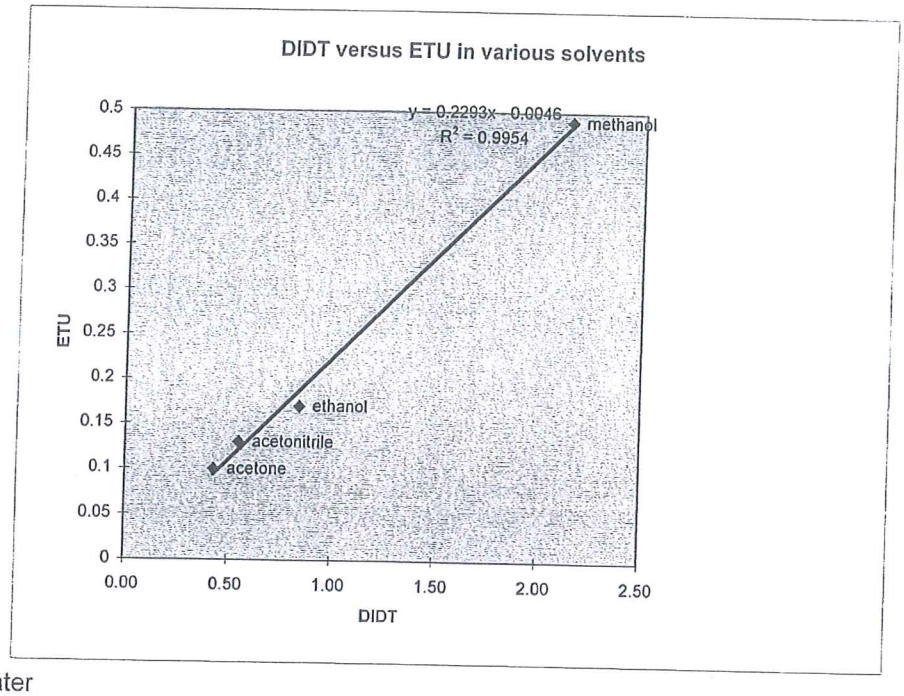
Graph 3 DIDT and ETU contents in maneb in various solvents excluding



water

The slope suggests the formation of 5 mol DIDT against 2 mol ETU. The large difference in content of ETU and DIDT and sulphur found between solvent and maneb causing extra formation of ETU during extraction.

As the maneb solubility in water is sensitive to the presence of zinc ions and the solubility of EBDC could not be proven in methanol the difference between the ETU content in water and in methanol or zinc sulphate solution may be caused by the decomposition of dissolved EBDC in water. In aqueous sodium sulphite solution the direct decomposition can not be prevented so the same initial content of ETU is found in water but it inhibits the increase of ETU in time, inhibits oxidation reaction. The zinc sulphate inhibits the formation of ETU by preventing the maneb to dissolve. The decomposition reactions in acetone and acetonitrile may be prevented by the absence of a protic H.

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FINAL REPORT DL 07-004

STUDY TITLE

Validation of ETU analyses in EBDC and EBDC-mixed formulations

DATA REQUIREMENT

Support of Registration Procedure

AUTHOR

P.C. Diepenhorst

STUDY COMPLETED ON

22 January, 2007

TEST FACILITY

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STUDY SPONSOR

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CEREXAGRI STUDY NUMBER

DL 07-004

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STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

1. No claim of confidentiality under FIFRA §10(d)(1)(A),(B) or (C)

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: .....

Company Agent: .....Date:.....
(Typed name) (yymmdd)

....
(Title) (Signature)

2. Claim of confidentiality under FIFRA §10(d)(1)(A), (B), or (C).

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

Information claimed confidential on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B) or (C) has been removed to a confidential appendix, and is cited by cross-reference number in the body of the study.

Company: .....

Company Agent: .....Date:.....
(Typed name) (yymmdd)

....
(Title) (Signature)

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STATEMENT OF GLP COMPLIANCE

Report number DL 07-004

The reported study:

Validation of ETU analyses in EBDC and EBDC-mixed formulations

has been performed at the Development Laboratory of Cerexagri B.V. in accordance with the valid procedures at the Development Laboratory.
For the type of compilation study no GLP compliance is applicable nor requested.
The study has **not** been conducted in compliance with Good Laboratory Practice (GLP) principles as defined in:
Directive 2004/10/EC of the European Parliament and the Council, of 11 February 2004; Official Journal of the European Union L50/44 – L50/59 of 20.2.2004.

Study Director:

P.C. Diepenhorst.

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QUALITY ASSURANCE STATEMENT

On the Study	:	**Validation of ETU analyses in EBDC and EBDC-mixed formulations**
Study and Report number	:	DL 07-004

Not applicable

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AUTENTICATION

Names and positions of investigators who participated in the major parts of this study.

NAME (Position)	SIGNATURE	DATE (yymmdd)
P.C. Diepenhorst (Study Director and author)	.....	070122

Copies sent to: 1 x GLP Archive Cerexagri B.V., Rotterdam, The Netherlands
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SUMMARY

The present (CIPAC) methodology of assessment of the ETU content in EBDCs does not measure the actual ETU content present in the sample but also as artifact an amount of ETU that is formed within 15 minutes of stirring with methanol. The result of the measurement is depending on extraction time and the kind of solvent used. This phenomenon is known at CIPAC. The actual ETU content in the EBDCs is most probably significantly lower than the results obtained from the used methodology.

The formation of ETU during extraction by decomposition of the EBDC is the reason why the accuracy of the methodology and the extraction efficiency cannot be established by standard addition because EBDCs, that will not generate ETU on extraction, do not exist.

The necessity to obtain a better (specific) method for the determination of the actual ETU in EBDCs has been doubted in CIPAC discussions as the potential danger of the compound ETU has been downgraded. Because of that reason the interest for the impurity has been minimized as expressed in a more or less public discussion between British Registration authorities.

The used methodology is a measure to characterize the quality of an EBDC, but the actual ETU content is always lower than the result of the analysis.

SAMENVATTING

De huidige (CIPAC) methodologie om het ETU-gehalte in EBDCs te bepalen meet niet het actuele ETU gehalte aanwezig in het monster maar ook als artefact een hoeveelheid ETU gevormd in 15 minuten roeren met methanol. Het resultaat van de meting hangt af van de extractietijd en het soort oplosmiddel wat wordt gebruikt. Dit fenomeen is bekend bij CIPAC. Het actuele ETU gehalte in EBDCs is zeer waarschijnlijk aanzienlijk lager dan de resultaten verkregen met de gebruikte methodologie.

De vorming van ETU tijdens de extractie door ontleding van het EBDC is de reden, dat de juistheid van de methodologie en de extractie-efficientie niet bepaald kunnen worden door standaardadditie omdat EBDCs, die geen ETU vormen, niet bestaan.

De noodzaak om een betere (specifieke) methode voor de bepaling van het actuele ETU-gehalte in EBDCs te krijgen wordt in CIPAC discussies betwijfeld daar het potentiële gevaar van de stof ETU gedegradeerd is. Om die reden is de interesse voor de vervuiling geminimaliseerd zoals gesteld in een min of meer publieke discussie tussen Britse Registratie autoriteiten.

De gebruikte methodologie is een maat om de kwaliteit van een EBDC te karakteriseren, maar het actuele ETU gehalte is altijd lager dan de uitkomst van de analyse.

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PROCEDURE

1 Introduction and purpose

In the registration procedure for Nautile DG (mancozeb/cymoxanil) in the U.K. the PSD asked for additional validation data beyond what is available in the concerned SOP and validation report.
The essential elements of our scientific position were already subject of a presentation for CIPAC and more or less discussion between British registration authorities.
This report contains a summary of the difficulties that arise during the extraction of ETU from ethylenebis(dithiocarbamates) (EBDCs) and formulations containing EBDCs.

2 Materials

2.1 Test Items

Name	:	Maneb
Type	:	TC
Name	:	Maneb 75 % WG
Type	:	WG
Name	:	Mancozeb 75 % WG
Type	:	WG
Name	:	Benthiavalicarb/Mancozeb 17.5/700 g/kg WG
Type	:	WG
Name	:	Mancozeb/Cymoxanil 680/50 g/kg WG
Type	:	WG
Name	:	Dimethomorph/mancozeb 75/667 g/kg WG
Type	:	WG

2.2 References

Name	:	**Ethylenethiourea standard**
Chemical name	:	2-imidazolidinethione
CAS RN	:	[96-45-7]
Origin	:	Cerexagri B.V., Rotterdam
Lot number	:	SP 2-42
Purity	:	99.9 %
Appearance	:	white crystals
Storage conditions	:	< 10 °C
Expiry date	:	August 2002
Development lab reg.no	:	MRF0054

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Name	: "Reference WG formulation without EBDC"	
Composition	: adjuvants	: 11.65 % according to CSF mancozeb product code 5950.62 without stabiliser hexamine
	balance Argirec B24	: 88.35 % (kaolin)
Lot	: P77-1-3	
Development lab reg.no.	: MRG0147	
Name	: "Reference WG formulation 0.05 % ETU"	
Composition	: adjuvants	: 11.65 % according to CSF mancozeb product code 5950.62 without stabiliser hexamine
	ETU	: 0.05 %
	balance Argirec B24	: 88.30 % (kaolin)
Lot	: P77-1-4	
Development lab reg.no.	: MRG0148	

2.3 Chemicals

Methanol GR	: Merck 1.06009
Water HPLC grade	: Millipore Alpha-Q
Methanol gradient grade	: Merck 1.06007
Acetonitrile gradient grade	: Merck 1.00030
Tetramethylammonium bromide	: Merck 1.08127
Sodium dihydrogen phosphate monohydrate	: Merck 1.06346
Disodium hydrogen phosphate dihydrate	: Merck 1.06580
N,N,N'-trimethylthiourea (TrMTU)	: Cerexagri B.V
Hexamine	: Merck 1.04343

2.4 Test Systems

The following apparatus has been used as Test System:

- HPLC system 3 (Development lab.no. A120 - A124, A179, A181 - A183) equipped with a Reversed Phase column Zorbax Bonus-RP 4.6 x 250 mm column, Agilent Technologies no 880668-901, column no. AC1244.

2.5 Test method

The certification was performed according to method SOP DLA-010.6, "Ethylenethiourea (ETU) by HPLC in WG formulations of ethylenebis(dithiocarnbamates).