute and relative liver weight, increased blood cholesterol and decreased total protein in males observed at the next dose level of 2.61 mg/kg bw/d in a chronic study in dogs with oral exposure via feed (Exp Key Repeated dose toxicity: oral.003).

Thiram caused reduction in body weight gain and food consumption starting from doses as low as 2.94 and 4.61 mg/kg bw/d in male and female rats, respectively, (Exp Key Toxicity to reproduction.001) and ca. 6 mg/kg bw/d in dogs (Exp Key Repeated dose toxicity: oral.002). In rabbit, 5 mg thiram/kg bw/d caused reduced body weight gain (Exp Key Developmental toxicity/teratogenicity.002).

Changes in haematological and/or clinical chemistry parameters were consistently observed in sub-acute, sub-chronic, and/or chronic studies in both sexes and across different species (dog, rat, and mice). These effects were observed starting from doses 1.94 – 2.58 mg/kg bw/d in dogs (Exp Key Repeated dose toxicity: oral.002), 7.31 mg/kg bw/d in rats (Exp Key Carcinogenicity.002), and 24 mg/kg bw/d in mice (Exp Key Carcinogenicity.001).

Between the dose ranges of ca. 6 and 27 mg/kg bw/d, hepatocellular degeneration was observed in dogs (Exp Key Repeated dose toxicity: oral.002 and oral.005). In rats, between 1.46 and 80 mg/kg bw/d, effects on kidney, liver, brain, and right ovary weights, non-glandular stomach and mesenteric lymph nodes were observed (Exp Key Repeated dose toxicity: oral.001 and Exp Key Carcinogenicity.002). Effects on brain weight and non-glandular stomach were observed also in mice in the range 24 – 112 mg/kg bw/d (Exp Key Carcinogenicity.001).

In a chronic toxicity study in rats and dogs by Maita et al. (1991), thiram caused retarded growth and slightly decreased food consumption in rats at 11.6 – 13.8 mg/kg bw/d and anemia in females at this dose level. At 40 mg/kg bw/d, dogs had severe toxic signs including nausea or vomiting, salivation, occasional clonic convulsion and opthalmological changes. At 4 and 40 mg/kg bw/d, liver failure, kidney damage (only in females) and anemia were also observed in dogs.

The haematological and other effects from different *in vivo* studies seem to correlate with the toxicokinetic data from rats where the highest percentage of the administered dose was found in blood (0.9 - 1.99%) followed by liver (0.4-1.8%), muscle (0.05-0.6%), bone (~ 0.5%) and kidney (0.07- 0.16%). All other tissues, in both sexes, contained less than 0.1% of the administered dose.

In rats, thiram at single oral doses of 26 mg/kg bw inhibited the active transport of leucine and methionine (Witkowska et al., 1992). At single oral dose of 290 mg/kg bw in rats, thiram decreased lipoprotein lipase (LPL) activity in adipose tissue and increased the levels of total plasma cholesterol, triacylglycerols and high density lipoprotein (HDL) cholesterol; such effects on LPL activity and HDL cholesterol were observed also after six day treatment with 29 mg thiram/kg bw/d (Sadurska and Boguszewski, 1993).

In a study by Flippin et al. (2009), after four days oral treatment in rats at doses ranging from 6.25 to 800 mg/kg bw/d, thiram caused dose-dependent decrease in the circulating levels of T4 with an ED50 (the dose which elicited a 50% decrease in T4) of ca. 250 mg/kg. At ≥ 50 mg/kg bw/d, thiram caused decreased body weight gain. The purpose of this study was to test "the hypothesis that serum T4 concentrations of rodents exposed to a mixture of both TH synthesis inhibitors (pesticides [thiram, pronamide, and mancozeb]) and stimulators of T4 clearance in the liver (polyhalogenated aromatic hydrocarbons, PHAHs [18]) could be best predicted by an integrated addition model."

Thiram was hepatotoxic in rats at single intraperitoneal doses of 80, 100 (Rahden-Staron et al., 2001) or 120 (Dalvi et al., 1984) mg/kg bw. Thiram at single oral dose of 100 mg/kg bw increased the adrenal dopamine content and reduced plasma dopamine-β-hydroxylase activity in rats (Caroldi and De Paris, 1995).

In vitro data

In a recent study, thiram induced apoptotic and necrotic cell death in a dose- and time-dependent manner in human natural killer cells, NK-92CI (Li et al., 2014). In Chinese hamster fibroblasts (V79 cells) thiram altered antioxidant defence systems in the cell suggesting that it can act through the production of free radicals and induce apoptosis (Grosicka et al., 2008 and 2005). Thiram also caused rapid oxidation of glutathione levels in cultured human skin fibroblasts leading to oxidative cellular damage suggested by increased lipid peroxidation and cell death (Cereser et al., 2001). Thiram affected the glutathione reductase activity also in the yeast, *Saccharomyces cerevisiae* (Elskens and Penninckx, 1995).

Conclusion on systemic toxicity

Thiram caused systemic toxicity in several *in vivo* studies even at low dose ranges. The available *in vitro* data shows that thiram is cytotoxic.

Endocrine disrupting properties

Thiram was included in the priority list of chemicals developed within the EU-Strategy for Endocrine Disruptors. In 2002, after evaluation at the expert meeting thiram was placed in Category 1[6] for human health relevant endocrine disruption based on Stoker et al. (1993) as the key-study.

In 1993, Stoker et al. published the results of three experiments carried out to investigate the acute effects of thiram on the hormonal control of ovulation in rats given single intraperitoneal doses of 6, 12, 25, 50, or 100 mg/kg bw/d in the first experiment and 12, 25, or 50 mg/kg bw/d in second and third experiments. In the first experiment, thiram caused complete suppression of estradiol-induced luteinizing hormone surge in a dose-dependent manner in the ovariectomised estrogen-primed rats. In the second experiment, thiram blocked the ovulation in intact proestrous rats and in the third experiment, it caused complete suppression of luteinizing hormone surge also in intact animals. The NOEL in the first experiment was 6 mg/kg bw and 12 mg/kg bw in second and third experiments.

In two more experiments by Stoker et al. (1996 and 2006), single intraperitoneal dose of 50 mg thiram/kg bw in rats caused decrease in the rate of foetal development, reduction in the number of live foetuses, increase in number of resorptions on gestation day 20 and polyspermic zygotes.

Mishra et al. (1993 and 1998) investigated the morphological and biochemical effects in testes of rats from sub-acute to chronic (30 to 360 days) exposure of thiram via oral gavage at doses 5, 10, or 25 mg/kg bw/d. Thiram exposed for at least 90 days lead to diarrhoea, salivation, nasal bleeding, dyspnoea, ataxia and decreased body weight gain in a dose-dependent manner. Testicular effects observed in these studies include increased gonadosomatic index, degeneration of seminiferous tubules as well as dose and time dependent changes in testicular enzyme activities. However, in these two studies there was a dose-dependent high mortality starting with 20% at the lowest dose. Moreover, thiram did not show any testicular toxicity in mice at intraperitoneal doses of 25 (five daily doses) or 75 (single dose) mg/kg bw (Traina et al., 1994); but, this study too had 29 and 15% mortality within 5 days after acute and sub-acute treatment, respectively.

Adverse effects on reproduction and/or teratogenicity were also reported in rats, mice (Lee et al., 1978 and Short et al. 1976), and hamsters (Robens, 1969) at LOAEL's ≥ 30 mg/kg bw/d. Effects observed in these studies are not discussed here as the assessor has reservations about their reliability due to high mortality and missing information on the purity of the test material.

No treatment related adverse effects on fertility or development were observed in GLP-compliant studies performed according to standard guidelines (Exp Key Toxicity to reproduction.001; Exp Key Developmental toxicity/teratogenicity.001, .002, and .003) which could overshadow the results observed in the Stoker et al. studies with a non-relevant route of exposure to humans (intraperitoneal), high mortality in Mishra et al. studies and effects at dose levels that caused general systemic toxicity in addition to

[6] "At least one study providing evidence of endocrine disruption in an intact organism. Not a formal weight of evidence approach."

questionable reliability of the studies by Lee et al. (1978), Short et al. (1976) and Robens (1969).

In vitro data

Thiram was found to be not estrogenic (no effect on proliferation of human breast cancer cells, MCF-7) in the E-SCREEN assay (Soto et al., 1995). Thiram had no effect on either iodination or oxidative activity of thyroid peroxidase (TPO) in Chinese Hamster Ovary cells transfected with the human TPO gene (Marinovich et al., 1997).

Thiram inhibited human 11β-hydroxysteroid dehydrogenase 2 (HSD2) and zebrafish HSD2 activities with IC50s of 96 ± 17 nM and 18.3 ± 6 µM, respectively (Meyer et al., 2012). In human lung epithelial (NCI-H441) cells, thiram inhibited HSD2 oxidase activity and inhibited dexamethasone and cortisol binding to glucocorticoid receptors (Garbrecht et al., 2006). In human embryonic kidney (HEK-293) cells thiram inhibited HSD2 activity but did not affect HSD1 activity (Atanasov et al., 2003).

Conclusion on endocrine disrupting properties

In the light of general systemic toxicity, the available data set does not allow concluding that thiram alters function of the endocrine system and consequently causes adverse health effects.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The registrant generated exposure scenarios and made exposure estimations for manufacture and for all the identified uses (see Table 7) of thiram using ECETOC TRA v2 model. In the eMSCA's opinion the registrant has adequately described the operational conditions and the risk management measures for all the scenarios. Since thiram is a skin sensitiser, the registrant aims to avoid dermal exposure to workers to the extent possible. Local exhaust ventilations are placed at potential emission sources. Workers are required to wear dust masks while handling thiram. Respiratory protective equipment is used where necessary to further reduce the exposure.

The registrant calculated exposure estimates with 99% glove efficiency. In eMSCA's opinion using such higher glove efficiency is not a common practice. Furthermore, the ECETOC TRA v3 guidance document indicates glove efficiency of a maximum 95% for modelling of exposure with the use of Tier 1 model. Thus the eMSCA recalculated the exposure estimates with 95% glove efficiency.

7.12.1.2. Consumer

Not applicable as no consumer uses were identified in the registration dossier.

Significant consumer exposure to thiram through rubber articles is not expected as thiram is technically consumed during the vulcanisation process by getting embedded in the polymer matrix through cross-links (Bergendorff et al., 2007).

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

The combined RCRs (inhalation + dermal) calculated by the registrant for workers for all the exposure scenarios are below 1. The combined RCRs were below 1 even when the eMSCA reassessed the risk using 12% dermal absorption value and 95% glove efficiency. With the proposed operational conditions and risk management measures the risks to workers are under control for the identified uses of thiram.

7.14. References

Note: The references citing the studies reported in the registration dossier can be found on the ECHA dissemination webpage http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

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7.15. Abbreviations

CoRAP	Community Rolling Action Plan
DDC	Dimethyldithiocarbamate
DNEL	Derived No Effect Level
DNT	Developmental Neurotoxicity
ECHA	The European Chemicals Agency
ED	Endocrine Disruption/Disrupting
GLP	Good Laboratory Practice
eMSCA	The Evaluating Member State Competent Authority
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
RCR	Risk Characterisation Ratio
RMS	Rapporteur Member State
SVHC	Substance of Very High Concern
US EPA	The United States Environmental Protection Agency