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DOSSIER ETU DETERMINATION FOR CIPAC 2011

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TEST FACILITY

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1 x GLP Archive Cerexagri B.V., Rotterdam, The Netherlands
1 x Head Product Chemistry, Development Laboratory
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Property	Validation

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Dear Mr. Bura

At the CIPAC symposium of 1999 in Budapest I have given a presentation on the determination of ethylenethiourea (ETU) in ethylenebis(dithiocarbamates) (EBDC) according to CIPAC MT 162.
The main conclusion of my presentation was that the results of ETU content are not the actual ETU amounts in the tested EBDC but the amount of ETU that was generated during the extraction procedure of CIPAC MT 162. The amount of ETU found is to a high degree dependent on the type of extraction solvent applied and on the extraction time and thus mainly the result of the amount of EBDC that is decomposed during the extraction procedure.

After several discussions with a.o. Dr. A. Hill and Dr. R. Schreuder and the at that time PSD in the UK, the conclusion was made, that there was no necessity for further method development. This because it was unlikely that the amount of ETU, that is present in the product, is cause of concern even for regular users.
Further no follow up occurred.

For the registration of EBDC's all over the world ETU analysis is still required because ETU is considered to be a relevant impurity and defined as such in the (tentative) FAO specification. The employed methodology should be validated under the provisions of GLP. According these provisions validation of the method has to be performed as required by SANCO/3030 for the EU.
That means for accuracy and LOQ assessment of the method ETU added at a low level to the plant protection product should be recovered within certain limits and relative standard deviation. This is starting from the principle that a pesticidal product can be purified to a(n) (almost) impurity free product.
In the case of ETU in EBDC's (maneb, mancozeb, metiram, zineb) this is not possible. In practice the amount of ETU made during the analytical procedure from the tested EBDC is decisive for the results for accuracy and LOQ and not the analytical methodology.

It is also the intention for the preliminary analysis of the technical active ingredient to determine the actual amount of impurities and not the amount made during analysis.

This leads in practice to endless discussions with Rapporteur Member States (RMS's) again and again because persons move around and every two or three years the same discussion has to be held.

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To avoid this discussions I have made a report of the history concerning this matter and it is send frequently to an RMS for products that need to be (re-)registered. However even then it is a problem. Because the EU makes references to CIPAC methodology, comments on CIPAC methods are not lightly accepted.

Therefore the proposal is that CIPAC will make a public statement that the methodology to determine ETU in EBDC's does not determine the actual free ETU in the tested EBDC, but gives an indication of the amount of ETU formed by decomposition of the product during extraction with methanol and therefore is merely an indication of the quality of the examined product.
Even then, though ETU dissolves very well in aprotic polar solvents like acetone and acetonitrile, use of these solvents will result in significantly lower ETU results compared to methanol extraction, the results are still higher at longer extraction times. Therefore it can not be concluded that the assessed contents with those solvents are representing the actual free ETU in the product.

To support this proposal I will send you a copy of the Report I issued, which I have sent several times to RMS's, and of the sheets I have used at the Symposium you were hosting in Budapest.

Unless you have other suggestions to support this issue I ask to send me the postal address where you want me to send the papers above.

Thanks in advance

Best regards

Carel Diepenhorst

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Determination of Ethylenethiourea

Ethylenebisdithocarbamates (EBDC`s)

Successful Fungicides: Maneb
Zineb
Metiram
Mancozeb

Fungicidal Activity: Via Decomposition of
Parent Compound
Degradation products

Disadvantage: Formation of ethylenethiourea (ETU)
suspected carcinogen
Concentrations 0.1- 2.0 %

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History

Analytical methodology:

PAC-GB in UK: **Chairman Dr. A. Stevenson**

Paper Chromatography
HPLC
Spectrometric method

CIPAC Method MT 162: **1984**

HPLC Referee Method
Paper Chromatography

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Nowadays

Product Quality improved:
ETU concentrations: 0.001 – 0.2 %

CIPAC symposium 1998
9th International Congress on Pesticides Chemistry of IUPAC August 1998 London, U.K.

Presentations by Dr. Daniel F. Clarke 1998
Central Science Laboratories,York U.K.

Repeated serial extraction of EBDC with methanol:

2nd yield ETU 200 %
5th yield ETU 250 %

Conclusion:

ETU is generated during extraction with methanol !

Alternative methodology

Brittish investigators preference:

use water as extraction solvent

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ETU analysis by HPLC CIPAC MT 162

1. Extraction solvent: methanol

2. Extraction procedure:
   - disperse in methanol
   - filter crucible
   - filter after 3 min
   - repeat another 2 times

3. Part of the combined filtrates dried by evaporation

4. Dissolution in water,
5.
6. filtration and measuring the concentration by HPLC against external standard

SOP DLA-10.4 of Elf Atochem

1. Extraction solvent: methanol

2. Extraction procedure:
   - disperse in methanolic internal standard solution
   - magnetic stirring for 10 min.
   - direct filtration.

3. Dilution with eluent

4. HPLC determination against internal standard

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Factors influencing the extraction efficacy

Influence of the solvent?

Monitor extraction in time for several solvents:

What solvents?

- Methanol
- Water
- Ethanol
- Acetone
- Acetonitrile

What EBDC ?

Rule of Thumb:

A metal EBDC is the least stable when it is dissolved !
Exception: Aqueous Sodium EBDC is relatively stable

Most soluble fungicidal transition metal complex of EBDC in water: Maneb

Investigated to establish decomposition effects:

extractions of Maneb TC with different solvents monitored on ETU concentration in time.

Method HPLC, internal standard, modified for different solvents