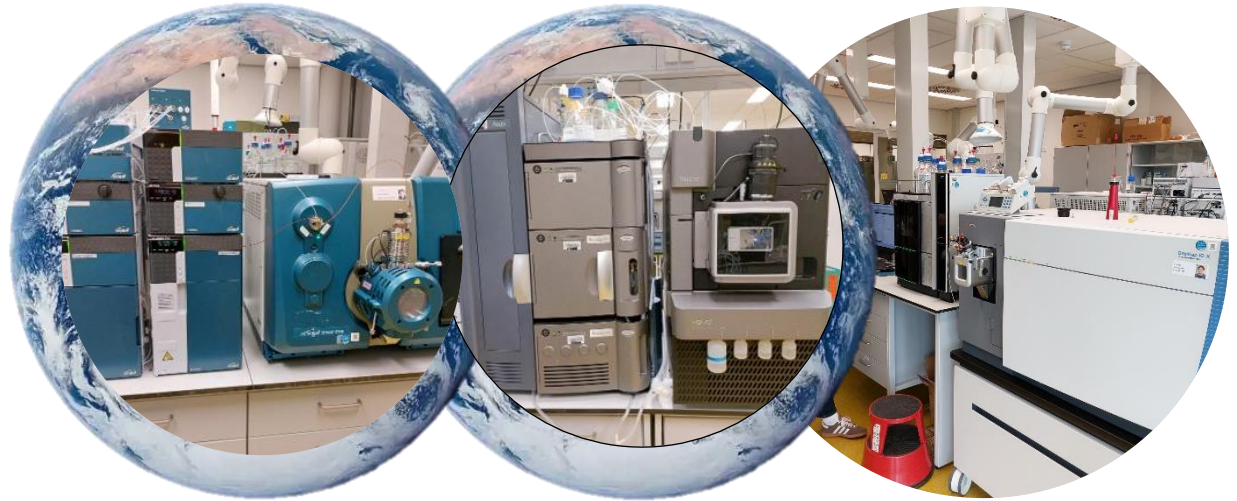


LC-HRMS based screening: approaches and experiences in pesticide residue analysis



Hans Mol, Wageningen Food Safety Research (WFSR)
NRL pesticides in food & feed, The Netherlands

LC-HRMS based screening: approaches and experiences in pesticide residue analysis



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NRL pesticides in food & feed, The Netherlands

Pesticide legislation

ANALYTICAL QUALITY CONTROL AND METHOD VALIDATION PROCEDURES FOR PESTICIDE RESIDUES ANALYSIS IN FOOD AND FEED SANTE 11312/2021 v2

Supersedes Document No. SANTE/11312/2021. Implemented by 01/01/2024

Coordinators:

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Guidance (but referred to in legislation). Revised every 2 years.

Quan: LOQ = lowest level validated that meets requirements for trueness (recovery), precision, identification, and MU

Qual: SDL, the lowest concentration for which it has been demonstrated that the analyte is detected in at least 95 % of the samples of a commodity group.

REGULATION (EC) NO 396/2005 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 February 2005

on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC

(Text with EEA relevance)

https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en

MRLs: if not set then default 0.01 mg/kg

⇒ There is always an MRL*

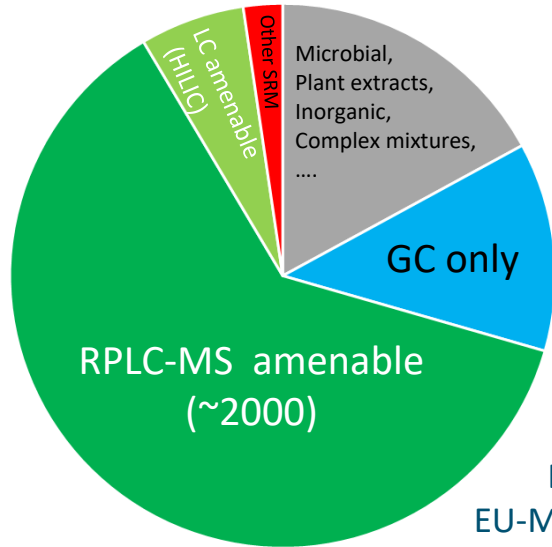
⇒ Target LOQ or SDL for validation is 0.01 mg/kg

*Exception: 'no MRL required' for non-hazardous substances, e.g. acetic acid, plant extracts, microbial pesticides

https://food.ec.europa.eu/system/files/2023-11/pesticides_mrl_guidelines_wrkdoc_2021-11312.pdf

Pesticides

Pesticides: total > 3200 active substances (plus RD metabolites!)



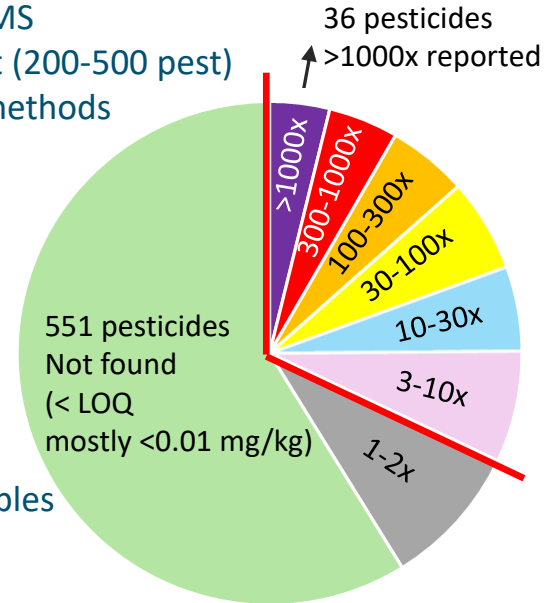
Current approach:

LC-MS/MS; GC-MS/MS
Target measurement (200-500 pest)
Quantitative multi-methods

Scope limitations
High QC burden

Reality check:

EFSA report* on
EU-MACP 13,246 samples
National risk-based 132,793 samples
937 pesticides



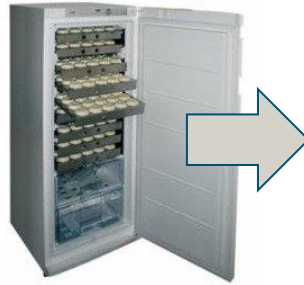
Better approach:

LC-HRMS; GC-HRMS
Non-target measurement
No scope limitations
Suited for:
Quan./confirmatory analysis
Screening TS/SS/NTS

300 found $\geq 3x$
Combined quan/qual.

HRMS bonus

Full scan raw data sets
Digital sample storage



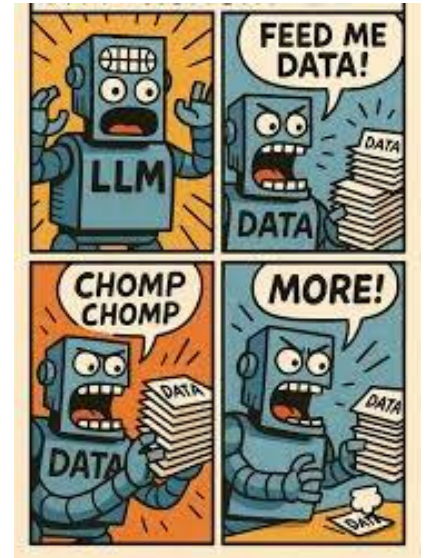
from freezing samples
to 'freezing' data



Asset for future advanced computational mass spectrometry possibilities
Stock up on food for data-hungry AI

Do what we normally do and at same time create data for
comprehensive (food toxicant) analysis now or later

Take advantage of the unique and extensive food safety control infrastructure
and all efforts/money spend on sampling and sample preparation



HRMS bonus

Retrospective screening
(already possible for >10 years!)

Target/suspect screening

Name of chemical => formula => exact mass (Da)

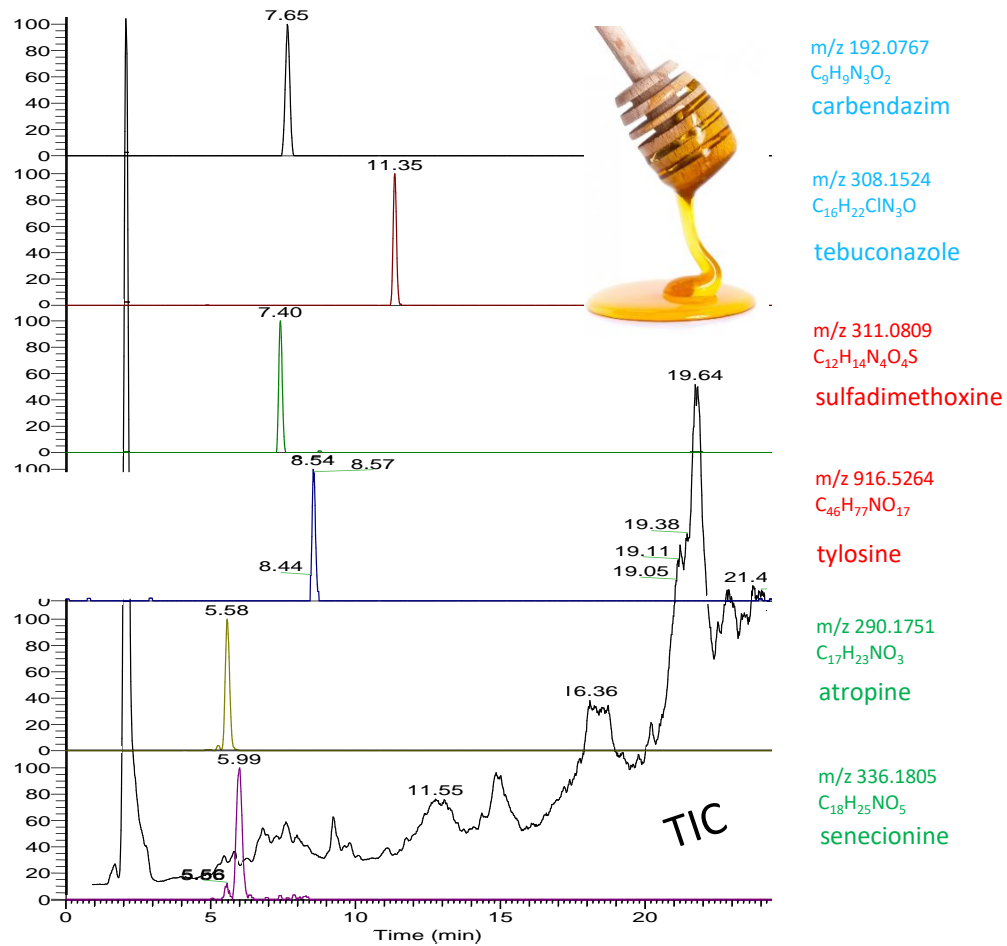
Extract signal of exact mass \pm x Da (ppm)

Example

Senecionine = $C_{18}H_{25}NO_5$ = 335.1733 Da

XIC = $[M+H]^+$ = 336.1805 ± 5 ppm (± 0.0017 Da)

Honey spiked with pesticides,
veterinary drugs, plant toxins
at 10 μ g/kg



Definitions* screening, (non)target analysis

Three types of screening (depending on what you know and what you have):

You know the molecule you are looking for:

- you **have the analytical reference standard**: quan/confirmatory analysis; **target screening**
- you **don't have the reference standard**: **suspect screening**

You don't know the molecule you are looking for: **non-target screening**

- feature based screening, e.g. substructure (fragments), element (e.g. halogens), differential analysis (w/o treatment)
- effect directed analysis (EDA): bioeffect assay, fractionation if positive, identify feature in positive fraction(s)

Target measurement: dedicated/optimized sample prep + analyte instrument settings (MS/MS), best quan/LOQ

Non-target measurement: generic sample prep, full scan HRMS, generic settings, sufficient quan/LOQ/LOD (or not)

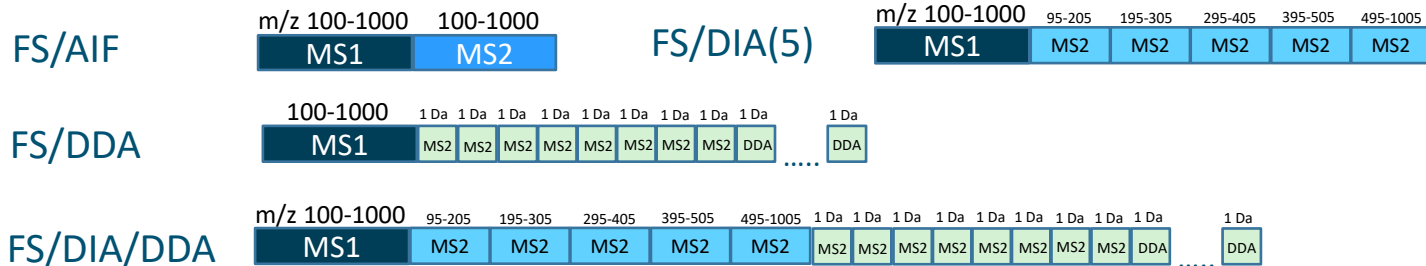
Quantitative/confirmatory methods: quantification and identification according to set (regulatory) requirements (full validation, LOQ, trueness, precision, linearity, matrix effects, selectivity, measurement uncertainty,)

Screening methods: any method not meeting the requirements for quan/confirmatory method

LC-HRMS: acquisition options

Acquisition	MS1	MS2	Precursor isolation window	XIC
Non-target	Full scan m/z 100-1000 (high resolution)	DIA (AIF, all-ions MS/MS, MS ^E , broadband CID)	m/z 100-1000 (high res)	MS1 precursor MS2 fragment ion(s)
		DIA (vDIA, SWATH,	adjacent m/z window together covering m/z 100-1000	MS1 precursor MS2 fragment ion(s)
		DDA MS2 intensity triggered (top N)	1 Da	MS1 precursor
Target	SIM (m/z ± 1 Da) high res	tMS2 (multiplexing)	1 Da	SIM: MS1 precursor; tMS2: MS2 transitions
	Full scan m/z/ 100-1000 (survey scan) (high res)	DDA MS2 with inclusion list [known analytes]	1 Da	MS1 precursor

Target / Non-target combinations



FS: R ≥ 50-60K*
Cycle time ≤ 1s

Detection and scope

← data processing
time & complexity

Analysis	Reference std.		Detection	Number of substances
	once	each seq.		
quan analysis	yes	yes	t _r , + XIC of 2 ions (precursor + 1 fragment)	100-300
target screening	yes	no		>500
suspect screening		no	MS1: accurate m/z => mol.form. MS2: spectra	size of suspect database/list available MS2 spectra
non-target screening		no	Features: e.g. common fragments, structural alerts, halogens, analogues.... Data filtering / prioritization / molecular networking	General compound databases: Pubchem, Chempider, Comptox,... <i>de novo</i> identification

Similar to
triple quad

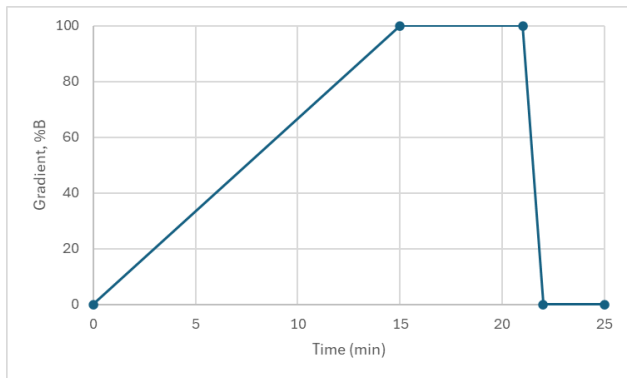
Screening when the ref.std. is available in your lab

Screening when the ref.std. is NOT available in your lab

Screening when ref. std. is available in lab

Approach: non-target measurement followed by target screening

Set up fixed generic LC method with linear gradient



Column BEH C18 column (2.1 mm × 100 mm, 1.7 μm)

Column temperature: 50 °C

Flow rate 0.3 mL/min

For ESI⁺

Mobile phase A: water, 2 mM NH₄COOH, 0.1% HCOOH

Mobile phase B: methanol, 2 mM NH₄COOH, 0.1% HCOOH

For ESI⁻

Mobile phase A: water 10 mM (NH₄)₂CO₃

Mobile phase B: methanol/water 95/5 10 mM (NH₄)₂CO₃

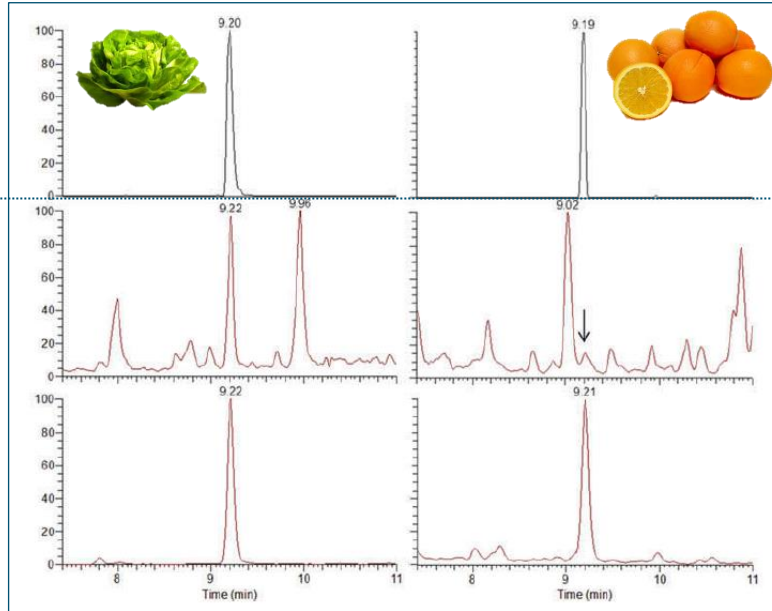
Build up screening database*

⇒ Determine t_r, precursor in FS, and 1 fragment from DIA @ used CE

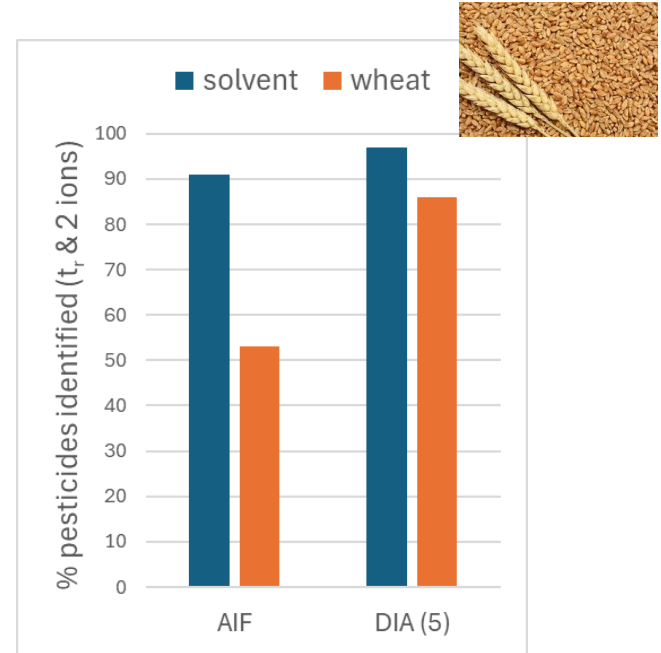
Setup MS acquisition method: FS m/z 100-1000 (R = 60K) + AIF or vDIA.....

MS2 DIA in more detail: AIF vs vDIA

XIC MS1 precursor
Carbaryl (10 µg/kg)
m/z 202.08630±5 ppm



Zomer & Mol, Food Add. & Contam. A 32 (2015) 1628-1636



145 pesticides 1.25 ng/mL (10 µg/kg in wheat)
QuEChERS, UPLC-ESI-Q-Orbitrap (IQ-X)

Target screening: example application

Animal products:

Extraction*: ACN/water 75/25 1%FA

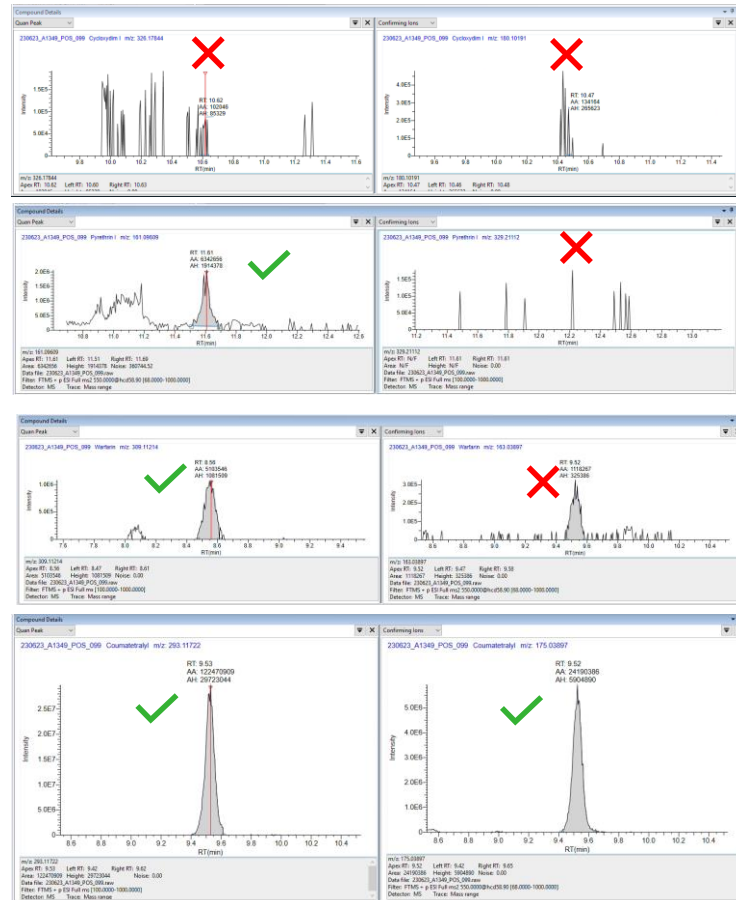
LC-HRMS, quan scope 138 pesticides

Target screening scope 748 pesticides

TraceFinder software, intensity threshold

25-50 hits/sample, 50 samples reviewed in <1.5h

Samples	Filename	Sample Name	Compound Results	Compound	Height	Area	Flag Details	Actual RT	Peak Label	RT	Type	RT Delta	Formula	Adduct
1	240614_A1349_LC-OT3_POS_008	std 50 ng/ml lever	1	Atrazine-deethyl	632024472	517404		5.29	T1	5.29	Target Compound	0.55	C6H10ClN3	M+H
2	240614_A1349_LC-OT3_POS_009	ispod	2	Milbemectin A3 no frag.	26919176	17309419		12.30	T1	12.60	Target Compound	-0.30	C31H44O7	M+NH4
3	240614_A1349_LC-OT3_POS_010	bl chem	3	Neptalam	1489188	136144696		5.29	T1	5.88	Target Compound	-0.59	C18H13NO	M+H
4	240614_A1349_LC-OT3_POS_011	30659	4	Neptalam (no frag.)	14877933	135280324		5.29	T1	5.38	Target Compound	-0.09	C18H13NO	M+H
5	240614_A1349_LC-OT3_POS_012	30659 + 10	5	Methoprene (green parent)	6349302	63726204		13.22	T1	12.73	Target Compound	0.49	C18H30O2	M+H
6	240614_A1349_LC-OT3_POS_013	30659 + 50	6	Pinoxaden	12765651	53714949		11.51	T1	10.80	Target Compound	0.77	C23H24N2C	M+H
7	240614_A1349_LC-OT3_POS_014	13169	7	Hydroxyquinoline B-	11545295	49121210		6.09	T1	7.24	Target Compound	-0.02	C9H7NO	M+H
8	240614_A1349_LC-OT3_POS_015	21365	8	13C-Caffeine	3000649	30107070		6.09	T1	5.52	Target Compound	0.57	C12H13N5O2	M+H
9	240614_A1349_LC-OT3_POS_016	21403	9	Imazapyr (no frag.)	1936400	14630190		5.23	T1	5.33	Target Compound	-0.10	C13H11N3O2	M+H
10	240614_A1349_LC-OT3_POS_017	21403	10	Kinoprene	429614	14281568		12.63	T1	13.25	Target Compound	-0.62	C18H26O2	M+H
11	240614_A1349_LC-OT3_POS_018	30797	11	Indoxacarb acid 3-	1215750	10065432		6.63	T1	6.58	Target Compound	0.05	C13H13NO	M+H
12	240614_A1349_LC-OT3_POS_019	31090	12	Clethodim sulfonate I	761151	7429352		6.29	T1	6.73	Target Compound	-0.44	C17H26ClN3	M+H
13	240614_A1349_LC-OT3_POS_020	ispod	13	Carbendazim	1037657	5118300		6.99	T1	7.52	Target Compound	-0.53	C12H16N2C	M+H
14	240614_A1349_LC-OT3_POS_021	31092	14	Allethrin	1647544	4397837		11.32	T1	11.38	Target Compound	-0.04	C19H26O3	M+Na
15	240614_A1349_LC-OT3_POS_022	31098	15	Propachlor oxalinic derivate	870934	4347711		6.48	T1	6.61	Target Compound	-0.13	C11H13NO	M+H
16	240614_A1349_LC-OT3_POS_023	31098	16	Cinerin I (no frag.)	2019004	3469921		11.26	T1	11.57	Target Compound	-0.31	C20H28O3	M+H
17	240614_A1349_LC-OT3_POS_024	31143	17	Imazamiz	950762	3447346		5.39	T1	5.72	Target Compound	-0.33	C19H19N3O	M+H
18	240614_A1349_LC-OT3_POS_025	21452	18	Prallethrin	875441	3006960		10.18	T1	10.67	Target Compound	-0.49	C19H24Cl3	M+
19	240614_A1349_LC-OT3_POS_026	31948	19	Indox-3-Butyric Acid	424788	2564025		5.32	T1	5.71	Target Compound	-0.39	C12H13N3O2	M+H
20	240614_A1349_LC-OT3_POS_027	32207	20	Terbuthylazine	567084	2259564		9.35	T1	9.70	Target Compound	-0.35	C8H16ClN3	M+H



Example findings target screening

Animal products Found and confirmed

>0.01 mg/kg	<0.01 mg/kg
Rodenticides (mostly liver)	fluopyram
<i>brodifacoum</i>	piperonyl butoxide
<i>coumatetralyl</i>	pyraclostrobin
<i>dicoumarol</i>	tetraconazole
<i>difenacoum</i>	
DDAC-C10 (liver, muscle)	
fluralaner (egg)	
moxidectin (fat)	



DE: Bei Untersuchungen von Fleisch (Schweinefleisch) wurde festgestellt, dass es mit dem Wirkstoff Coumatetralyl kontaminiert ist. Foto: BfL/Charmé/DAV/Thomas/DAV/Heinze



To the Head of Agency of the NVWA
To the Minister of Agriculture, Nature and Food Quality

Advice from the Director of the Office for Risk Assessment & Research

Risk assessment coumatetralyl in products of animal origin

1 Background

In 2023, coumatetralyl was found in calf's liver twice as part of the National Residues Plan (NPR). In both cases, the concentration was above the legal limit (MRL²) of 0.01 mg/kg for this substance in liver.

Coumatetralyl is the active substance in the anticoagulant rodenticide Racumin Foam, authorised in the Netherlands for the control of house mice.

Office for Risk Assessment & Research
PO Box 43006
3540 AA Utrecht
www.nvwa.nl
Contact person
nicolabeoordeling@nvwa.nl
Date
20 June 2024
Our reference
TRC/WA/2024/2190

Additional target screening analysis fruit/veg for updating scope (100 samples)

Extraction QuEChERS (no dSPE)

2,6-dichlorobenzamide	Cyetyprafen	Isotianil	Propachlor oxalinic derivat
Atrazine desisopropyl	Cyromazine	Mandestrobin	Propamocarb-N-oxide
CGA 304705 (cyprodinil-OH)	Dithianon-diol	Mefenpyr-diethyl (safener)	Terbucarb
CGA 32113 (trifloxystrobin acid)	imidacloprid-desnitro	Metolachlor OA	Terbutylazine-desethyl
Chlorbenzuron	Indole-3-butyric acid	Oxolinic acid (antibiotic)	TFNA-AM

chilipepper

Screening when the ref.std. is available in your lab

Screening when the ref.std. is NOT available in your lab

Screening when no ref. std. available in lab (1)

Approach-1: MS1-based (molecular formula)

Needed:

Accurate mass of precursor + software => molecular formula

List/database of compounds of interest (pesticides, (predicted)metabolites, more....)

Data processing software

Approach-2: MS2-based (spectrum)

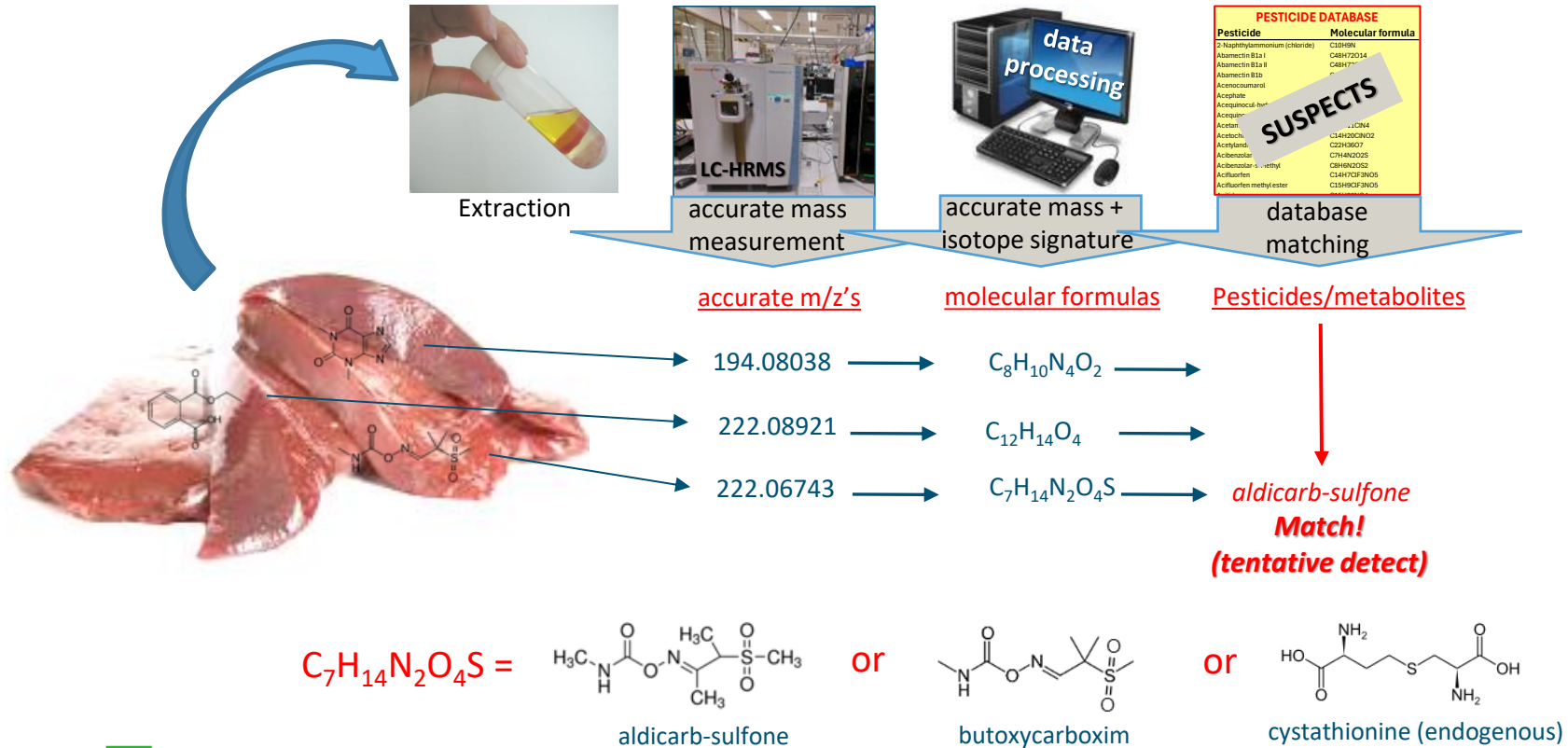
Needed:

MS2 spectra (DDA data, 1 Da precursor ion window)

MS2 library

Data processing software

MS1 based suspect screening



Screening when no ref. std. available in lab (2)

Approach-1: MS1-based

Needed:

Accurate mass of precursor + software => molecular formula

List/database of compounds of interest (pesticides, (predicted)metabolites, more....)

Data processing software

Approach-2: MS2-based (spectrum)

Needed:

MS2 spectra (DDA data, 1 Da precursor ion window)

MS2 library

Data processing software

MS2 DDA in more detail

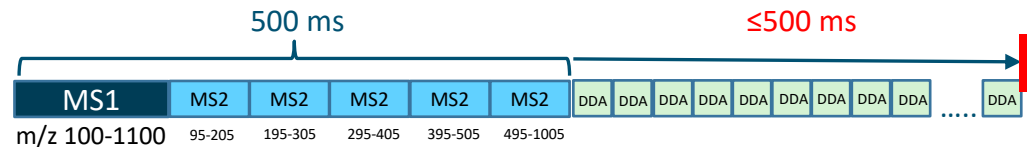
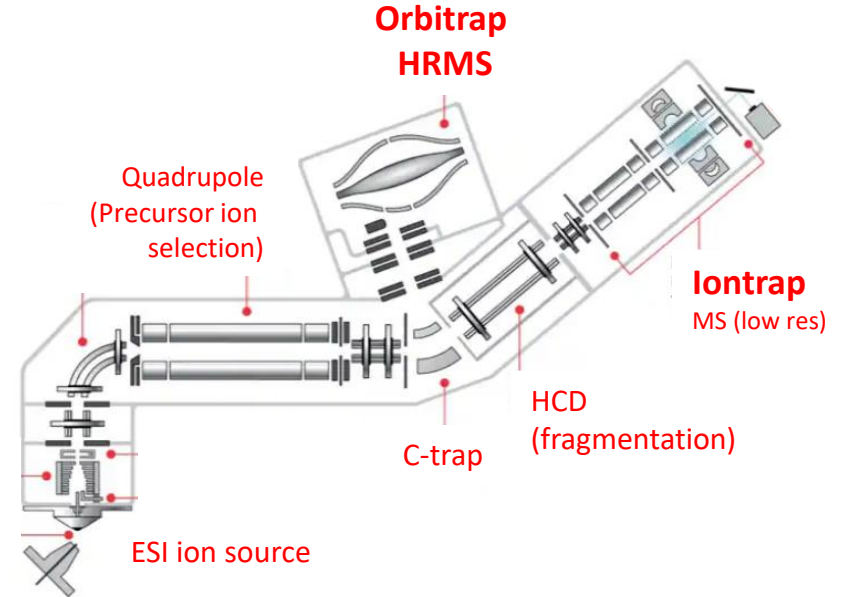
Data Dependent Acquisition

Full scan followed by multiple MS/MS (PIW = ~1 Da) events triggered by predefined conditions:

- 1) Intensity dependent: m/z with highest intensities
- 2) List dependent: only trigger predefined m/z (=compound precursors: inclusion list)
- 3) Start with 2, then do 1

Key parameters: collision energy, cycle time,
settings: intensity threshold, dynamic exclusion, exclusion lists,

Investigating combined FS-DIA-DDA acquisition



FS: 60K DIA: NCE 30/80; 30K DDA: NCE 45; 7.5K or Iontrap

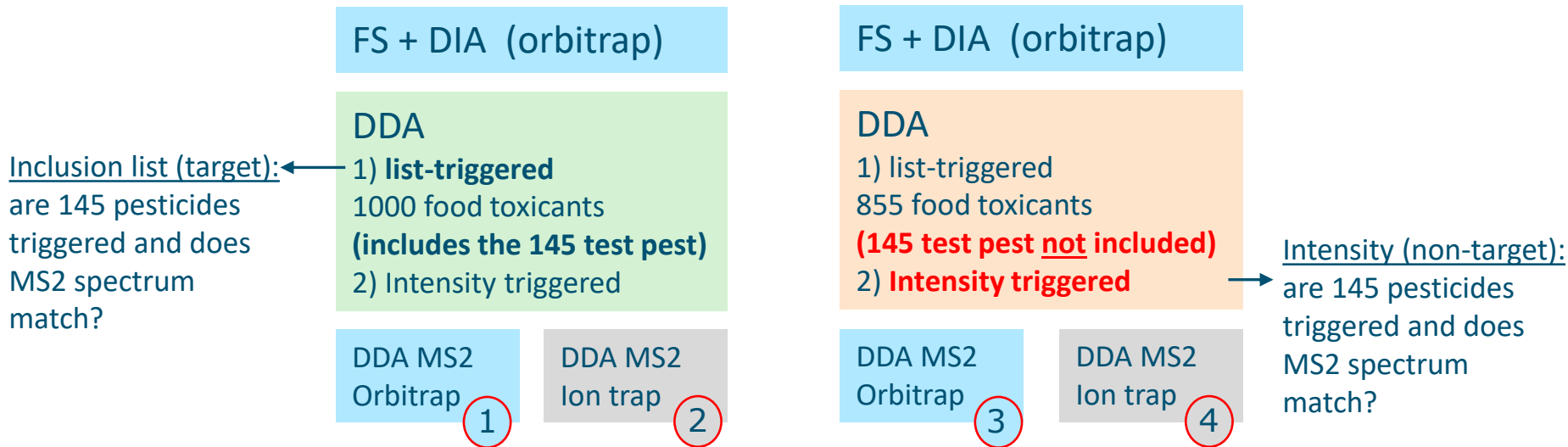
Investigating combined FS-DIA-DDA acquisition

Experimental set up:

3 cereals/products (wheat, bread, breakfast cereals)

QuEChERS, spiked with test set 145 pesticides @ 10 µg/kg (2.5 ng/mL in final extract)

4 types of DDA measurements:



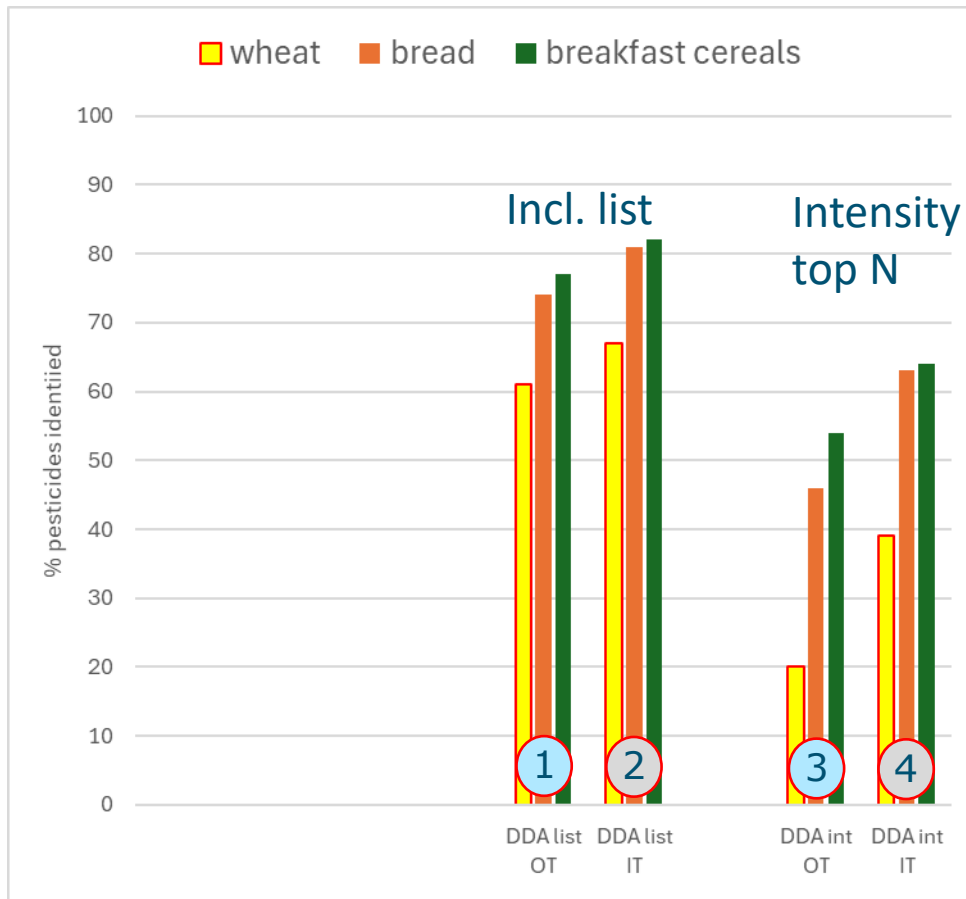
detection by matching MS2 spectrum in WFSR library

Investigating combined FS-DIA-DDA acquisition

Results of experiments:

145 pesticides@ 10 µg/kg
%pesticides detected/identified
through MS2 spectrum & library
search (WFSR-lib)

- 1 3 Orbitrap
~18,000 DDA MS2 spectra
- 2 4 Iontrap
~39,000 DDA MS2 spectra



Investigating combined FS-DIA-DDA acquisition

Results of experiments:

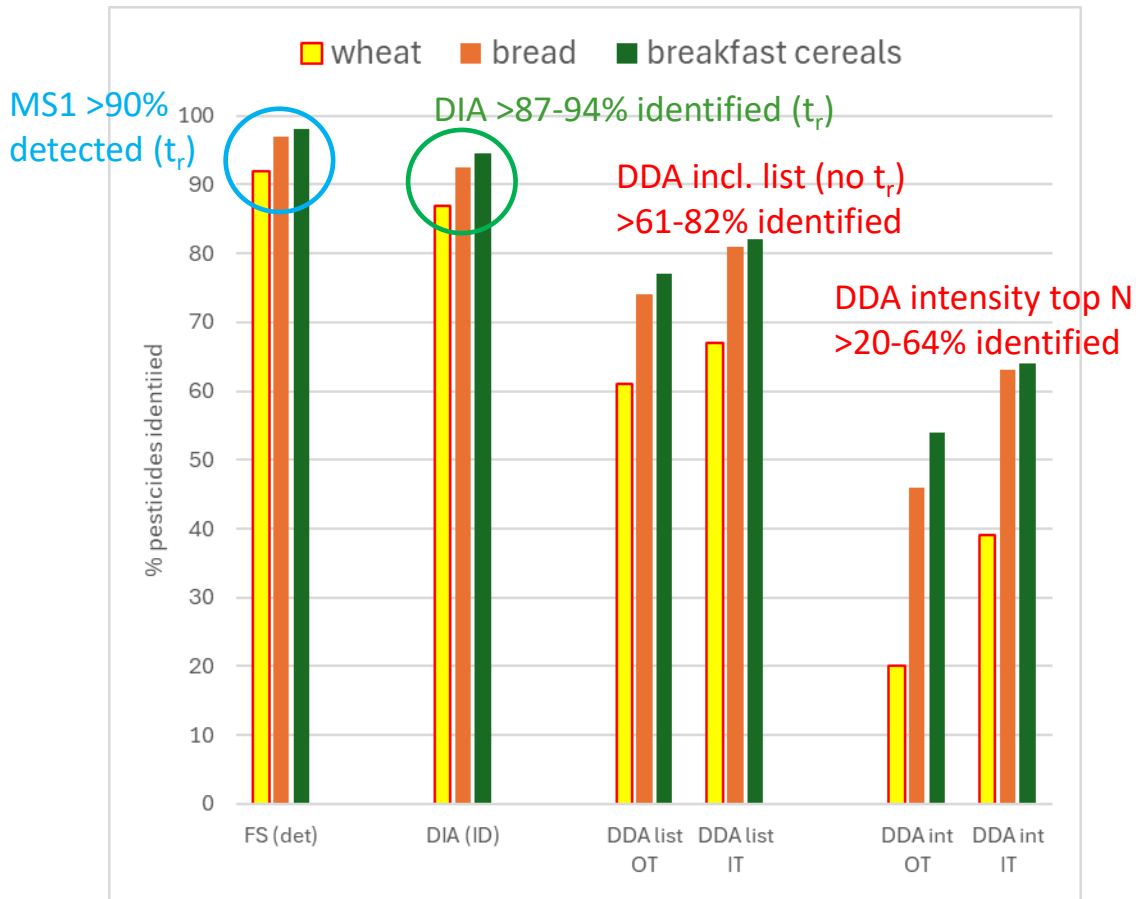
145 pesticides@ 10 µg/kg

Comparison with DIA and MS1

DDA spectral matching (no t_r)

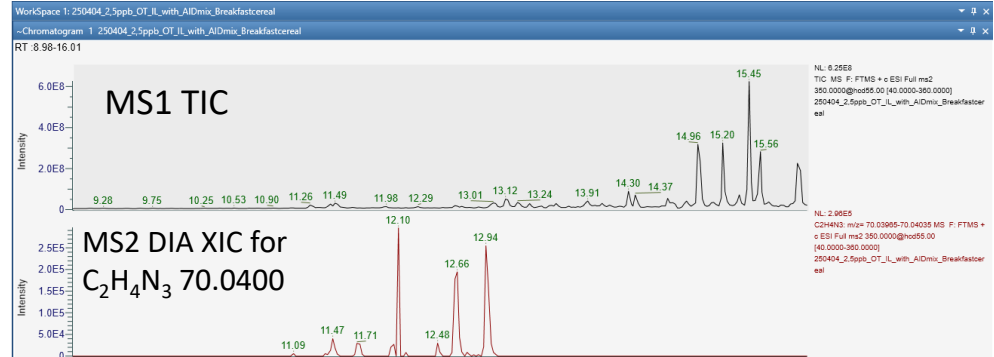
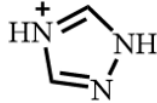
MS1/MS2 DIA identification
 t_r + 2-ion XIC approach

MS1 XIC detection with t_r



Non-target screening

Common fragments and neutral losses
e.g. triazole moiety



Non-target screening

Common fragments and neutral losses

e.g. triazole moiety

$C_2H_4N_3$ 70.0400

WorkSpace 1: 250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal
-Chromatogram 1 250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal
RT: 8.98-16.01

MS1 TIC
Intensity
6.0E8
4.0E8
2.0E8
0
9.28 9.75 10.25 10.53 10.90 11.26 11.49 11.98 12.29 13.01 13.12 13.24 13.91 14.30 14.37 14.96 15.20 15.45 15.56

MS2 DIA fragment
 $C_2H_4N_3$ 70.0400
Intensity
2.5E6
2.0E6
1.5E6
1.0E6
5.0E4
0
11.09 11.47 11.71 12.48 12.64 12.10 12.66 12.94

MS1 308.1524
 $C_{16}H_{22}ClN_3O$
(tebuconazole)
Intensity
4.0E3
3.0E3
2.0E3
1.0E3
0
12.10

MS1 312.0665
 $C_{14}H_{15}Cl_2N_3O$
(prothioconazole-desthio)
Intensity
1.5E4
1.0E4
5.0E3
0
12.10

MS1 320.1524
 $C_{17}H_{22}ClN_3O$
(metconazole)
Intensity
1.0E4
8.0E3
6.0E3
4.0E3
2.0E3
0
12.94

Time (min)
9.0 9.5 10.0 10.5 11.0 11.5 12.0 12.5 13.0 13.5 14.0 14.5 15.0 15.5 16.0

NL: 0.25E8
TIC MS F: FTMS + e ESI Full ms2
350.0000@ms05.00 [40.0000-350.0000]
250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal

NL: 2.06E5
C2H4N3 m/z= 70.0305-70.0403 MS F: FTMS + e ESI Full ms2 350.0000@ms05.00 [40.0000-350.0000]
250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal

NL: 4.00E3
C16H22ClN3O m/z= 308.1506-308.1534 MS F: FTMS + e ESI Full ms2 350.0000@ms05.00 [40.0000-350.0000]
250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal

NL: 1.87E4
C14H15Cl2N3O m/z= 312.0644-312.0680 MS F: FTMS + e ESI Full ms2 350.0000@ms05.00 [40.0000-350.0000]
250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal

NL: 1.15E4
C17H22ClN3O m/z= 320.1500-320.1540 MS F: FTMS + e ESI Full ms2 350.0000@ms05.00 [40.0000-350.0000]
250404_2.5ppb_OT_IL_with_AIDmix_Breakfastcereal

 **WAGENINGEN**
UNIVERSITY & RESEARCH

26

Application suspect & non-target screening

Routine compliance testing & monitoring: -----

Research projects: searching for expected/predicted pesticide metabolites

Environment International 168 (2022) 107452

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

A large scale multi-laboratory suspect screening of pesticide metabolites in human biomonitoring: From tentative annotations to verified occurrences

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HBM: pesticide metabolites in urine

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Suspect and nontarget screening of pesticides and their transformation products in agricultural products using liquid chromatography–high-resolution mass spectrometry

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Transformation products/metabolites in strawberry and soil

Identification suspect / non-target screening

MS1 accurate mass, MS2 spectrum

Schymanski* confidence level

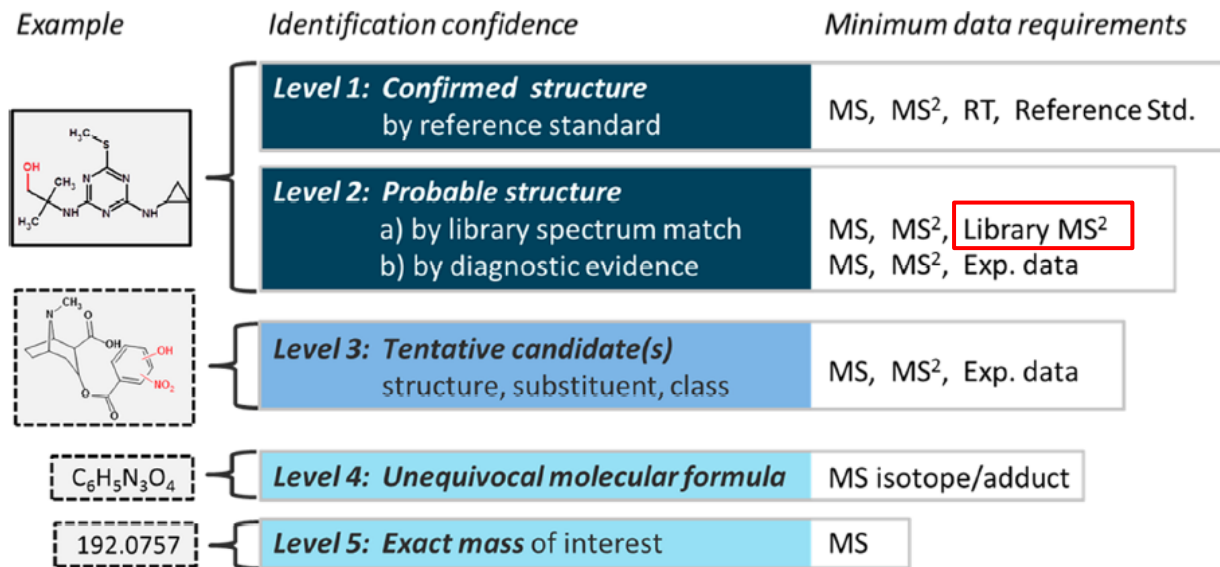


Figure 1. Proposed identification confidence levels in high resolution mass spectrometric analysis. Note: MS² is intended to also represent any form of MS fragmentation (e.g., MS^s, MSⁿ).

Estimation of concentration without standard?

LC-HRMS: Kruve et al, overview:

Prediction of ESI response factors

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RESEARCH ARTICLE

Rapid Communications in Mass Spectrometry **WILEY**

Quantitative electrospray ionization efficiency scale: 10 years after

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Jaanus Liigand | Riin Rebane | Sigrid Selberg | Kristel Ets |
Koit Herodes | Ivo Leito

Software tool:

Input: smiles of pesticides found, t_r , eluent compositions, gradient

'anchor' set of pesticides (25) with known conc. analysed @ lab's system/conditions as input for model

Evaluation: test set of 159 pesticides in solvent

Quantem
ANALYTICS

	#pesticides	Factor error of calculated concentration					
		Avg.	<2	<3	<4	<5	<10
Quantem model	159	2.9	50%	77%	84%	89%	97%

Validation of screening methods

Target screening

SANTE/11312/2021 v2

For each commodity group (AO: muscle, dairy, egg, fat):
multiple matrices, in total at least 20 samples

SDL = lowest level with 95% detection confidence

Batch QC: monitored through quan QCs (>100 pest)

Reporting validated pesticides:

Not found: <SDL

Found: go to quan/confirmatory analysis

Reporting not validated pesticides:

Not found: - (absence cannot be reported)

Found: go to quan./confirmatory analysis

Suspect screening/non-target screening

No validation at compound level possible

Instead: definition of 'chemical space' through QC-mix (50-100 chemicals) representing all phys./chem.

Batch QC: monitor method/system performance through QC-mix



analytical chemistry

pubs.acs.org/ac Article

A Proposed Quality Control Standard Mixture and Its Uses for Evaluating Nontargeted and Suspect Screening LC/HR-MS Method Performance

Ann M. Knolhoff,*[†] Jacob H. Premo,[†] and Christine M. Fisher

 Cite This: *Anal. Chem.* 2021, 93, 1596–1603  Read Online



WP4.3 SS/NTS incl.
QA/QC requirements

<https://www.eu-parc.eu/>

Conclusions

LC-HRMS technology matured and suited for combined quan/qual analysis

Target screening (still) best way to go for monitoring & control

- straightforward data acquisition and data processing
- low hanging fruit for expanding scope of analysis

Added value demonstrated: pesticides beyond usual scope found (and >MRL)

Suspect/non-target screening: discovery and input for future regulatory monitoring

Take home message: replace triples by HRMS where possible

to obtain the free bonus: MS1, MS2 DIA & non-target DDA for future screening

AI is booming, time for big data collection = NOW

LC-HRMS based screening: approaches and experiences in pesticide residue analysis



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NRL pesticides in food & feed, The Netherlands



16th European Pesticide Residue Workshop

8 - 12 June 2026 | Rotterdam, The Netherlands

30th anniversary 1996-2026



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EPRW 2026 Co-Chair



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