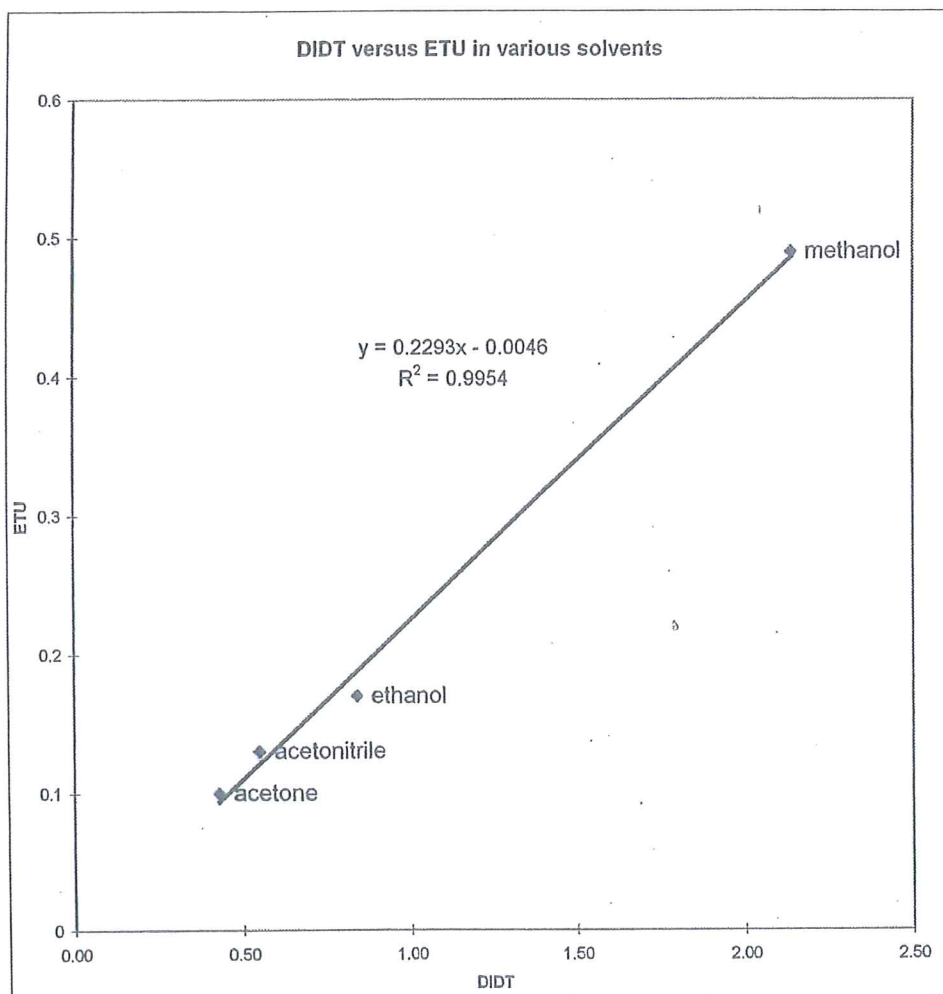


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Maneb washed with a good solvent for ETU and dried with caution, extracted with methanol, acetone and acetonitrile followed by HPLC analysis:

extraction solvent	ETU in g/kg Maneb		
	acetonitrile	acetone	methanol
washing solvent			
dichloromethane 1 st	0.058	0.038	0.600
dichloromethane 2 nd	0.052	0.031	0.550
acetone dried air stream	0.479	0.536	0.764
acetone dried vacuum	0.070	0.037	0.545
methanol	0.063	0.043	0.136

After washing the actual ETU from the sample material the extractions with the investigated solvents of the vacuum dried product are quite repeatable.

Also there is hardly no change in found ETU when washed for the second time

The product dried with a stream of air shows degradation of maneb with all solvents.

In methanol most of the ETU is formed, compared to acetonitrile ten times more, compared to acetone fifteen times more!



Conclusions

- 1. All solvents investigated are capable for dissolving the expected amount of ETU.**
- 2. In all solvents increasing amounts of ETU are found at increasing stirring times.
Not only in methanol ETU is generated.
In all investigated solvents ETU is generated.
Especially in water and aqueous solutions most of the ETU is found initially and formed on stirring.**
- 3. All indications are that not the actual ETU content is determined but also ETU formed by degradation of the maneb.**
- 4. If the actual ETU content has to be determined the sample preparation must be as simple as possible, no drying steps and carried with the solvent in which maneb is most stable: acetone.
Use an internal standard.**
- 5. The extraction time must be as short as possible:
5 minutes max.**

ETU extraction

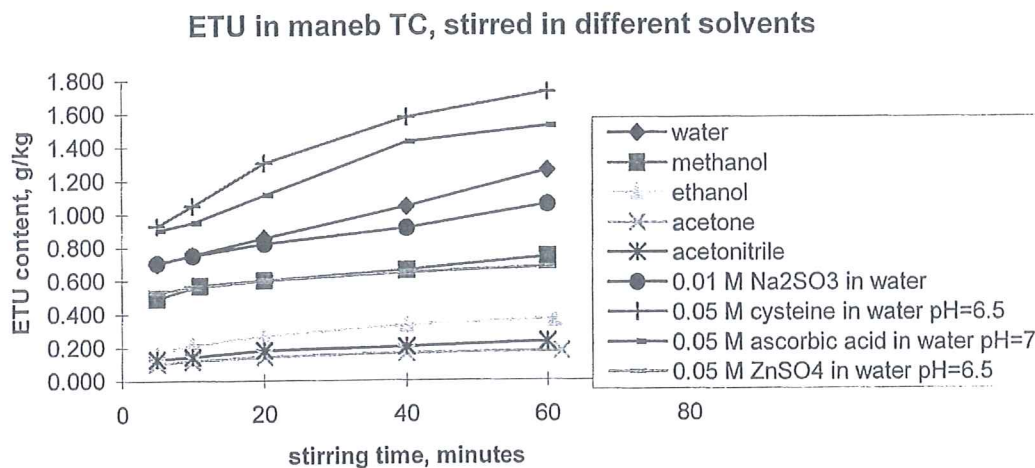
ETU extraction with several solvents

ETU (ethylenethiourea) content has been determined in maneb technical batch 9704-259/32 by extracting it from the sample with several solvents during increasing stirring time. The quantification was performed with HPLC against an internal standard. The results are presented in Table 1 and Graph 1.

Table 1: Content of ETU (g/kg) found in maneb TC 9704-5259/32

stirring time (min.)	water	methanol	ethanol	acetone	acetonitrile	0.01 M Na ₂ SO ₃ in water	0.05 M cysteine in water pH=6.5	0.05 M ascorbic acid in water pH=7	0.05 M ZnSO ₄ in water pH=6.5
5	0.701	0.494	0.169	0.102	0.129	0.706	0.928	0.901	0.533
10	0.753		0.211	0.119	0.144	0.752	1.050	0.948	0.557
11		0.572							
20	0.855	0.599	0.263	0.142	0.180	0.820	1.304	1.111	0.600
40	1.043	0.660	0.330	0.163	0.202	0.913	1.576	1.428	0.647
60	1.260	0.741			0.232	1.057	1.728	1.524	0.679
61			0.365						
62				0.173					

Graph 1



In all solvents the observed ETU content in maneb increases with increasing extraction times.

The results above show that extracting with ethanol, acetone and acetonitrile initially lower contents of ETU are found than using methanol or water and solutions of water. If the relation between the observed ETU concentration and the stirring time is regarded as second order polynomial the initial concentration (in situ) can be estimated by extrapolation and will be equal to the intercept. The initial rate of increase of the

ETU content in time is characterised by the parameter of x , the slope. The influence of the x^2 parameter is in the first instance negligible. In Table 2 the parameters of the regression analysis of the ETU content determination with the investigated solvents are presented.

Table 2

Regression data on observed ETU content vs. stirring time
2nd order polynomial

Solvent	parameters			correlation coefficient
	x^2	x	intercept	
water	$1 \cdot 10^{-5}$	0.0094	0.66	0.9998
methanol	$-3 \cdot 10^{-5}$	0.0059	0.49	0.981
ethanol	$-6 \cdot 10^{-5}$	0.0071	0.14	0.998
acetone	$-3 \cdot 10^{-5}$	0.0029	0.09	0.996
acetonitrile	$-2 \cdot 10^{-5}$	0.0032	0.12	0.989
0.01 M Na ₂ SO ₃ in water	$4 \cdot 10^{-6}$	0.0059	0.69	0.996
0.05 M cysteine in water pH=6.5	$-2 \cdot 10^{-4}$	0.0290	0.79	0.9993
0.05 M ascorbic acid in water pH=7	$1 \cdot 10^{-4}$	0.0215	0.77	0.9948
0.05 M ZnSO ₄ in water pH=6.5	$-4 \cdot 10^{-5}$	0.0049	0.51	0.9986

For acetone, acetonitrile and ethanol the initial ETU concentration are found near 0.1 g/kg (0.01 % w/w). For methanol and zinc sulphate solution the initial value approaches 0.5 g/kg (0.05 % w/w). In water and aqueous sodium sulphite solution the initial value approaches 0.7 g/kg (0.07 %w/w) while for ascorbic acid solution and cysteine solution the initial value nears 0.8 g/kg (0.08 % w/w).

The increase rate for ETU in time is for aqueous cysteine solution the fastest followed directly by the aqueous ascorbic acid solution (0.29 and 0.22 g/kg per 10 min). Then at less than half the rate of the former aqueous solutions, in water the ETU content increases with 0.09 g/kg per 10 min. The increase rate in ethanol is found to be 0.07 g/kg /10 min while for methanol and sodium sulphite solution the increase rate is the same: 0.06 g/kg /10 min. After zinc sulphate solution (0.05 g/kg 10 min) the smallest increases are found for acetone and acetonitrile at 0.03 g/kg /10 min.

The result of extraction with methanol is almost equal to the extraction of the zinc sulphate solution, which both are lower than water and the other water solutions. All solvents show an increasing ETU content at increasing extraction time. This increase is larger with water and water solutions, followed by alcohols, except for the sodium sulphite solution, which follows the alcohols.

Extraction with zinc sulphate solution has been carried out because this will inhibit the dissolution of maneb in water. Extraction with sodium sulphite solution, cysteine solution and ascorbic acid has been done to prevent degradation of maneb by oxidation reactions.

The different result in initial ETU content and in formation of ETU in time (degradation of maneb) between the zinc sulphate solution and water can probably be explained by the difference in concentration dissolved maneb. In water the maneb will be dissolved for 176 mg/l (Table 6) while the solubility in zinc sulphate solution will be less than 1 mg/l.

The sulphite solution starts at the same ETU content compared to water but the degradation of the maneb is inhibited. Ascorbic acid and cysteine obviously have no positive effects on the stability of maneb in water.

Solubility of ETU in several solvents

The solubility of ETU in the investigated solvents has been determined by stirring and ultrasonication for 5 minutes of approximately 200 mg ETU in 2 ml solvent. After filtration the ETU content was determined in the filtrate. Results are presented in Table 3.

Table 3
solubility ETU

solvent	solved ETU (%)		ETU in filtrate (mg/ml)	
	stirring	sonication	stirring	sonication
water	21	25	21.9	24.9
ethanol	7	9	6.9	8.5
methanol	17	20	17.4	20.0
acetone	10	10	9.6	9.8
acetonitrile	10	11	9.9	10.9

Using these concentrations of ETU in the solvent, the content of ETU can be calculated in a sample maneb if this level is reached at a normal ETU content determination. These results are presented in table 4.

Table 4
Maximum ETU concentration in maneb TC
when using solvent to saturation in 5 min

solvent	ETU (g/kg)	
	stirring	sonication
water	438	498
ethanol	139	171
methanol	349	401
acetone	191	197
acetonitrile	198	218

It appears that ETU dissolves less easy in ethanol, acetone and acetonitrile than in methanol or water. These three solvents also showed the lowest ETU contents at the extraction experiment (see table 1 and graph 1).

If the ETU content of a sample is calculated when, under these standardised extraction conditions, the concentration level of table 3 will be reached, extraordinary high contents are found (see table 4).

The solubility of ETU in the solvents under investigation has been determined at a level of 10 g/kg (1 % w/w) content in a sample (more than ten times the largest found concentration). The test was carried out by weighing ETU standard, equivalent to 10 g/kg in maneb, into the flask and extract (dissolve) for 5 minutes with the tested solvents. The recovery results for the different solvents are presented in table 5.

Table 5
Recovery of ETU at 10 g/kg level with various solvents

solvent	dissolved ETU (%)
water	103
ethanol	102
methanol	102
acetone	102
acetonitrile	102

For all the solvents under investigation the recovery is good. So as was expected from the data in Tables 3 and 4, if ETU is available at 10 g/kg product, all the ETU will be dissolved within 5 min of stirring time.

Solubility of maneb in solvents under investigation

The solubility of maneb TC in the solvents is determined by extraction of the product with the standardised method during 5 min, followed by filtration and derivatisation of dissolved maneb with iodomethane to dimethyl-EBDC. The amount of dimethyl-EBDC was determined by HPLC. The results are presented in Table 6.

Table 6
Maneb dissolved as EBDC in various solvents

solvent	dissolved maneb (mg/l)
water	176
ethanol	n.d.
methanol	n.d.
acetone	n.d.
acetonitrile	6

It appears that only in water, and much less in acetonitrile, maneb will dissolve within normal extraction time for ETU content determination. In the other 3 solvent no dimethyl-EBDC was detected so no maneb was dissolved as EBDC.

The dissolution of other metabolites of EBDC in various solvents

The sample maneb TC has been extracted with the investigated solvents and subsequently analysed by HPLC for the EBDC metabolites 5,6-dihydro-3H-imidazo[2,1,c]-1,2,4-dithiazole-3-thione (DIDT) and sulphur (S). The results are presented in Table 7.

Table 7
DIDT and sulphur found after 5 min extraction

solvent	DIDT (g/kg)	sulphur (g/kg)
water	1.15	0.58
methanol	2.14	1.40
ethanol	0.84	0.59
acetone	0.43	0.49
acetonitrile	0.55	0.52

The amount of metabolites DIDT and sulphur are the highest in methanol. The amount of DIDT in water is the next largest amount, although the solubility for DIDT in acetone and ethanol must be considered significantly higher. Also for sulphur the solubility in acetone, acetonitrile and ethanol must be considered higher compared to water and methanol.

Conclusions

All solvents are suitable to dissolve the expected amounts of ETU from a maneb sample concerning solubility of ETU in these solvents. The increase of content ETU found in the sample at increasing extraction time is most probably caused by degradation of the maneb during extraction and occurs with all solvents. The degree of increase is solvent dependable. The increase of ETU content in time is for acetone and acetonitrile the slowest 0.03g/kg per 10 min. In zinc sulphate solution this rate is 0.05 g/kg per 10 min, for methanol this value is 0.06, for ethanol 0.07 and for water 0.09. For the aqueous solutions of cysteine and ascorbic acid the rate is 0.29 and 0.22 g/kg per 10 min.

It proves that cysteine and ascorbic acid have no stabilising effect on maneb dispersions.

The solvents acetone and acetonitrile are polar aprotic solvents with low viscosity (0.316 and 0.345 cp at 25 °C). Contrarily methanol, ethanol and water are protic polar solvents with higher viscosity (0.547, 1.10 and 0.890 cp at 25 °C). The solubility for ETU in the target concentration range has been proven more than adequate for all investigated solvents. The mass transport by diffusion for acetone and acetonitrile must be considered higher compared to methanol and water and should therefore increase the extraction speed.

Still in water and methanol higher amounts of ETU are found initially (6-7 times higher than in acetone acetonitrile and ethanol) and the increase of ETU on extraction for water, ethanol and methanol 2-3 times faster than for acetone and acetonitrile. Also in methanol and water the highest amounts of other EBDC metabolites are found 2.14 and 1.15 g/kg DIDT and 1.4 and 0.58 g/kg sulphur. In acetone and in acetonitrile only 0.43 and 0.55 g/kg DIDT and 0.49 and 0.52 g/kg are found and, while the solubility of DIDT and sulphur in these solvents are higher. That more DIDT is found in water than in acetone (while in acetone at least equivalent to 5 g/kg DIDT and sulphur dissolve and DIDT and sulphur are hardly soluble in water) gives strong indications for decomposition of EBDC in water and formation of DIDT.

When the found amounts of ETU in the various solvents are correlated with the observed amounts of DIDT at 5 min stirring time, except for the water observations a linear relation is observed with a correlation coefficient of 0.998. This is also an indication that the ETU and DIDT found in the diverse solvents is related to the decomposition of maneb. That the observations in water donot fit in that linearity is probably caused by the lack of solubility of DIDT in water. See graphs 2 and 3.

Graph 2 DIDT and ETU contents in maneb in various solvents

