

23RD WORLD STERILIZATION CONGRESS

16TH - 19TH OF NOVEMBER 2022

BARCELONA



METHODS FOR THE DETERMINATION OF PROCESS CHEMICAL RESIDUES AFTER REPROCESSING MEDICAL DEVICES

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Directives / Standards

Process chemicals

Residue analysis of surfactants

Results and Cytotoxicity

Determination of process chemicals after processing of medical devices using the example of surfactants

Process chemicals for the processing of medical devices have to be developed, tested and manufactured in the EU in accordance with the European Medical Devices Regulation .

*MDR - Article 2
Definitions*

*...
The following products shall also be deemed to be medical devices:*

- ...
– products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.*

4.4 Final rinsing

4.4.1 The WD shall be provided with a rinsing stage that ... reduces the concentration of process chemicals on the load to a level not exceeding that specified for the process chemical(s) as safe in the context of the intended use of the load.

4.4.2 Rinsing shall be deemed to have been achieved if ... the reduction of process chemicals has been determined and been shown to have been sufficient for the subsequent intended use of the load.

4.6 Process chemicals

... data on the maximum permitted residual level on devices and the method of detection to be used for determining process residuals shall be specified for each process chemical.

The sampling method and analytical method specified shall be capable of determining the presence of process chemical at concentrations below that specified as potentially harmful, i.e. as the maximum acceptable level.

LITERATURE

Residuals on medical devices following reprocessing.

Martiny H, Floss H, J Hosp Infect 2001, 48, Suppl A: 88-92

Automated method for determination of glutardialdehyde residues in flexible endoscopes after disinfection. Emmrich M, Floss H, Zühlendorf B, Martiny H, J. Chromatogr. 2003, B 795, 363-370.

Aldehyde residues on endoscopes - practical values and allowable limits. van Drongelen A W, de Bruijn A C P, Janssen P J C M, Orzechowski T J H, de Jong W H, Geertsma R E, Hygiene und Medizin 2006, 31 (10): 449-457.

Glutaraldehyde residues in flexible endoscopes. Part I: Method development. Emmrich M, Bloß R, Martiny H, ZentrSteril 2014, 22(1):46-49

Glutaraldehyde residues in flexible endoscopes. Part II: Analytical method and factors for detection of GA residues. Emmrich M, Bloß R, Martiny H, ZentrSteril 2014; 22(2):84-87

Methods to assess process chemical residues during the performance qualification.

Tschoerner M, 7th Colloquium "Medical Instruments" - Reprocessing, Maintenance, Reuse, 47. International Detergency Conference, 21st May 2015, Düsseldorf

Cleaning agents
Neutralizing agents
Rinse aids
Disinfectants
Care products



PROCESS CHEMICALS



Classic methods:

Amphoteric surfactants

Anionic surfactants

Cationic surfactants

Nonionic surfactants

- Titration (Epton, reverse)
- Methylene Blue Active Substance (MBAS, spectrophotometric)
- Disulfine Blue Active Substance (DBAS, spectrophotometric)
- Bismuth Active Substance (BiAS, potentiometric)
- Infrared spectroscopy (IR)
- Thin layer chromatography

Challenge: Identification + Quantification



- Heterogeneous substance classes
- Elements "only" C, H, O and (S, N)
- Properties structure determined

Examples of Non-ionic Surfactants

Fatty alcohol alcoxylate	$R-O-[EO]_x-[PO]_y-H$
Fatty acid alcoxylates	$R-C(O)O-[EO]_x-[PO]_y-H$
Fatty acid amide alcoxylates	$R^1-C(O)-NR^2-[EO]_x-[PO]_y-H$
Fatty amine alcoxylates	$R-NH-[EO]_x-[PO]_y-H$
Alkyl polyglycosides	$R-O-[C_6H_{10}O_5]_x-H$

RESIDUE ANALYSIS OF SURFACTANTS

Surfactants



- Agnique®
- Araphen®
- Arlypon®
- Crafol®
- Degressal®
- Dehydem®
- Dehydol®
- Dehypon®
- Dehypound®
- Dehyquart®
- Dehyton®
- Demelan®
- Disponil®
- Deriphat®
- Emulan®
- Glucopon®
- Lutensol®
- Lutensit®
- Maranil®
- Plantatex®
- Plurafac®
- Pluriol®
- Pluronic®
- Quadrol®
- Sulfopon®
- Texal®
- Texapon®
- Tresolit®

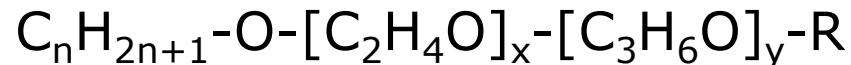
® = Registered trademark of BASF SE

Plurafac® LF types

- | | |
|-----------------|------------------|
| Plurafac LF 120 | Plurafac LF 403 |
| Plurafac LF 131 | Plurafac LF 404 |
| Plurafac LF 132 | Plurafac LF 405 |
| Plurafac LF 220 | Plurafac LF 431 |
| Plurafac LF 221 | Plurafac LF 500 |
| Plurafac LF 223 | Plurafac LF 600 |
| Plurafac LF 224 | Plurafac LF 711 |
| Plurafac LF 226 | Plurafac LF 731 |
| Plurafac LF 231 | Plurafac LF 7319 |
| Plurafac LF 300 | Plurafac LF 900 |
| Plurafac LF 301 | Plurafac LF 901 |
| Plurafac LF 303 | Plurafac LF 1300 |
| Plurafac LF 305 | Plurafac LF 1430 |
| Plurafac LF 400 | Plurafac LF 1530 |
| Plurafac LF 401 | |

Low-foaming nonionic surfactants

Type:



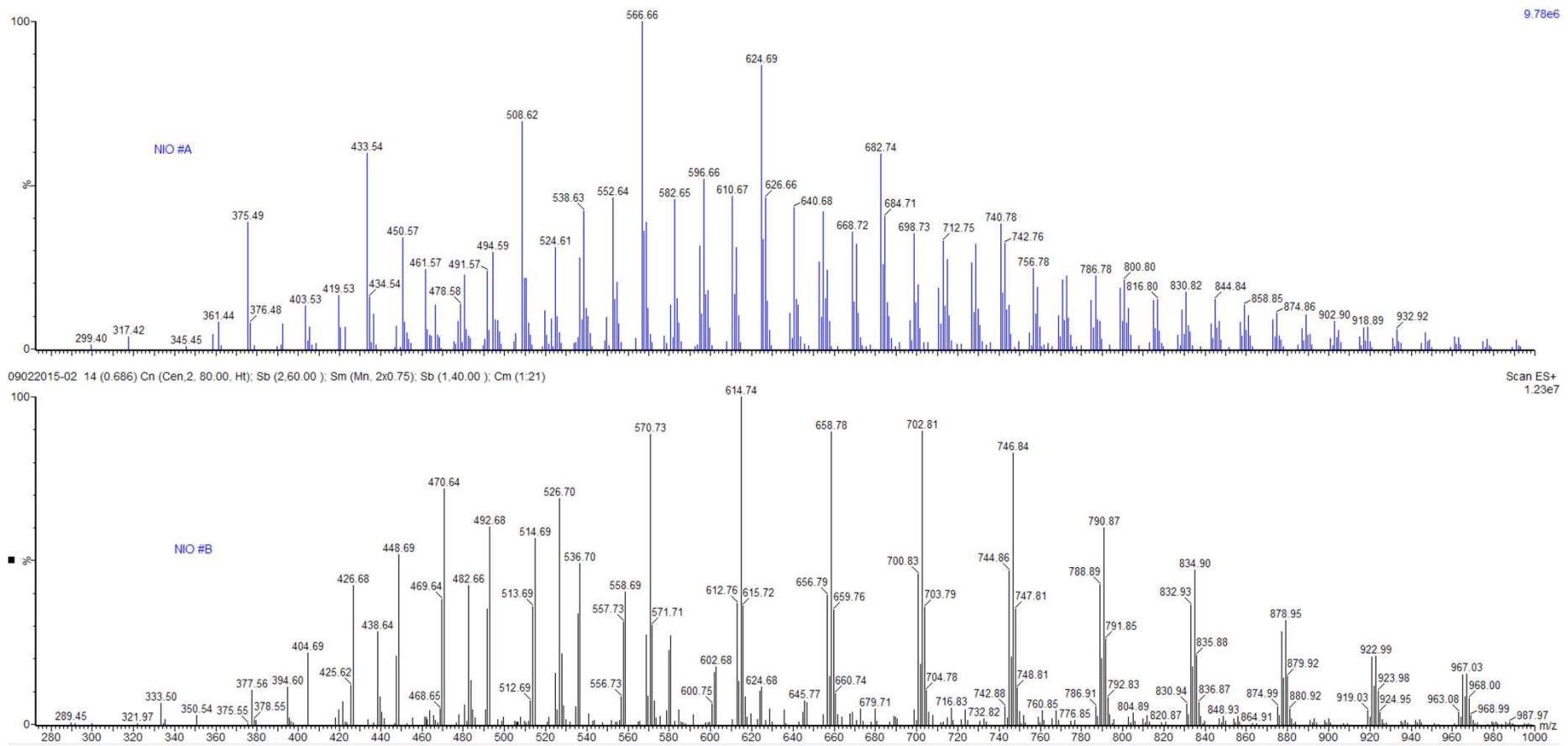
$$R = H, C_mH_{2m+1}$$

Instrumental analytical methods

- LC-MS
- ***LC-Triple Quad MS/MS (triple quadrupole mass spectrometer)***
- LC-Q-TOF MS/MS (quadrupole time-of-flight mass spectrometer)
- LC ion trap MS/MS (ion trap mass spectrometer)



RESIDUE ANALYSIS OF SURFACTANTS



EXCURS IN OIL CHEMISTRY

Chain length	6	8	10	12	14	16	18
Coco-Oil	1	5-10	5-8	45-53	17-21	7-10	8-16



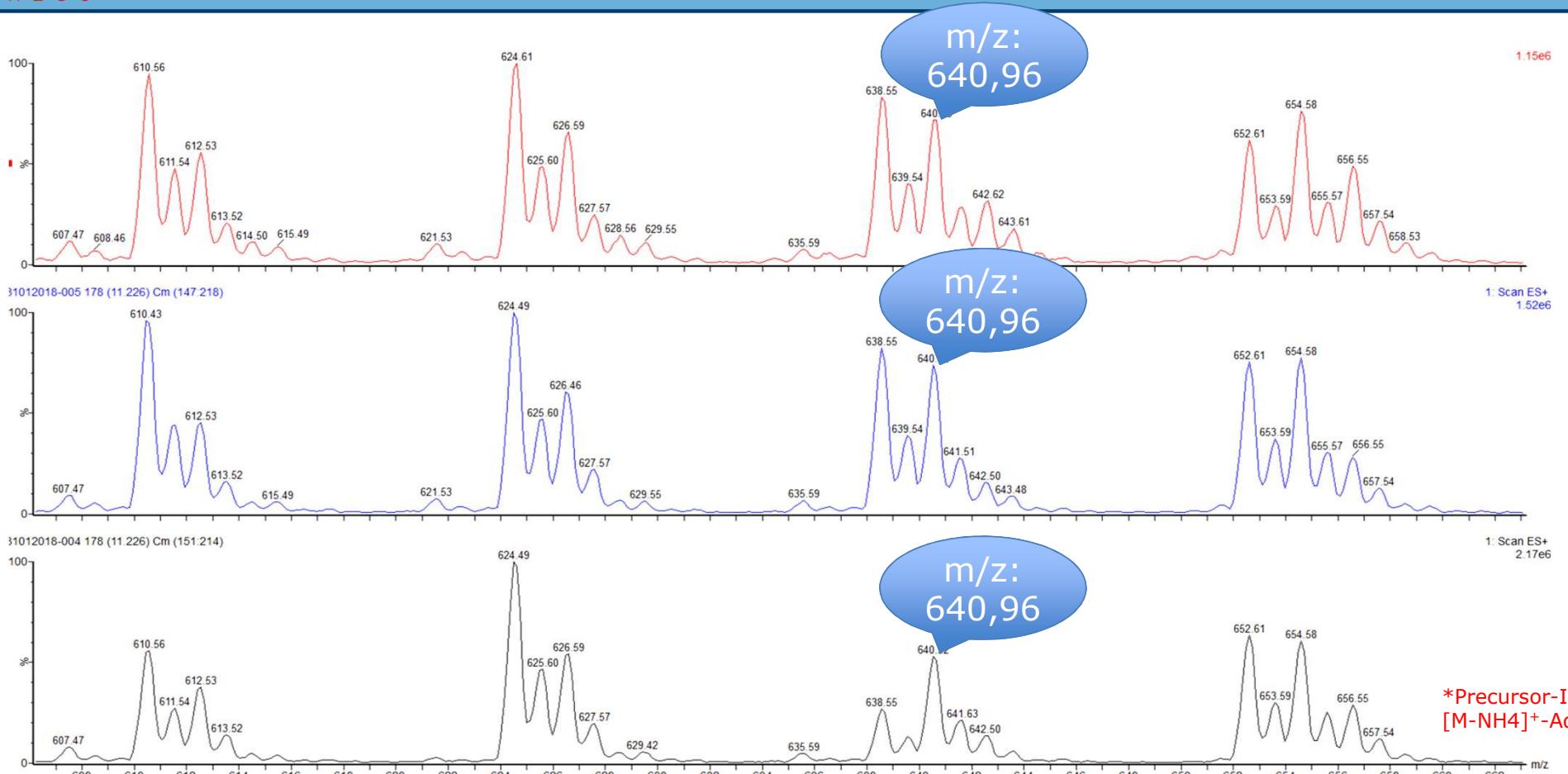
7 Fatty alcohol molecules

multiply with

1-x Ethylene oxide and 1-y Propylene oxide + End

e.g. 7 FA * 1-3 EO * 1-3 PO result in 63 molecules in 1 non-ionic surfactant

RESIDUE ANALYSIS OF SURFACTANTS



m/z: 640,9629*_(exact mass); Suggested Formula: C₃₄H₇₀O₉

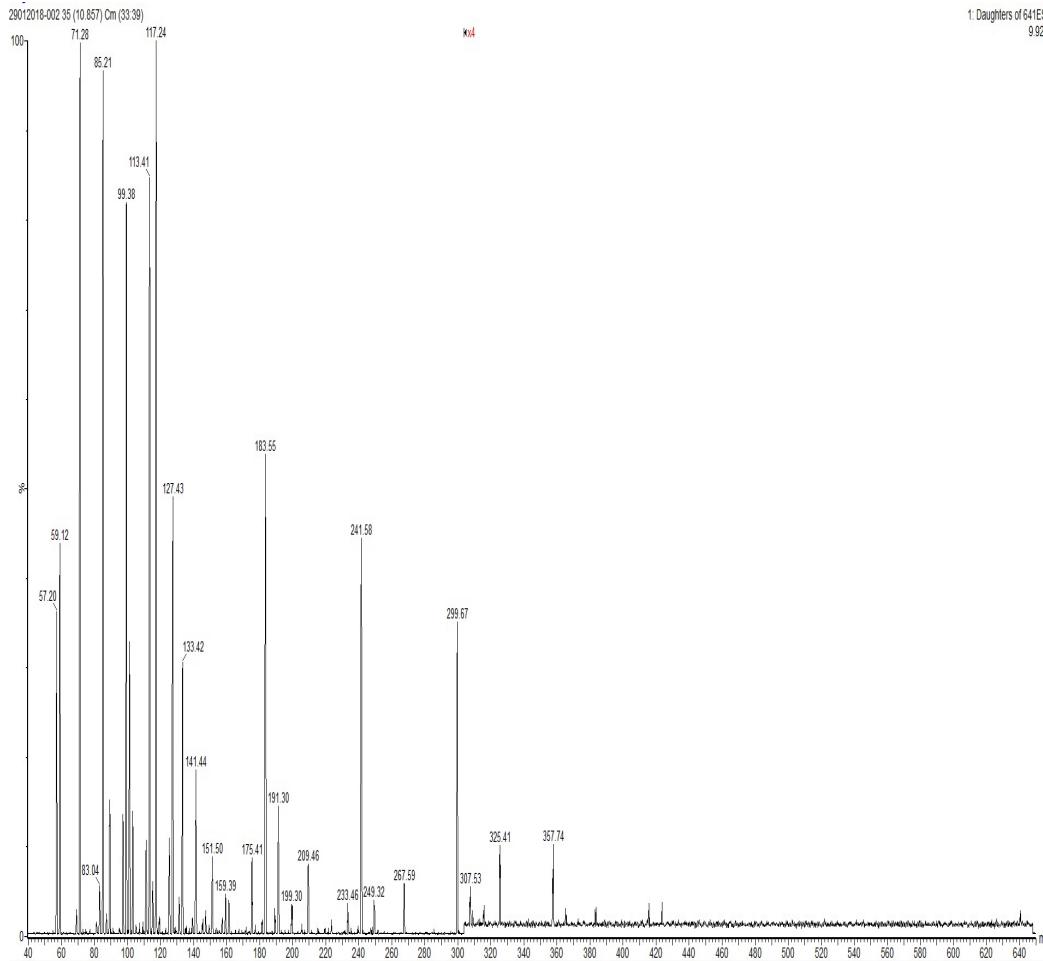
Theoretical configurations of molecule:

- ✓ C₁₈H₃₇-O-(CH₂-CH₂-O)₈-H
- ✓ C₁₇H₃₅-O-(CH₂-CH₂-O)₈-CH₃
- ✓ C₁₅H₃₁-O-(CH₂-CH₂-O)₈-CH₂-CH₂-CH₃
- ✓ C₁₄H₂₉-O-(CH₂-CH₂-O)₈-C(CH₃)₃
- ✓ C₁₄H₂₉-O-(CH₂-CH₂-O)₈-CH₂-CH₂-CH₂-CH₃
- ✓ C₁₁H₂₃-O-(CH₂-CH₂-O)-(CH₂-CH₂-CH₂-O)₇-H
- ✓ C₁₂H₂₅-O-(CH₂-CH₂-O)₂-(CH₂-CH₂-CH₂-O)₆-H
- ✓ C₁₃H₂₇-O-(CH₂-CH₂-O)₃-(CH₂-CH₂-CH₂-O)₅-H
- ✓ etc.

More than
30 variation
possibilities

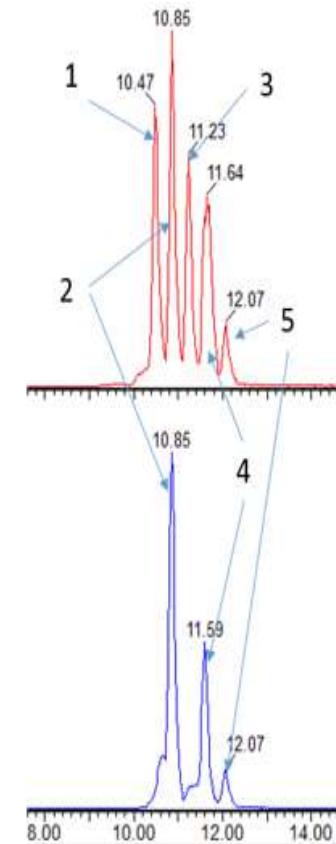
*Precursor-Ion: [M-NH₄]⁺-Adduct

RESIDUE ANALYSIS OF SURFACTANTS



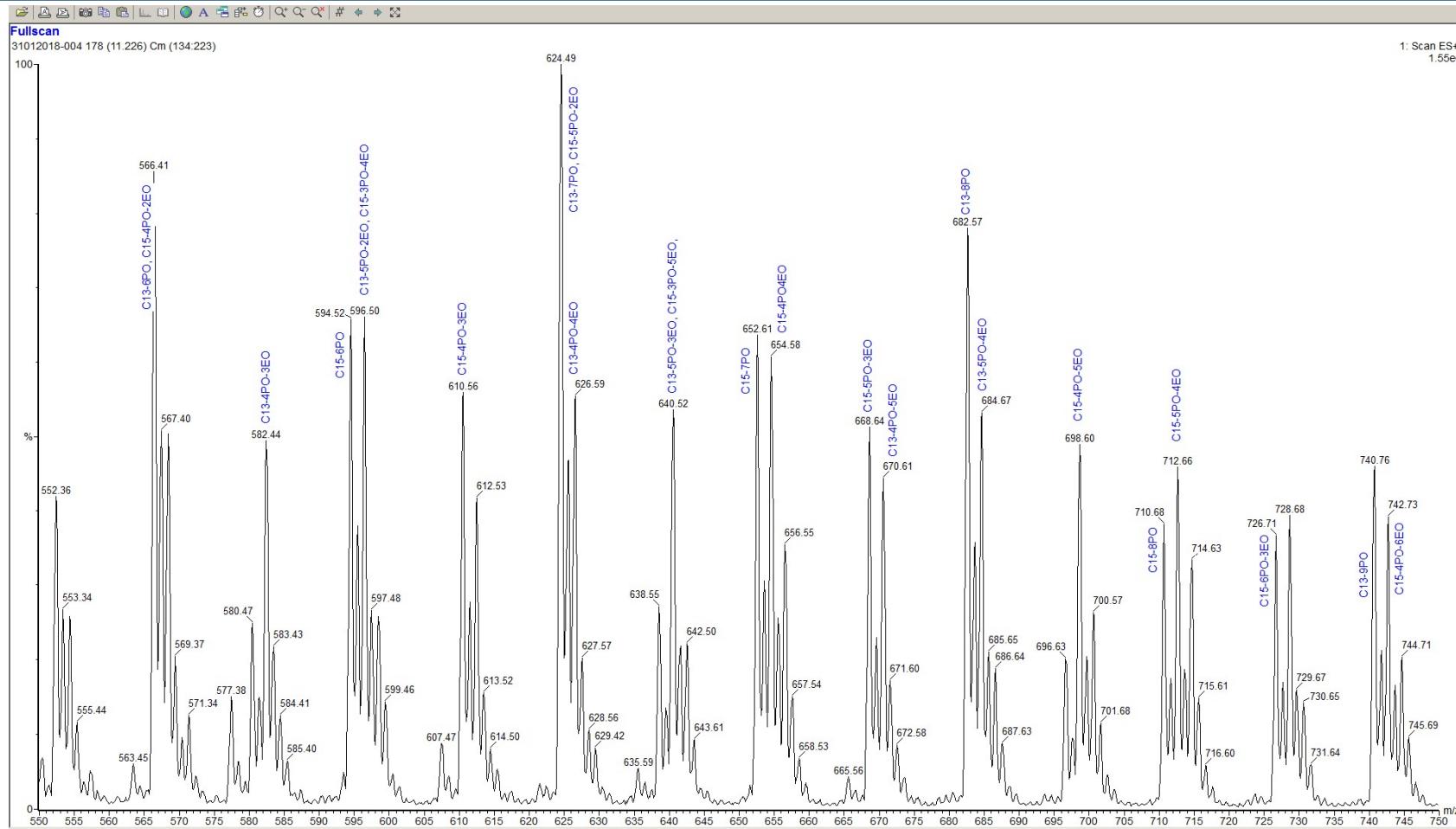
1: Daughters of 641ES+
9.92eL

- 1: C12-6PO-2EO
- 2: C13-5PO-3EO
- 3: C14-4PO-4EO
- 4: C15-3PO-5EO
- 5: C12-4PO-5EO?



Signal 1 and 3
Missing in Nio 3

RESIDUE ANALYSIS OF SURFACTANTS



Treatment process :

Cleaner A / Cleaner B

- Detergent concentration: 10 ml/l
- Water quality: deionized water
- Cleaning temperature: 45 - 55 °C
- Cleaning time: 10 minutes
- Intermediate rinse: 1 min.
(Cleaner B, 2 intermediate rinses)
- Final rinse including thermal disinfection
- Steam sterilization at 134°C, 5 min.

Screw test specimen based on ISO 15883-2:2009

Screws "M12x100mm" acc. ISO 4017,
product class A+B, stainless steel,
austenitic, EN 10088-2



Screw surface: 61 cm²
Elution ratio acc. ISO 10993-12:3 cm²/ml
Solvent: MeOH
Cytotoxicity acc. ISO 10993-5

RESULTS AND CYTOTOXICITY

Surfactant concentration in the eluate from screw test specimens



Cycles #	Cleaner A Non-ionic surfactant	In-Vitro- Cytotoxicity	Cleaner B Non-ionic surfactant	In-Vitro- Cytotoxicity
1	< 0,2 mg/l	negative	< 0,2 mg/l	negative
5	0,5 mg/l	negative	< 0,2 mg/l	negative
10	0,3 mg/l	negative	< 0,2 mg/l	negative
25	0,3 mg/l	negative	< 0,2 mg/l	negative
50	0,5 mg/l	negative	< 0,2 mg/l	negative
100	0,2 mg/l	negative	n.b.	
200	0,25 mg/l	negative	n.b.	
300	0,35 mg/l	negative	n.b.	
500	0,3 mg/l	negative	n.b.	

Cleaner A and Cleaner B, different surfactants

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Slide 20

RESULTS AND CYTOTOXICITY

Treatment process :

Cleaner A

- Detergent concentration: 6 ml/l
- Water quality: deionized water
- Cleaning temperature: 45 - 55 °C
- Cleaning time: 10 minutes
- Intermediate rinse: 1 min.
- Final rinse including thermal disinfection
- Steam sterilization at 134°C, 5 min.

Elution ratio: 3 cm²/ml

Solvent: MeOH

Cytotoxicity acc. ISO 10993-5

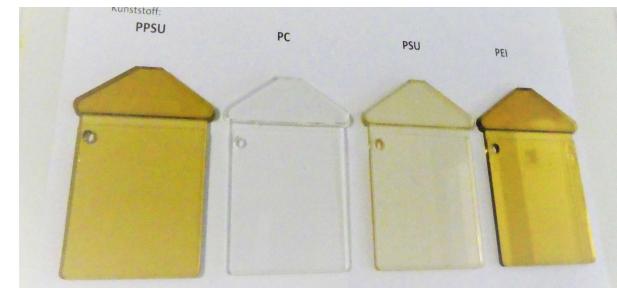
Thermoplastics:

PC polycarbonate

PEI polyetherimide

PSU polysulfone

PPSU polyphenylene sulfone

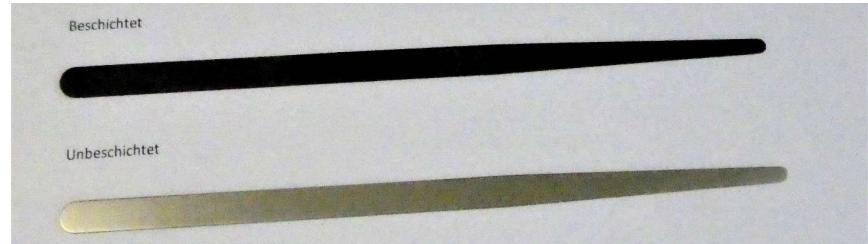


25 Cycles	Cleaner A	In-Vitro-Cytotoxicity
PC	3,0 ppm	1,0 µg/cm ²
PEI	4,1 ppm	1,4 µg/cm ²
PSU	2,7 ppm	0,9 µg/cm ²
PPSU	2,2 ppm	0,7 µg/cm ²

Treatment process :

Cleaner B

- Detergent concentration: 10 ml/l
- Water quality: deionized water
- Cleaning temperature: 55 °C
- Cleaning time: 10 minutes
- 2 x Intermediate rinse: 1 min.
- Final rinse including thermal disinfection
- Steam sterilization at 134°C, 5 min.
(every 25 cycles)



500 Cycles	Cleaner B
Non-ionic surfactant	< 0,3 ppm

Elution ratio: 3 cm²/ml

Solvent: MeOH

DIN 32645

Chemical analysis - Decision limit, detection limit and determination limit under repeatability conditions - Terms, methods, evaluation

38402-51

German standard methods for the examination of water, waste water and sludge - General information (group A) - Part 51: Calibration of analytical methods - Linear calibration

ISO 8466-2

Water quality - Calibration and evaluation of analytical methods and estimation of performance characteristics - Part 2: Calibration strategy for non-linear second-order calibration functions

ISO/IEC 17025

General requirements for the competence of testing and calibration laboratories

METHOD VALIDATION

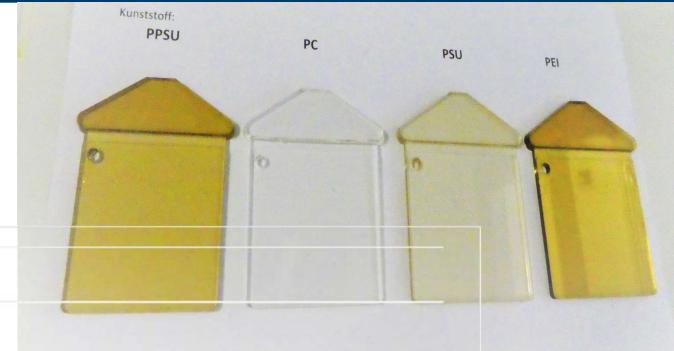
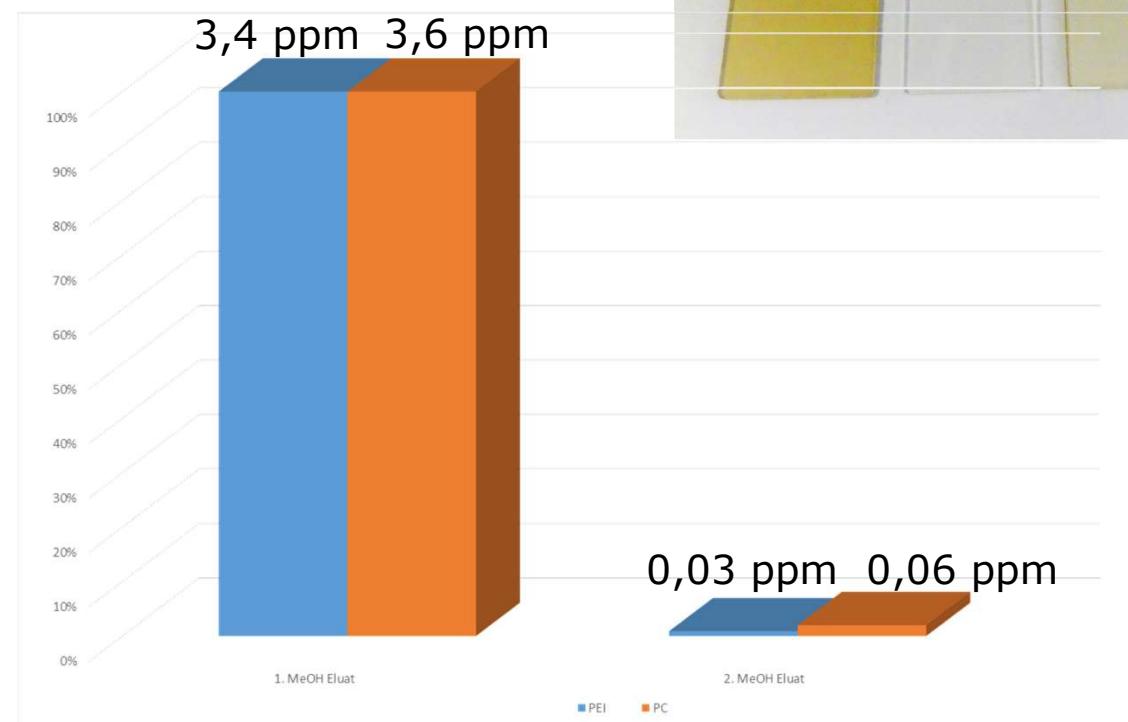
Recovery rates:

Target contamination

Repeated Elution

Reduction: 99 – 98 %
based on the initial value

Thermoplastics:



**Target Contamination Monitor
= 1,25 µg/cm²**

#1	1,36
#2	1,30
#3	1,32
#4	1,23
#5	1,41
Median	1,32
Var.-coeff.	5,1 %

Results:

Recovery rates: 95-105%

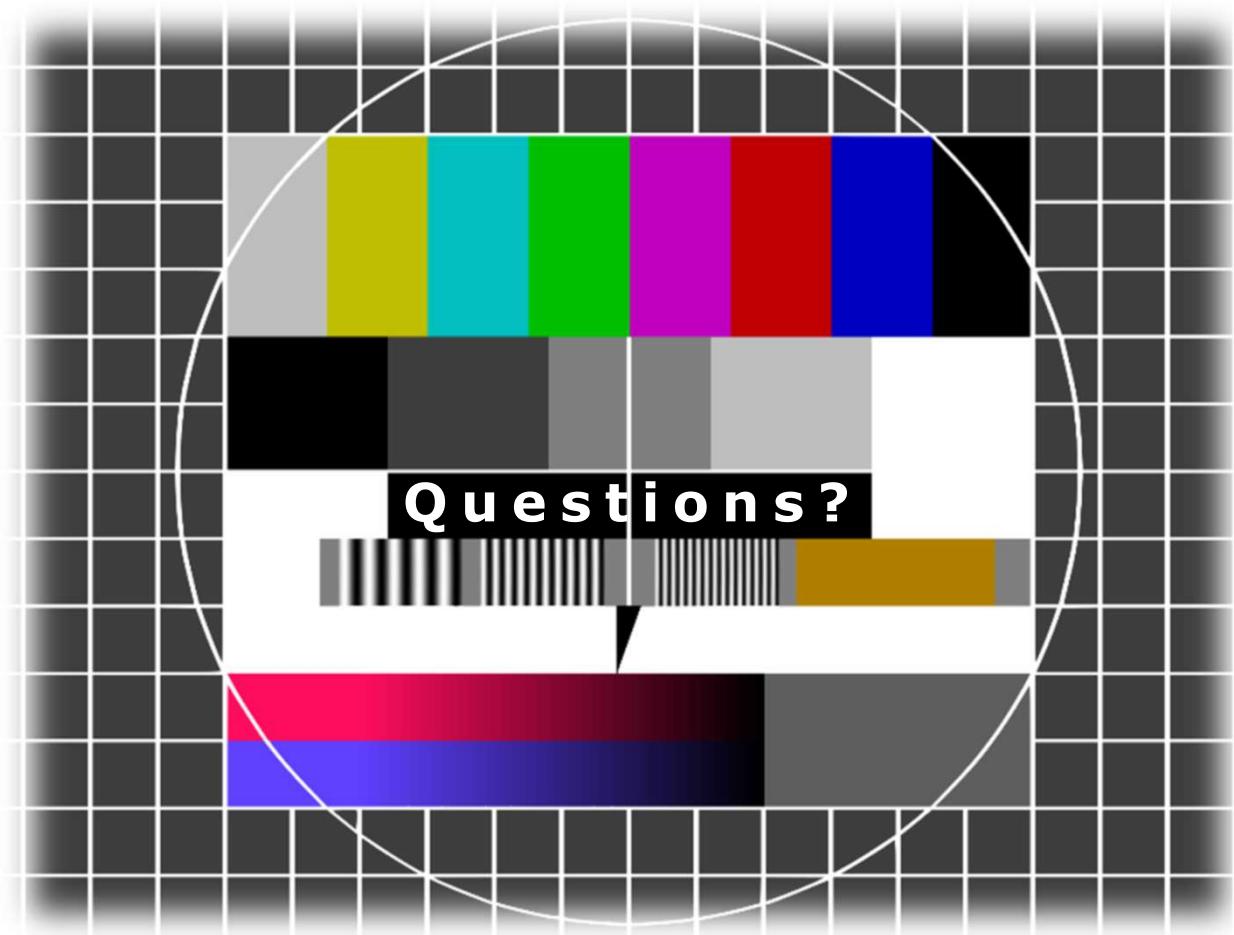
Cleaning result: all Monitors < LoD

LoD = 0,25 µg/cm²

LoQ = 1,0 µg/cm²

(alpha = 0,05; k = 3)

- ✓ Identification and quantification of process chemicals may need high sophisticated analytical methods
- ✓ Identification and quantification of process chemical on devices after processing demonstrates concentrations below the maximum acceptable level
- ✓ Compliance with requirements acc. ISO 10993-5 after repeated processing
- ✓ Compliance with requirements acc. ISO 15883 after repeated processing



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