ETH zürich

Chemical Warfare Agents

Monique Kuonen
Andrin Ott
Zhiyuan Fan

Chemical Warfare Convention (CWC)

Convention on the Prohibition of the Development, Production, Stockpiling, and Use of Chemical Weapons and of their Destruction

- 24 Articles
- Annex on Chemicals
  - Guidelines for Schedules of Chemicals
  - 3 Schedules of Chemicals
- Annex on Implementation and Verification = Verification Annex
  - 11 Parts
- Confidentiality Annex
  - 4 Parts

Organization for the Prohibition of Chemical Weapons (OPCW)

Key Provisions:

- Destroy Stockpiles of all existing Chemical Weapons
- Monitor Chemical Facilities to prevent Chemcial Weapons from re-emerging
- Assist and Protect Member States against Chemical Threats
- Foster international Cooperation to strenghten the Implementations of the Convention and to promote the peceful Use of Chemistry

OPCW ensures that the State Parties fulfill the obligations under the CWC

Chemical Weapon

Definition:

a. Toxic Chemicals and their Precursors
   (except where intended for purposes not prohibited under this Convention)
b. Munitions and Devices, specifically designed to cause Death or other Harm through the toxic Properties of those toxic Chemicals
c. any Equipment specifically designed for Use directly in Connection with the Employment of those Munitions and Devices

Purposes not prohibited:

industrial, agricultural, research, medical, pharmaceutical and protective purposes (among others)

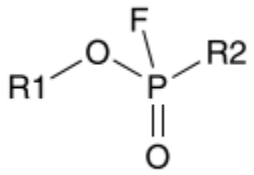
Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5

Analysis of CWC-related Chemicals
Schedules of Chemicals

Schedules list toxic Chemicals (A) and their Precursors (B)

List items are either individual Chemicals or Families of Chemicals with a common structural Backbone

1.A.01



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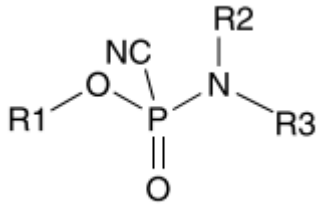
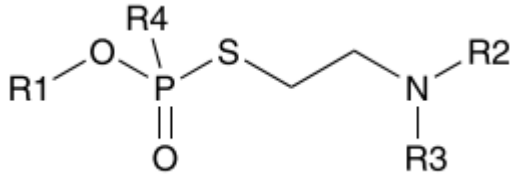
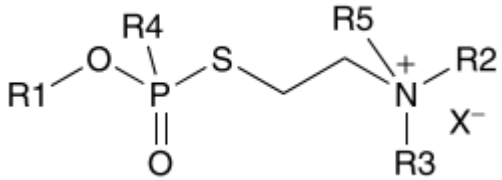


1.A.03





R_1 = H or ≤ C_{10}, incl. Cycloalkyl
$R_{2,3,4}$ = Me, Et, *n*-Pr or *i*-Pr
R_5 = H or alkyl
X= halogen

> 270'000 chemicals

Riot Control Agents are NOT included in the Schedules!

Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5

Analysis of CWC-related Chemicals
On-site VS Off-site Analysis

On-site

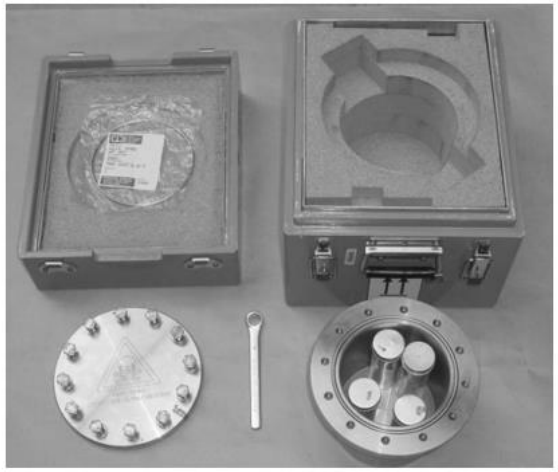
OPCW Inspection Team / Inspected State Party

- Sample Collection
- Sample Preparation
- Analysis by OPCW Mobile Laboratory
  - Portable GC-MS
  - (Portable FTIR)
- Sample Transport

Off-site

Accredited Designated Laboratories

- Sample Preparation
- Analysis
  - GC-MS
  - GC-MS/MS
  - LC-MS/MS
  - NMR
  - FTIR
  - ...



Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5

Analysis of CWC-related Chemicals
Sample Preparation of Environmental Samples

Environmental Samples:

- Air Samples
- Aqueous Liquid Samples
- Soil Samples
- Wipe Samples
- Active Charcoal Samples
- Concrete Samples
- Polymeric Samples

Preparations from the Recommended Operating Procedures (ROP)

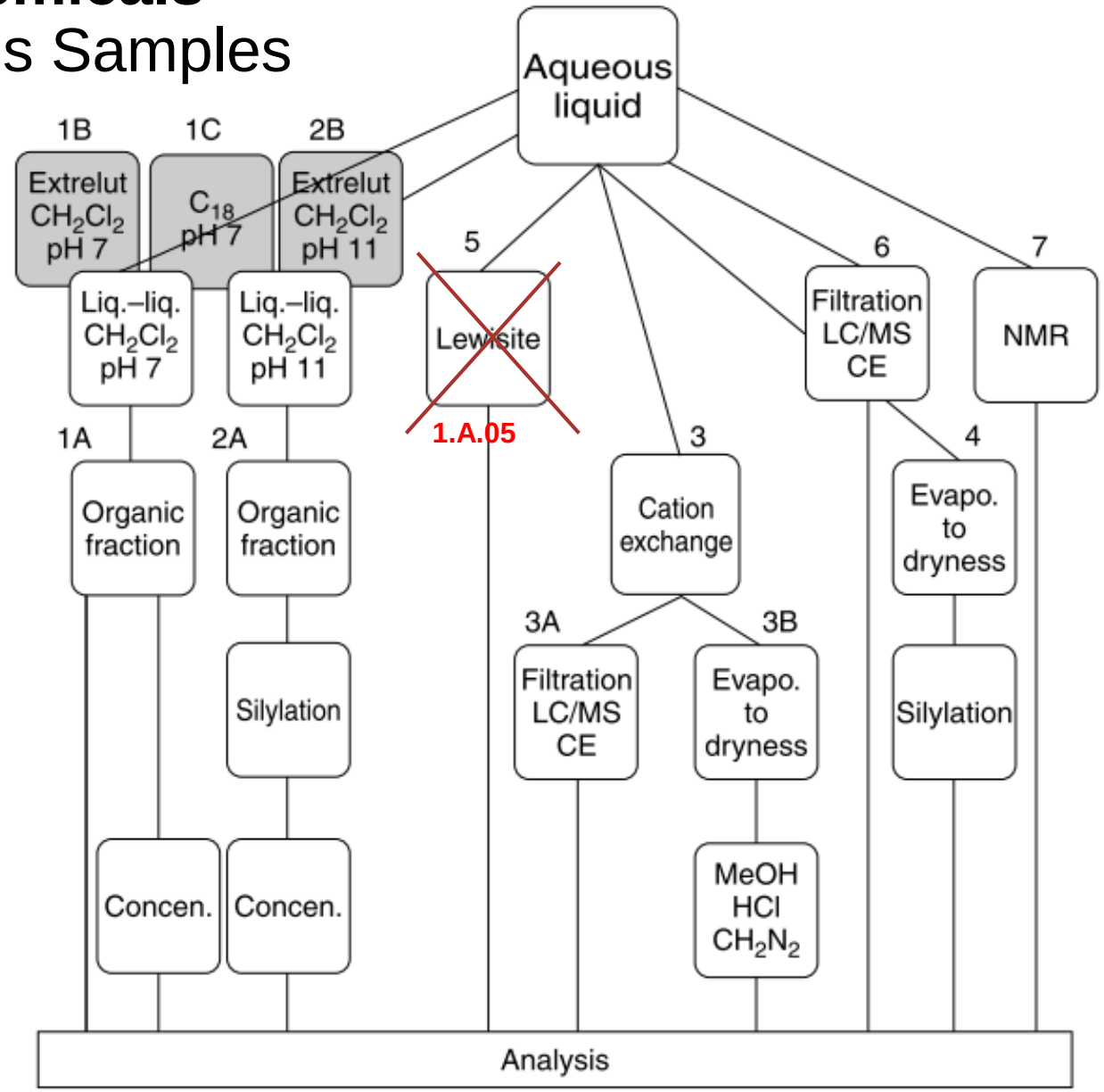
Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5
http://www.helsinki.fi/verifin/bluebook/

Analysis of CWC-related Chemicals
Sample Preparation of Aqueous Samples

1: No evaporation to dryness because certain CWC-related chemicals are firmly adsobed to glass surfaced

3: Aminoalcohols remain in the cation exchanger and cannot be recovered

4: No cation-exchange = large amount of inorganic cations in sample, which leads to low or no recoveries of smaller acids



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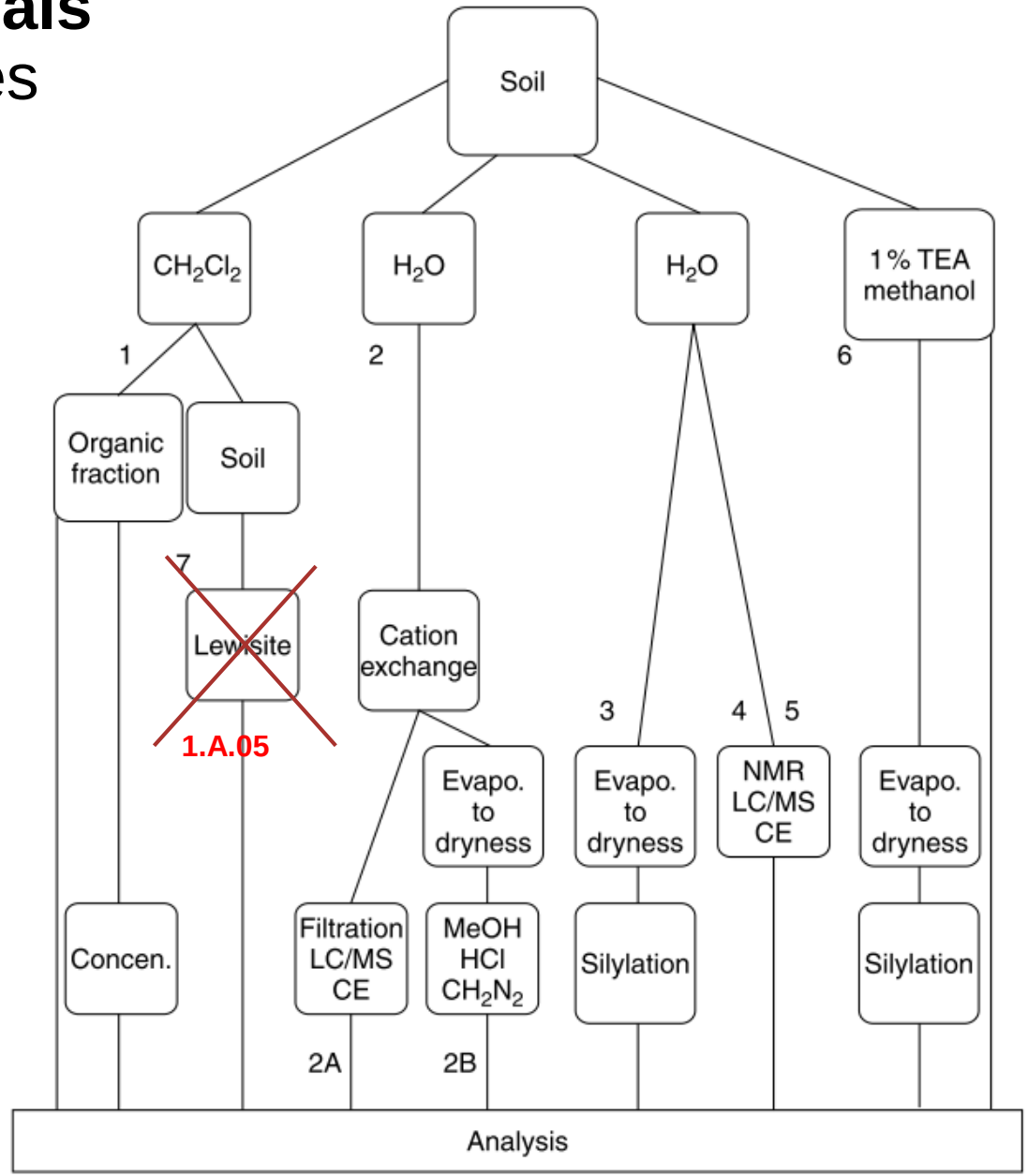
Analysis of CWC-related Chemicals
Sample Preparation of Soil Samples

1,6: No evaporation to dryness because certain CWC-related chemicals are firmly adsobed to glass surfaced

2: Aminoalcohols remain in the cation exchanger and cannot be recovered.

3: No cation-exchange = large amount of inorganic cations in sample, which leads to low or no recoveries of smaller acids



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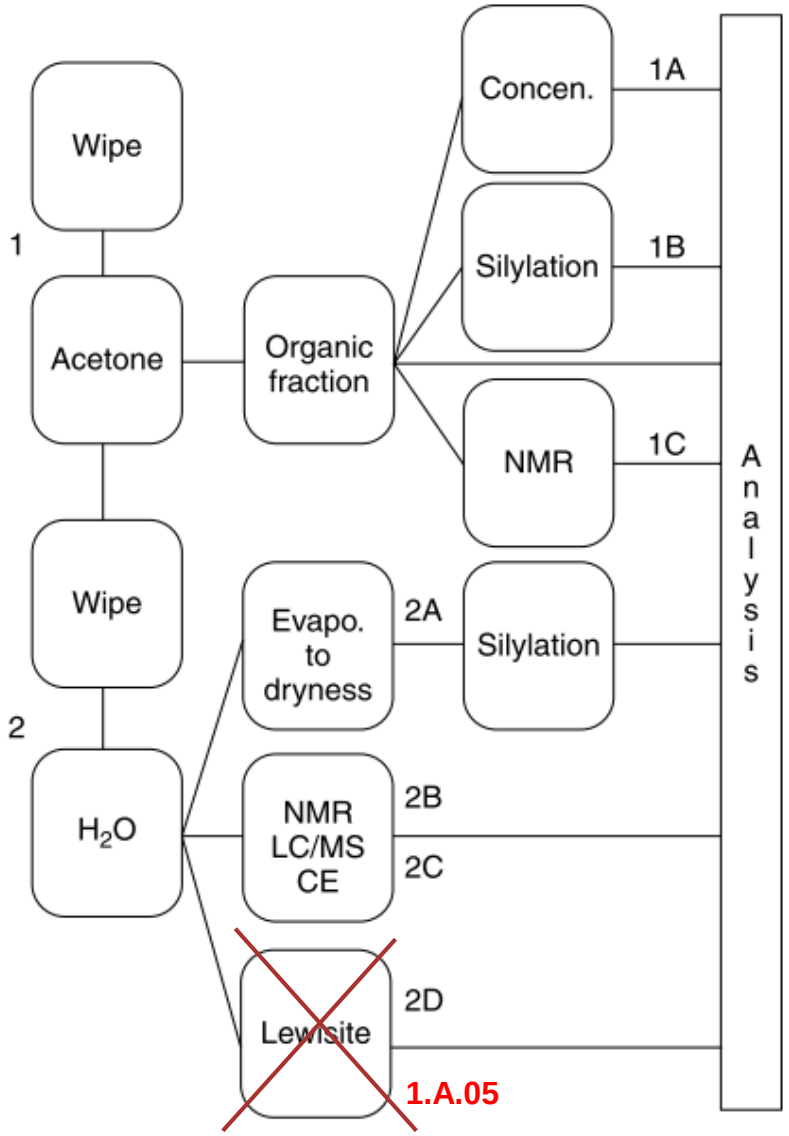
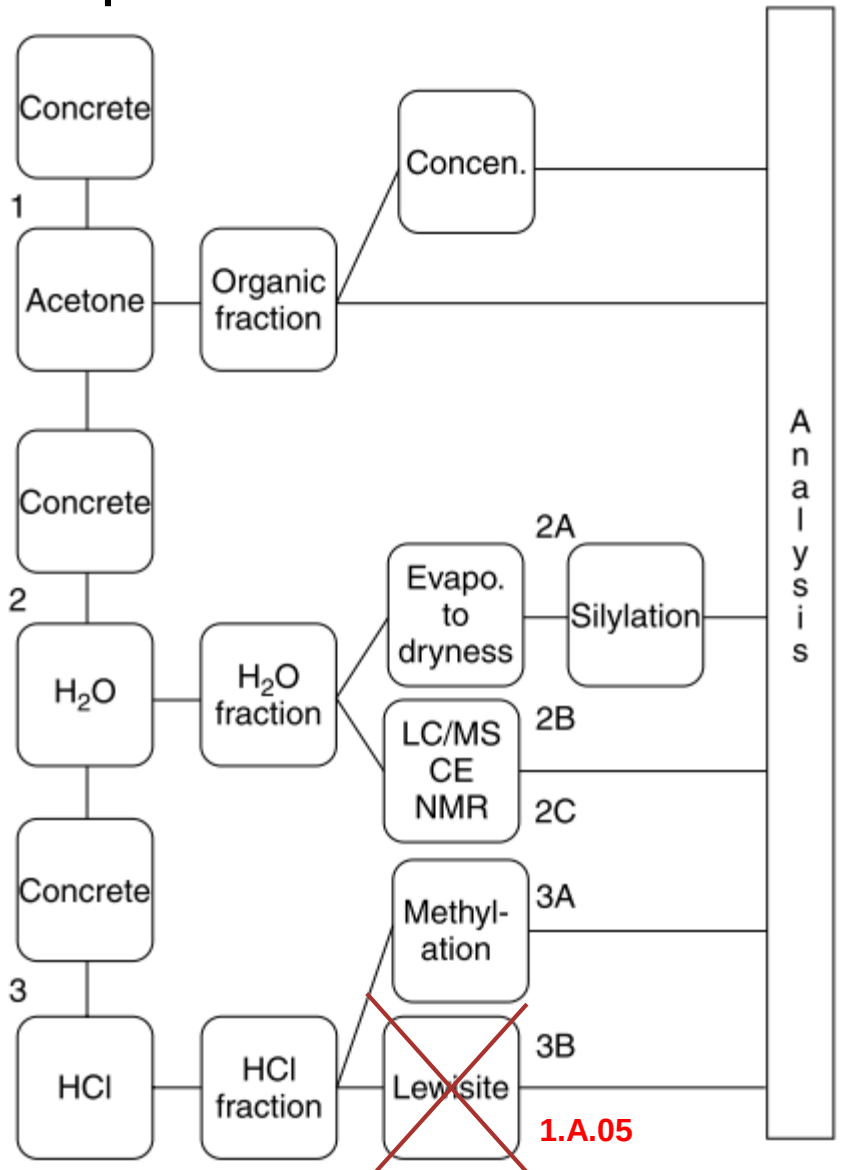
Analysis of CWC-related Chemicals

Sample Preparation of Wipe & Concrete Samples





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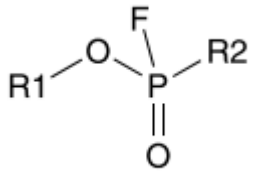
Analysis of CWC-related Chemicals
Analysis by NMR

- Advantages:
  - Nondestructive Method
  - Directly analyzable
  - Superior Method for Identification & structural Elucidation
  - Variety of 1-D and 2-D Experiments

- Disadvantages:
  - Low Sensitivity
  - Background Resonances
  - No Separation
  - Not suitable for on-site Analysis

1.A.01



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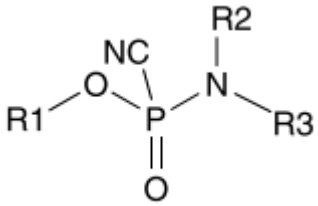
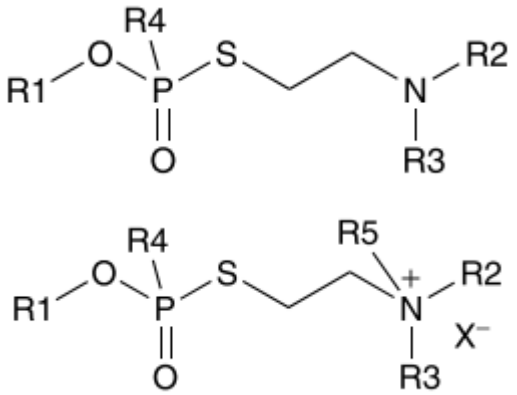


1.A.03



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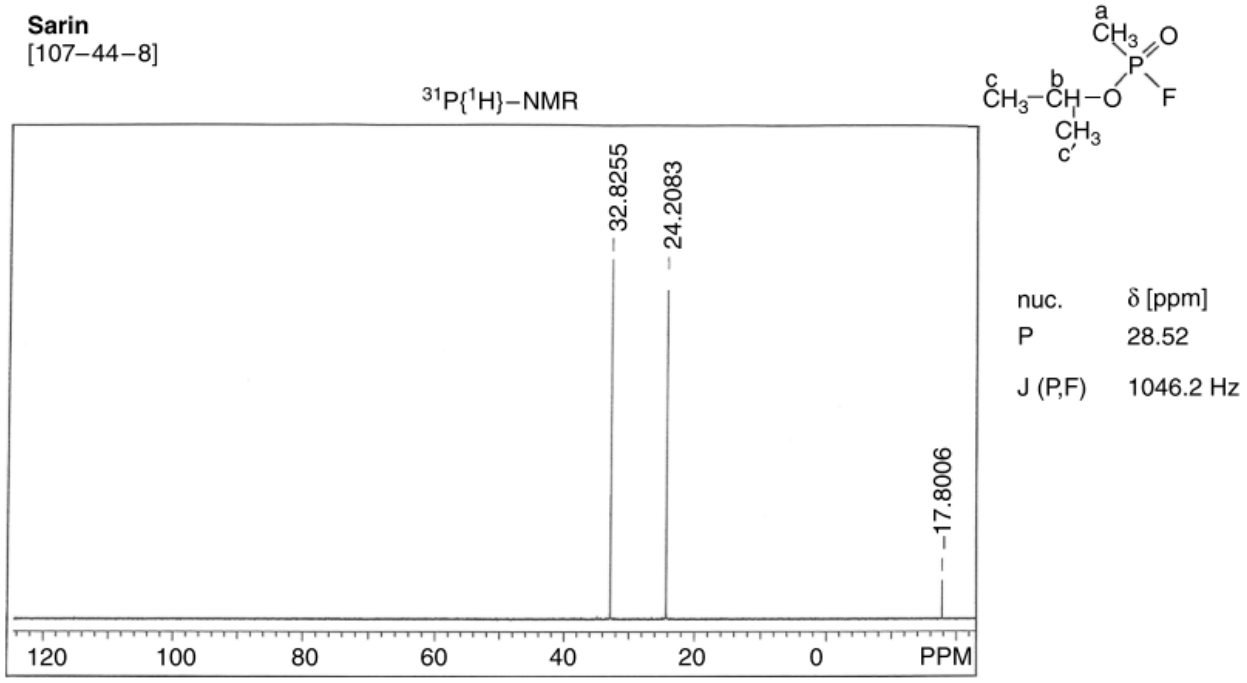
Analysis of CWC-related Chemicals
Analysis by NMR

- 1-D Experiments:
  - ^{1}H
  - ^{31}P & $^{31}P\{^{1}H\}$
  - ^{19}F
  - $^{13}C\{^{1}H\}$
  - $^{1}H\{^{31}P\}, ^{1}H\{^{19}F\}, ^{1}H\{^{1}H\}$

# of resonances, areas of resonances, chemical shifts and couplings

- 2-D Experiments:
  - COSY / TOCSY
  - HMQC



- Identification by Comparison:
  - ^{1}H, ^{19}F , $^{13}C\{^{1}H\}$ ± 0.1 ppm
  - $^{31}P\{^{1}H\}$ ± 1 ppm
  - J ± 0.5 Hz

- Limits of Detection (400MHz)
  - ^{1}H, ^{19}F 1 ppm
  - $^{31}P\{^{1}H\}$ 5 ppm
  - $^{13}C\{^{1}H\}$ 100 ppm

Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5

Analysis of CWC-related Chemicals
Analysis by IR

- Advantages:
  - Straight forward for pure liquid chemicals
  - Structural elucidation of unknown chemicals
  - able to detect non-volatile decomposition products
  - can be coupled to GC

- Disadvantages:
  - Spectral information is not enough for unambiguous identification
  - GC/MS delivers mostly the same and more information

Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5.

Analysis of CWC-related Chemicals
Analysis by GC-MS

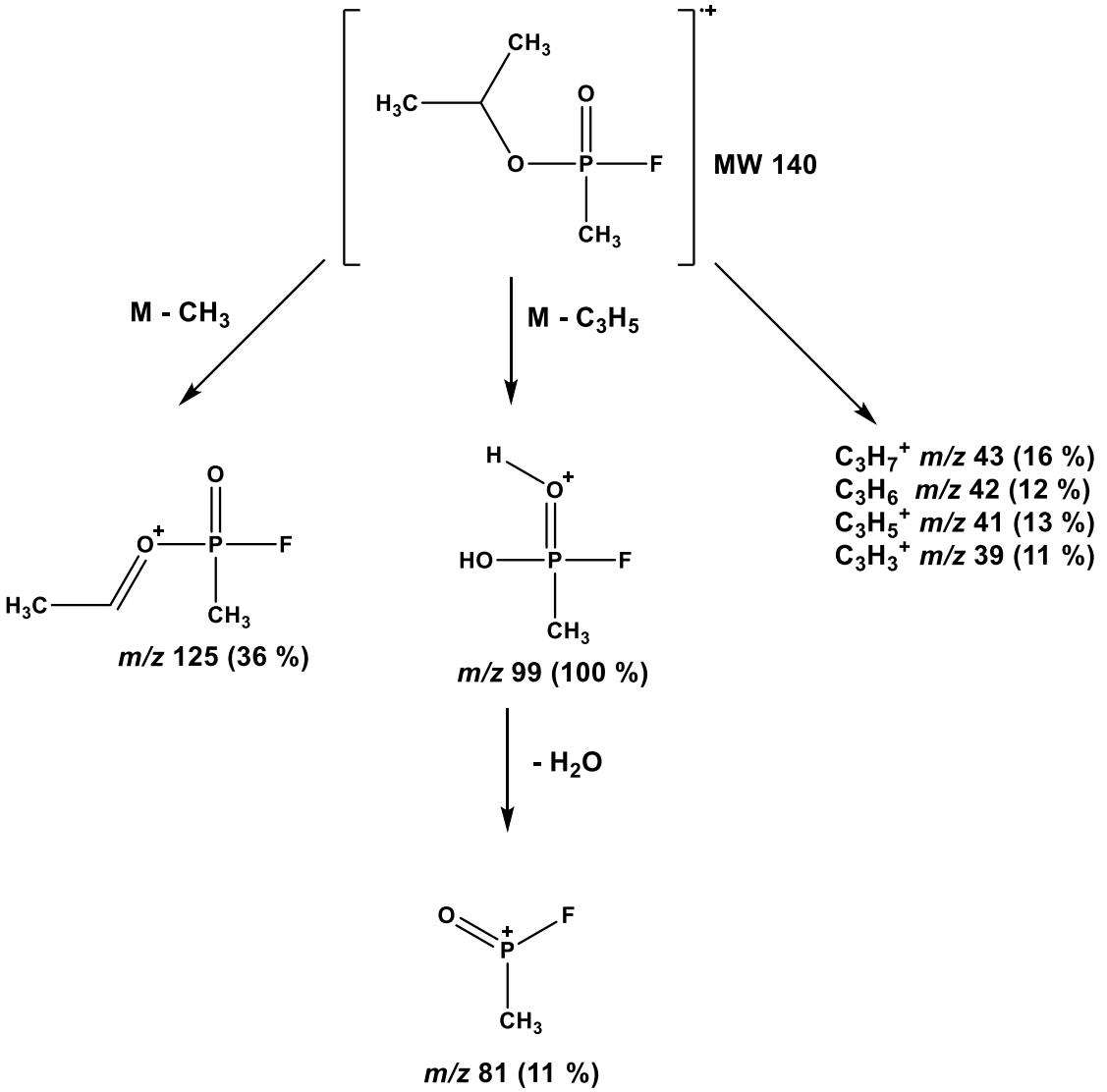
- Advantages:
  - Relatively fast
  - Relatively low LOD
  - Widely used for CWC relevant chemicals
  - Retention time information
  - Mass spectral information

- Disadvantages:
  - Destruction of the sample
  - Non-volatile decomposition compounds need to be derivatized
  - Large databases with MS-data for comparison necessary

Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005. ISBN: 0-470-84756-5.
Technology_and_Methodology_for_CWA_Verification_Analysis
https://www.labor-spiez.ch/en/lab/org/che/enlaborgcheora.htm

Analysis of CWC-related Chemicals
Analysis by GC-MS

- Electron ionization (EI) most common
- Large databases available:
  - OPCW Analytical Database
  - ROP
- Less informative, if branching is away from phosphor
- High-mass ions have a generally low intensity
- Additional information is necessary (GC retention times/ retention indices (RI) or chemical ionization (CI))



Fragmentation of sarin after EI

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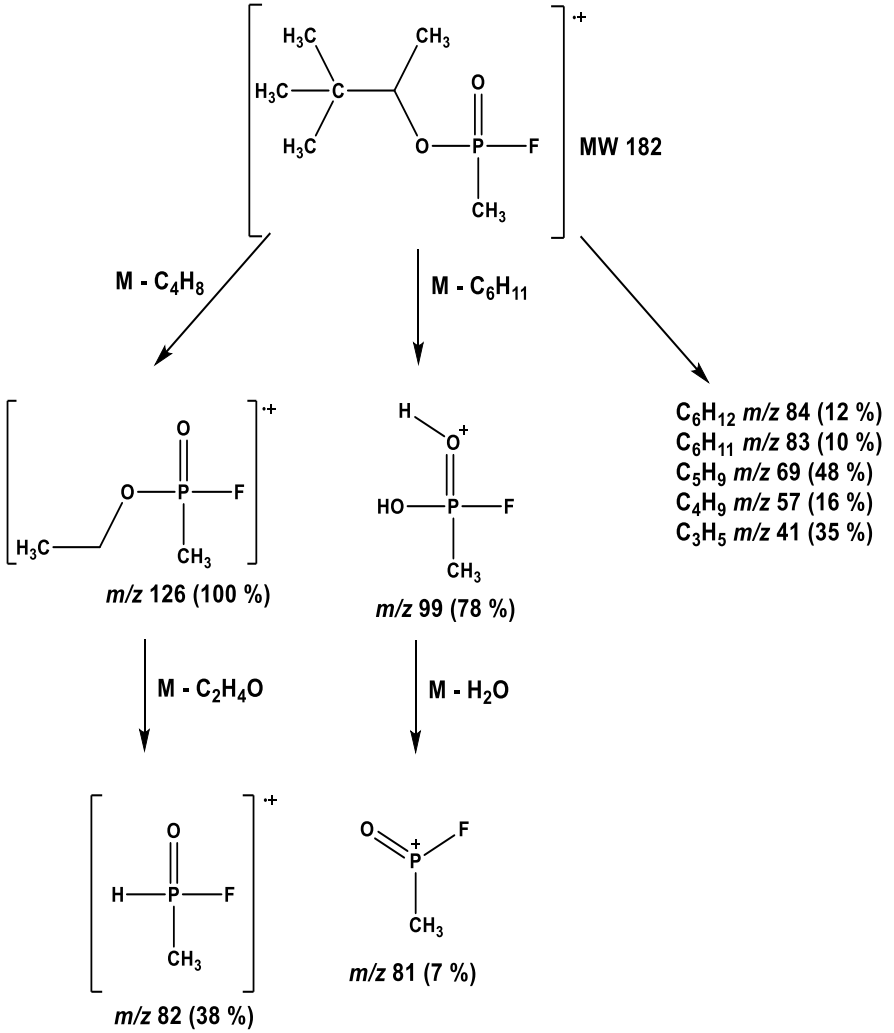
Analysis of CWC-related Chemicals

Analysis by GC-MS



Fragmentation of soman after EI

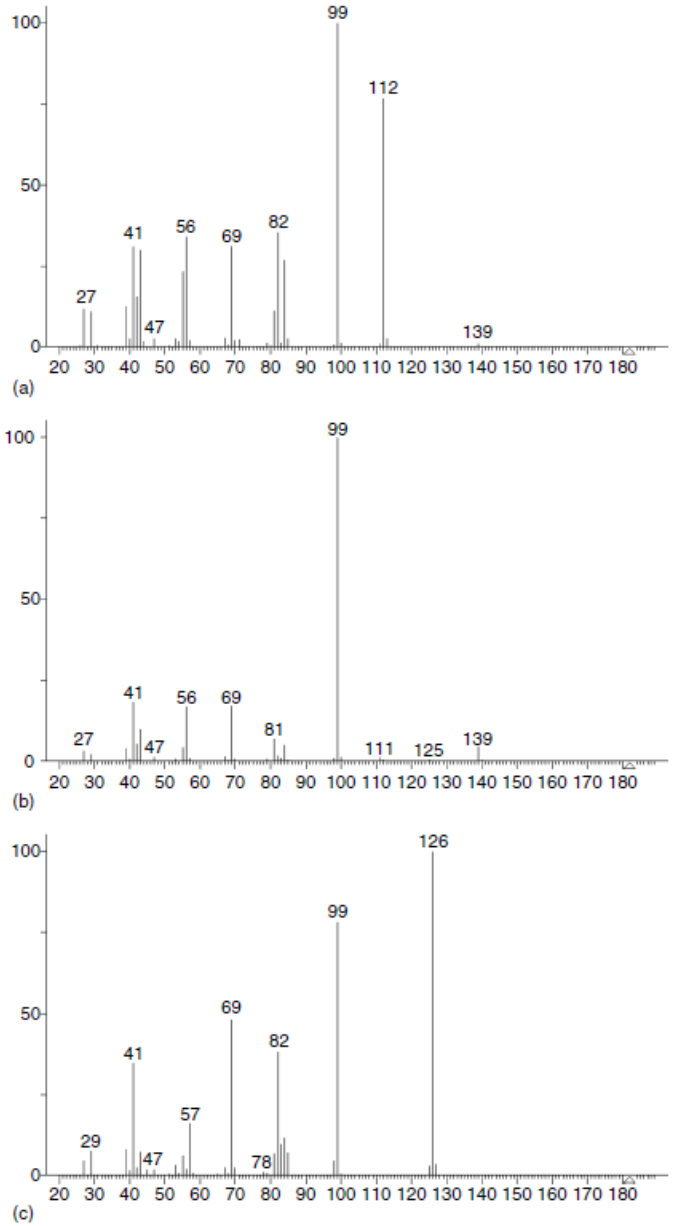


Figure 1. EI mass spectra of (a) 2-methylpentyl, (b) 4-methylpentyl, and (c) 1,2,2-trimethylpropyl methylphosphonofluoridate (soman, GD) recorded at TNO-PML (Rijswijk, The Netherlands) on a VG 70-250S GC/MS instrument (Micromass, UK)

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Analysis of CWC-related Chemicals
Analysis by GC-MS

- Chemical Ionization (CI)
- **Methane, isobutane, ammonia,** ethylene, methanol
- $[M+H]^+$ accessible, (for ammonia often $[M+NH_4]^+$)
- Highly dependent on conditions (ion source temperature, pressure, etc.)
- Compilations of CI/MS data not widely used
- Soft ionization conditions lead to loss of fragment ion information
- Can be compensated by tandem MS/MS

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Analysis of CWC-related Chemicals
Analysis by HPLC-MS

- Advantages:
  - No derivatization necessary for the analysis of degradation products
  - Can directly be applied to aqueous solutions and extracts
  - Broader range of compounds than GC/MS (including more complex toxins and peptides)

- Disadvantages:
  - Less suitable for certain reactive analytes (vesicants, some halogenated precursors of nerve agents)
  - Mainly molecular or quasi-molecular ions (especially with Athmospheric Preassure Ionization (API))
  - Spectra is partially dependent on the instrument and conditions
  - Few libraries available

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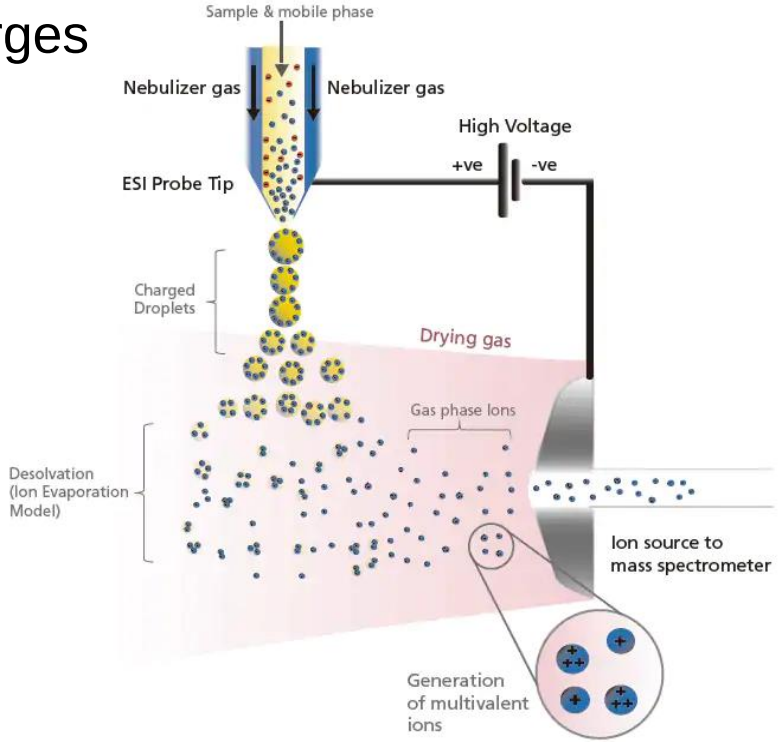
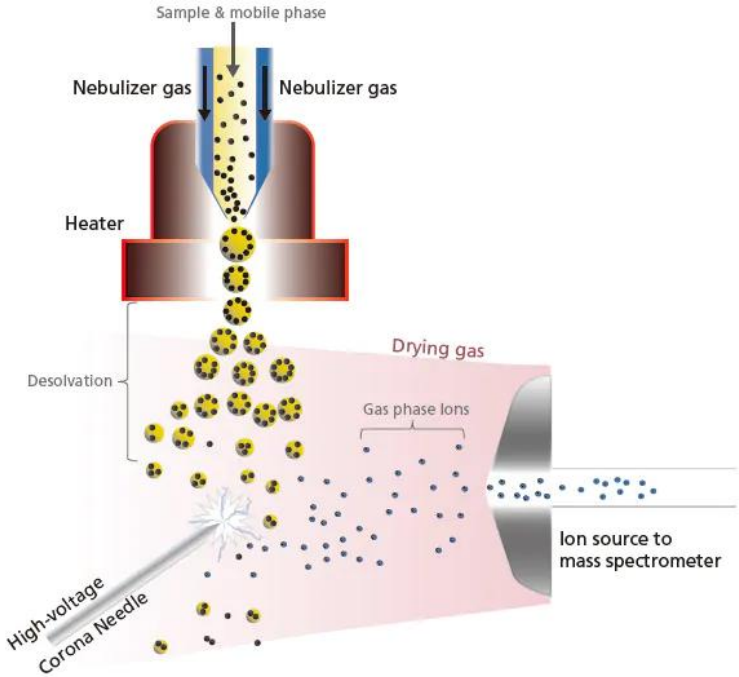
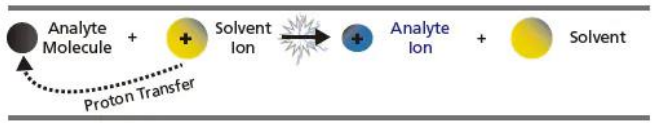
Analysis of CWC-related Chemicals
Analysis by HPLC-MS

- Electron spray ionization (ESI)
  - ± 3 to 5 kV voltage at capillary
  - Evaporation speed up by a heating gas
  - Generates mostly protonated (or deprotonated) molecular ions
  - Occasionally molecular ions with multiple charges



- Atmospheric pressure chemical ionization (APCI)
  - More suitable for low- and medium-polarity compounds
  - Heater temperature ≈ 400 °C





https://www.shimadzu.com/an/service-support/technical-support/analysis-basics/fundamental/interfaces_for_lcms.html#section1

Analysis of CWC-related Chemicals
Analysis by HPLC-MS

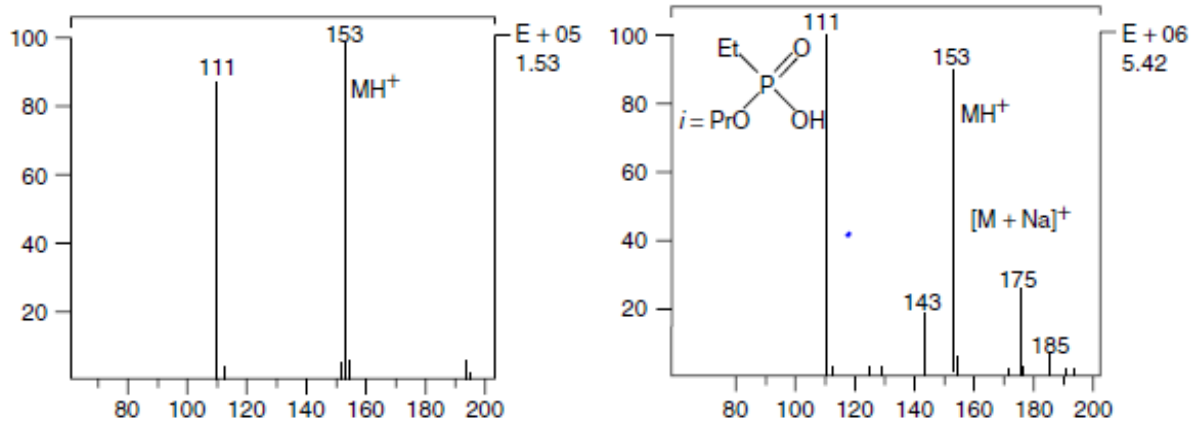


Figure 4. APCI (left) and ESI spectra of isopropyl ethylphosphonic acid, illustrating the lower abundance of adduct ions with APCI; ions at *m/z* 143 and 185 are adduct ions with MeOH; *m/z* 175 is $[M + Na]^+$. (Reprinted from Journal of Chromatography A, **794**, R.M. Black and R.W. Read, Analysis of degradation products of organophosphorus chemical warfare agents and related compounds by liquid chromatography–mass spectrometry using electrospray and atmospheric pressure chemical ionisation, pp. 233–244 (1998), with permission from Elsevier)

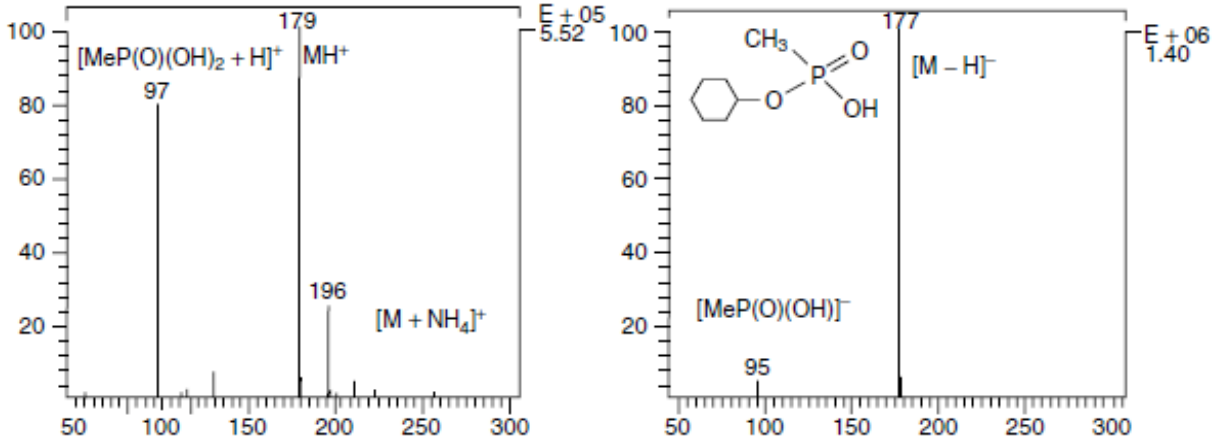


Figure 5. Positive (left) and negative (right) APCI spectra of cyclohexyl MPA

Mesilaakso, Markku. Chemical Weapons Convention Chemicals Analysis. John Wiley & Sons, 2005.
ISBN: 0-470-84756-5.

Analysis of CWC-related Chemicals
Analysis by HPLC-MS

- Reconstructed ion chromatogram of 19 analytes
- conventional column (250 × 3.2 mm i.d.) with a mixed C8/C18
- water-acetonitrile-0.05% TFA gradient

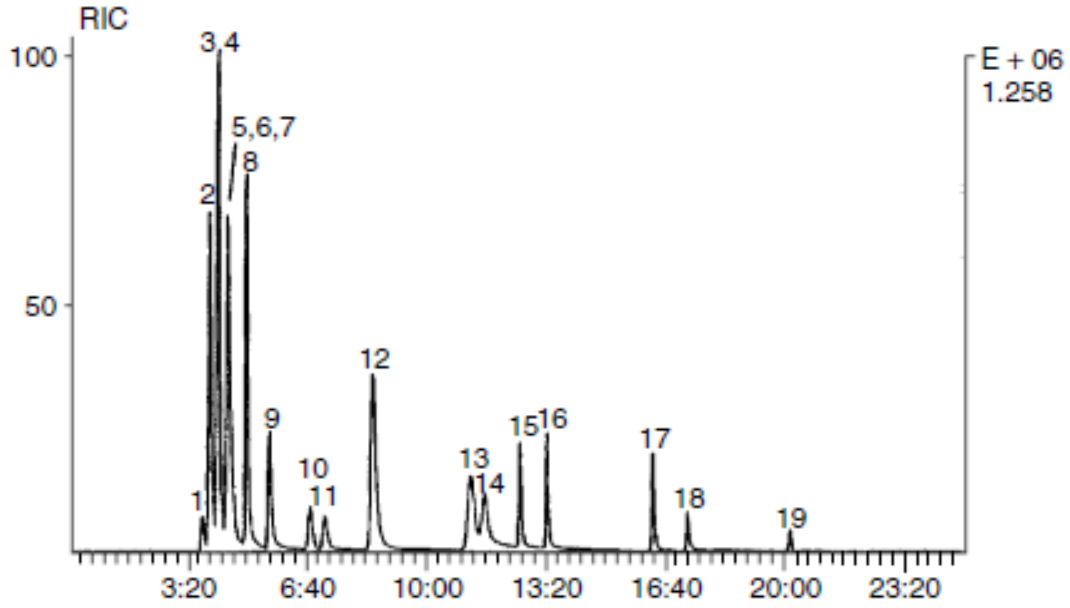


Figure 6. Reconstructed ion current LC/APCI/MS (positive ion) chromatogram of a mixture of 19 analytes (each 10 μg/ml in water). 1. MPA, 2. TDGO, 3. triethanolamine, 4. *N*-methyldiethanolamine, 5. EPA, 6. *N*-ethyldiethanolamine, 7. thiodiglycol sulfone, 8. 3-quinuclidinol, 9. EMPA, 10. TDG, 11. *n*-PrPA, 12. diisopropylaminoethanol, 13. EEPA, 14. *i*-PrMPA, 15. tert-BuPA, 16. *n*-BuPA, 17. cHexMPA, 18. Pin MPA, 19. benzilic acid. (Reprinted from Journal of Chromatography A, **759**, R.M. Black and R.W. Read, Application of liquid chromatography-atmospheric pressure chemical ionisation mass spectrometry, and tandem mass spectrometry, to the analysis and identification of degradation products of chemical warfare agents, pp. 79–92 (1997), with permission from Elsevier)

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Schedules of Chemicals

- **Schedule 1:**

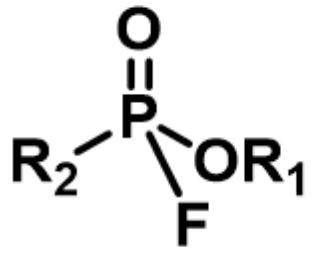
  Entry 1-8: Chemical warfare agents in the old convention
  Entry 13-16: Newly-added chemicals
  Entry 9-12: Precursors for entry 1-8

- **Schedule 2 & 3:**

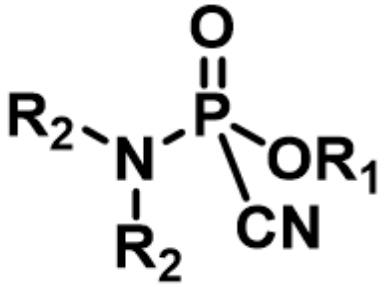
  Not as dangerous as those listed in schedule 1

  Phosgene: First entry in schedule 3

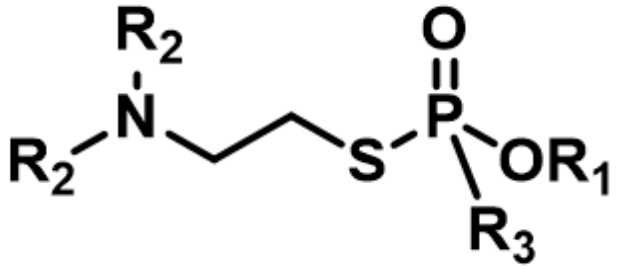
Chemicals in Schedule 1



1.A.1



1.A.2

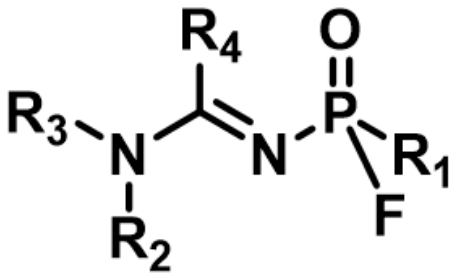


1.A.3
(also alkylated or protonated salts)

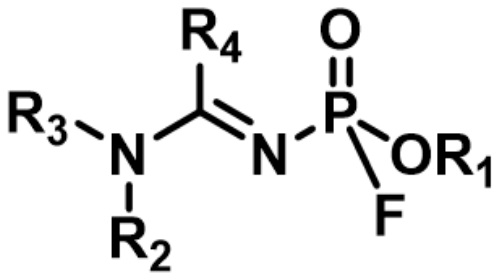
R_1: alkyl <=C10, incl. cycloalkyl
R_2, R_3: Me, Et, n-Pr or i-Pr

Examples:
1.A.1: Sarin, Soman;
1.A.2: Tabun;
1.A.3: VX

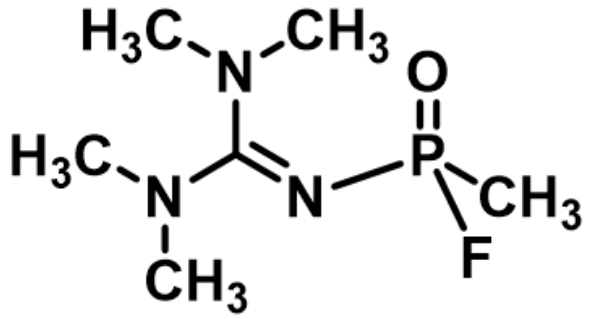
Chemicals in Schedule 1



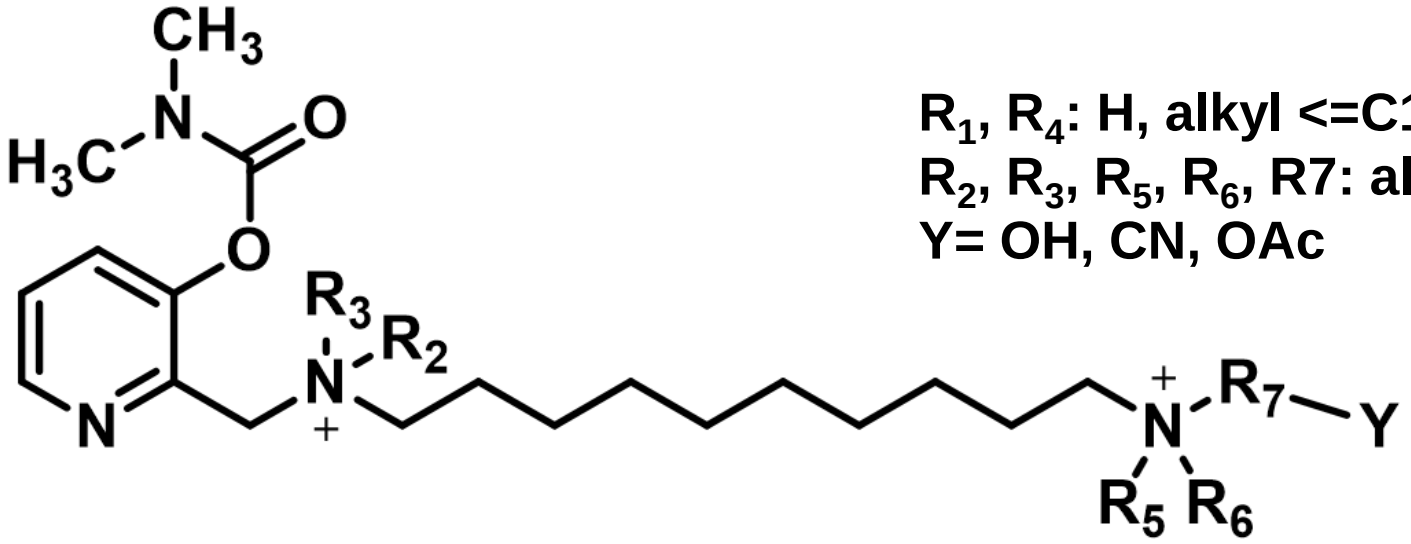
1.A.13
(also alkylated or protonated salts)



1.A.14
(also alkylated or protonated salts)



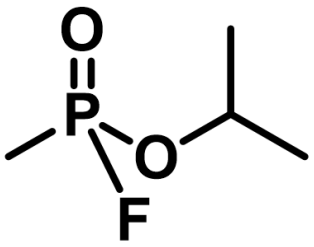
1.A.15



1.A.16

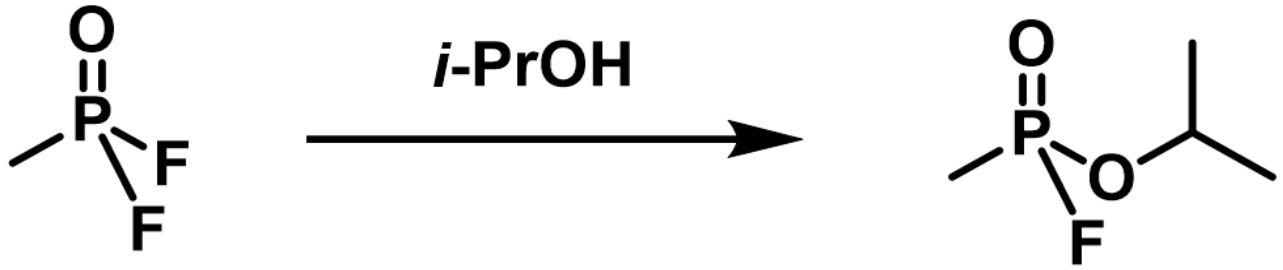
R_1, R_4: H, alkyl <=C10, incl. cycloalkyl
R_2, R_3, R_5, R_6, R7: alkyl <=C10, incl. Cycloalkyl
Y= OH, CN, OAc

Comparison of old and new entries



Sarin
1.A.1

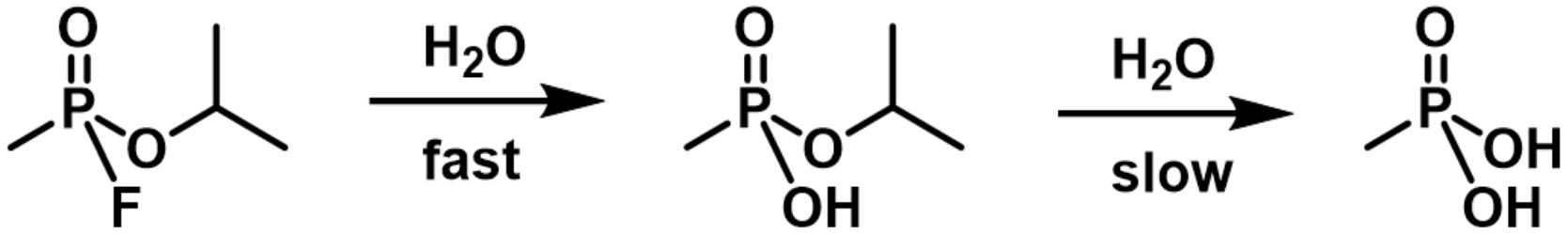
Production:



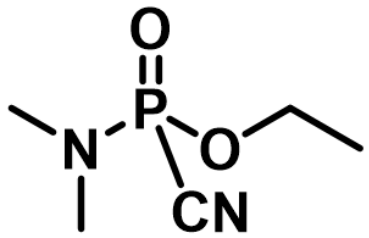
1.A.9

Molecular weight: 140
Melting point: -56 ° C
Boiling point: 158 ° C

Degradation:

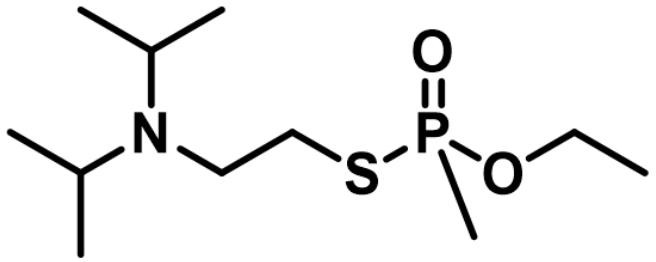


Comparison of old and new entries



Tabun
1.A.2

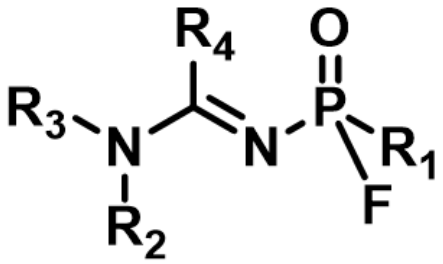
Molecular weight: 162
Melting point: -50 ° C
Boiling point: 248 ° C



VX
1.A.3

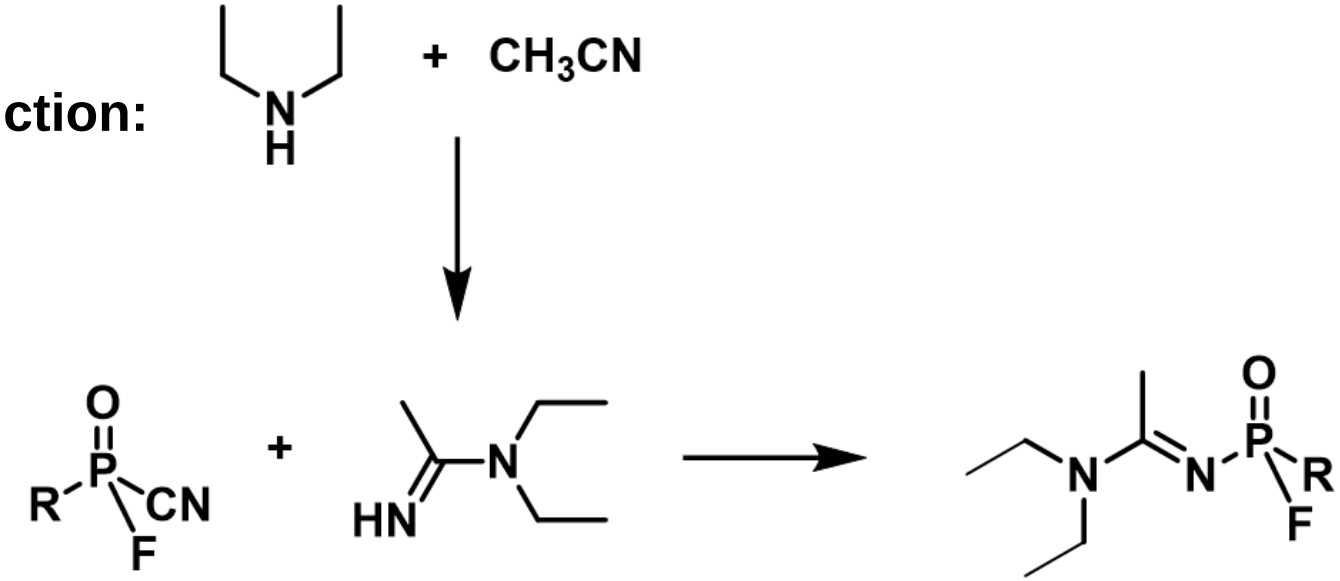
Molecular weight: 267
Melting point: -51 ° C
Boiling point: 300 ° C

Comparison of old and new entries



1.A.13

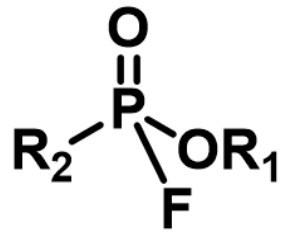
Production:



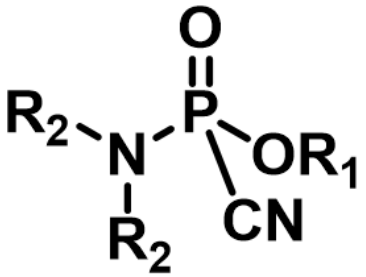
- **Hydrolysis: slower than both Sarin and VX**
- **Many physical and chemical properties unknown**
- **NMR and GC-MS data available**
- **Toxicity: higher or similar to VX**

S. P. Harvey et al., *Heliyon*, 2020, *6*, e03153
E. Nepovimova and K. Kuka, *Food and Chemical Toxicology*, 2018, *121*, 343
Handbook of Toxicology of Chemical Warfare Agents (Third Edition), Academic Press, 2020

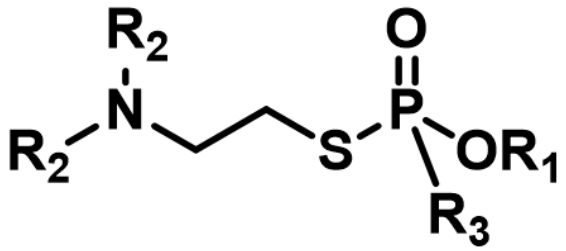
Comparison of old and new entries



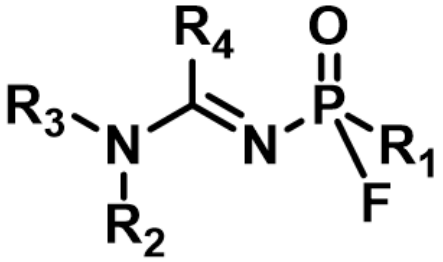
1.A.1



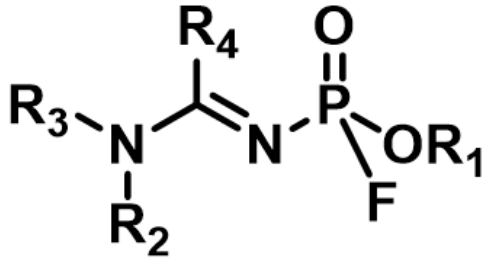
1.A.2



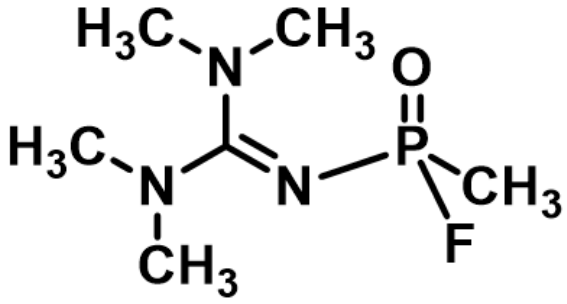
1.A.3



1.A.13



1.A.14



1.A.15

1.A.16

To-do List

- Searching for useful information from existing literature
- Analyze the spectra when some compounds could not be designated
- Share reference data with other laboratories
- Synthesize the molecule when no reference data is available
- Use best protective measures

Questions?

Thank you for your attention.