

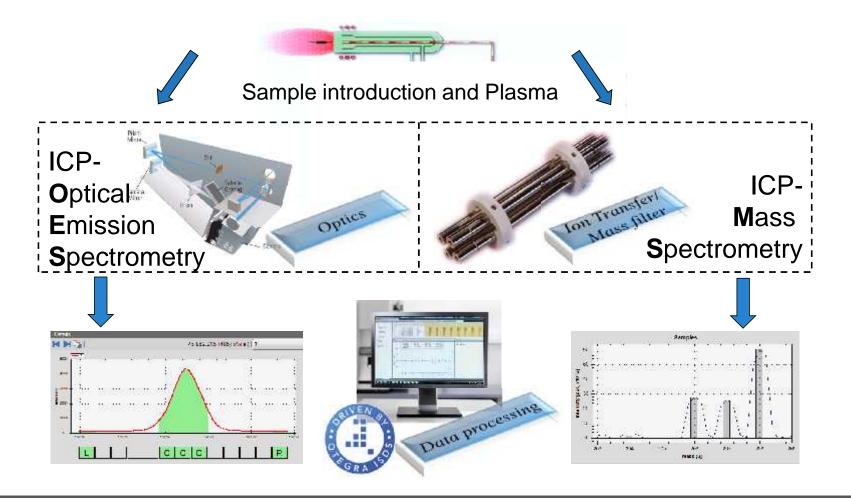
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Determination of Elemental Impurities in Pharma and food samples by ICP-OES and ICP-MS

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ICP – Optical Emission and Mass Spectrometry

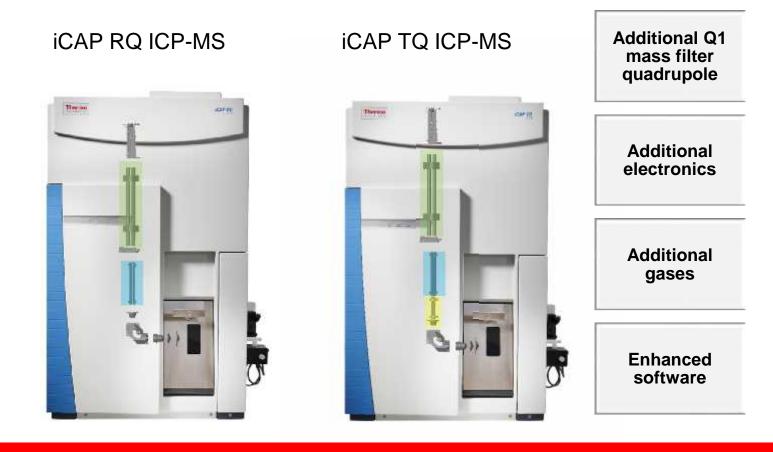


The iCAP 7000 Series ICP-OES Core Technologies



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What's the difference between a SQ and TQ-ICP-MS



Same platform – there are more differences than you think!

Pharmaceutical Testing of Elemental Impurities – Why?

- Why are metal impurities of concern?
 - Reduced shelf-life
 - Inherent toxicity of certain elements
- How is heavy metals testing done?
 - USP General Chapter for Heavy Metals <231>
 - Hundred-year-old colorimetric test
 - Precipitation of ten sulfide-forming elements
 - Visual comparison of colour to that of a 10 ppm lead standard
- Is the test fit for purpose?
 - · Unable to differentiate between the levels of individual contaminants
 - · Safety issues with the use of hazardous solvents such as thioacetamide
 - · Easy to lose volatiles such as mercury

Introduction to USP Chapters <232> and <233>

- Concerned with testing of elemental impurities in pharmaceutical products.
- New USP Chapters introduced to replace <231>
 - <232> Elemental Impurities Limits
 - <233> Elemental Impurities Procedure
 - <2232> Elemental Contaminants in Dietary Supplements
- Chapter 232 sets out the limits for 24 elements
 - 'Big Four' arsenic, cadmium, lead and mercury must test for these
 - Remainder are commonly used as catalysts must test if thought to be present
- Chapter 233 describes two analytical procedures:
 - Procedure 1 ICP-OES
 - Procedure 2 ICP-MS
 - Acceptance criteria for alternative procedures





• USP

7

On January 1, 2018, USP General Chapters <232> Elemental Impurities — Limits, <233> Elemental Impurities — Procedures, and <2232> Elemental Contaminants in Dietary Supplements became applicable to drug products and dietary supplements.

ICH Q3D

- Date of USP and ICH are now closley alinged
- Other regulatory bodies like EMA...
 - Delayed implementation dates for compliance for e.g. marketed products



USP <232> Elemental Impurities – Limits ug/day

Element	Class	Oral PDE	Parenteral PDE	Inhalation PDE
Cd	1	5	2	2
Pb	1	5	5	5
As	1	115	15	2
Hg	1	30	3	1
Со	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
ТІ	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
lr	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ва	3	1400	700	300
Мо	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

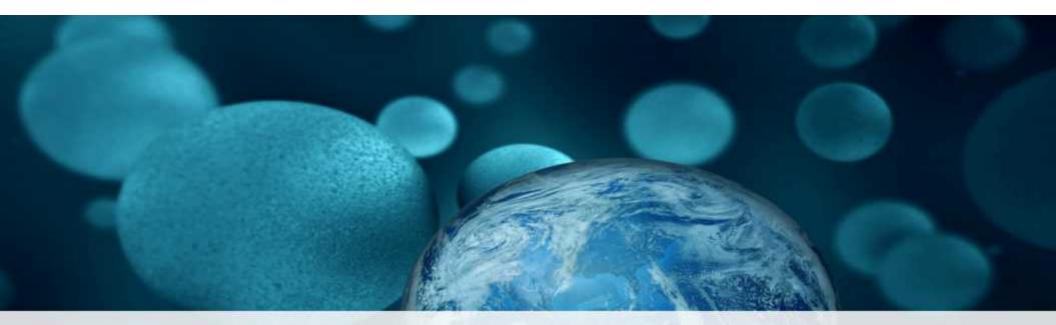
^a PDE = permitted daily exposure based on a 50 kg person

* Not a safety concern

Instrumentation



ICP-OES Procedure 1 ICP-MS Procedure 2

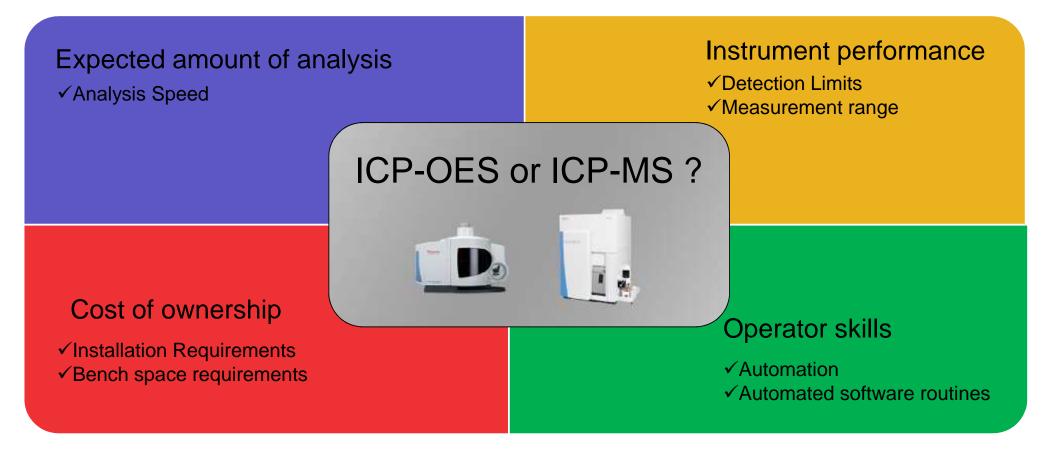


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Implementation of USP Elemental Impurities Testing in Your Facility?

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Instrument Decision Matrix



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ICP-OES or ICP-MS ???

Technology	ICP-OES	ICP-MS
Detection Power (USP)	+	+++
Dynamic Range	++	+++
Speciation Capabilities	+	+++
Lab Requirements	+++	+++
Operating Cost	++	++
Software	+++	+++
Investment	+++	++
Future Proof (USP)	+	+++







ICP-OES Analysis Example

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ICP-OES Procedure 1 USP <233>

The key benefits of ICP-OES

- Easy to use, learn & maintain
- Fast multi-element capability
- Robust plasma and flexibility for complex sample matrices

Flexible Matrix Handling

- Ability to analyse multiple matrix types in a single method
- Wide dynamic range spectrometer capable of analysing ppb to % in a single solution
- Axial viewing of plasma used to further improve detection limits



As, Cd, Hg and Pb	'The big four'
Cr, Cu, Mn, Mo, Ni, Pd, Pt, V, Os, Rh, Ru, Ir	Common catalysts

Analysis of Two Over the Counter Medicines

Preparing samples in DMSO

- DMSO (dimethyl sulfoxide) is a very strong solvent
- Less toxic than DMF (dimethylformamide)
- High-boiling point

Drawbacks of using DMSO

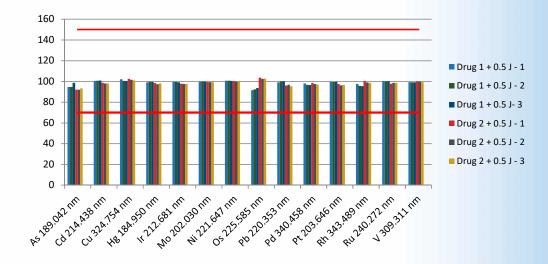
- Require silicone pump tubing
- O-rings on spray-chamber require changing more often
- Will not dissolve all excipients
 - For example: silica, titanium dioxide





Analysis of Two Over the Counter Medicines

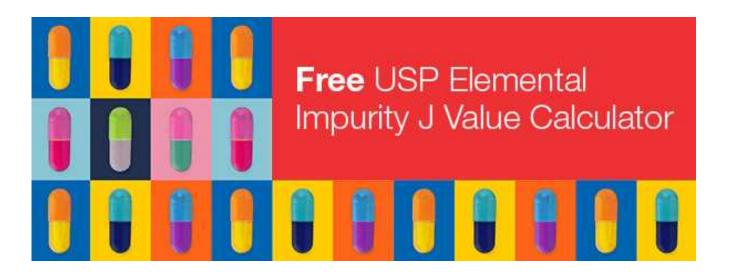
- Two over-counter-medicines were tested according to USP <233>
 - Drug 1 anti-inflamatory
 - Drug 2 antihistamine
- 0.5 g of dehydrated sample was dissolved in 25 g of DMSO
 - J defined as the w/w concentration of analyte at Target Limit <u>after</u> dilution
 - Target Limit > MDL; recoveries tested at the 0.5J and 1.5J



Elements	0.5 J (µg/kg)
Cadmium	125
Lead	25
Inorganic As	7.5
Inorganic Hg	75
Iridium	500
Osmium	500
Palladium	500
Platinum	500
Rhodium	500
Ruthenium	500
Molybdenum	500
Nickel	2500
Vanadium	500
Copper	5000

J Value

- J = The concentration of the element(s) of interest at the target limit, appropriately diluted to the working range of the instrument
- http://www.jvaluecalculator.com/



Analysis of Two Over the Counter Medicines

Precision

- Determined by analyzing six individual samples
- Samples spiked at J
- USP acceptance criteria < 20%

Elements	Drug 1	RSD					
	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	
	μg/L	μg/L	µg/L	µg/L	µg/L	μg/L	%
Cadmium	232.4	232.7	234.7	239.1	235.6	229.9	1.4
Lead	45.9	45.2	44.6	47	46.6	43	3.2
Inorganic arsenic	12.1	12.7	12.8	14	12.9	11.4	6.9
Inorganic mercury	130.7	130.8	132,5	136.5	131.8	127.4	2.3
Iridium	944.5	941.3	948.2	963.7	950.9	924.5	1.4
Osmium	954.8	952.7	959	974.9	960.5	940	1.2
Palladium	918.8	914.7	914.6	928.6	929.4	890.6	1.5
Platinum	924.4	917.6	931.5	949.9	934.6	910.7	1.5
Rhodium	921.5	907.2	907.5	917.6	915.8	874.9	1.9
Ruthenium	955.5	966.5	953.6	972.8	967.5	932.7	1.5
Molybdenum	956.8	952	959.6	974	959.5	937.7	1.2
Nickel	4669	4666	4706	4787	4718	4610	1.3
Vanadium	962.5	952.9	945.5	960.1	961.7	928.9	1.4
Copper	9680	9590	9522	9666	9668	9318	1.5







ICP-MS Application Examples

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ICP-MS Procedure 2 USP Chapter 233

- The key benefits of ICP-MS relative to ICP-OES are:
 - Improved detection limits:
 - Up to 1000x lower for USP regulated elements such As, Cd, Hg and Pb
 - More future proof with flexibility for future changes in target levels
 - Able to access a broader elemental package
 - Wider dynamic range, ppt to ppm
 - Straightforward interfacing to speciation techniques (IC etc.)

- Four over-the-counter products were locally sourced
- Two samples of each were weighed into 15 ml disposable glass vials
- 3 ml of conc. HNO₃ was added to each vial
- System was closed, and pressurized with N₂ at 40 bar
- Microwave digestion recipe:

Step	Time	Temperature	Power
	(min)	(°C)	(kW)
1	15	200	1.5
2	10	200	1.5

- When <60 °C, the digest was transferred to a polypropylene vial and made up to 50 ml with 1% HCl
- Samples were further diluted before analysis (with high purity 2% HNO₃) to give total dilution factors of between *100 and *1000

ICP-MS Instrumentation and Standardization:

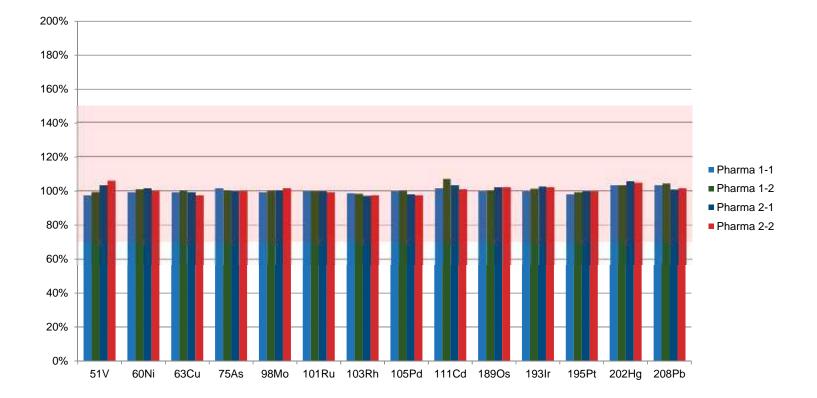
• ICP-MS:

- PFA-ST nebulizer
- Quartz peltier cooled spraychamber (~ 2.7 °C)
- 2.5mm ID quartz injector
- Ni cones
- Analysis
 - Single mode KED for all analytes
 - 5.5 mL/min 100% He
 - 3 V voltage step

Standardization:

- Internal standardization with Ga, In and TI (at 10, 5 and 5 ppb respectively) automatically added via a T-piece during analysis
- External calibration with standards (at 0.5 J, J and 2 J) for quantification
- For ICP-MS analysis, J values were defined as 1000 times lower than the oral solid drug product with a daily dose of 10 g/day

Results: Spike Recoveries (0.5 J)



ICP-MS Detection Limits Compared to Maximum Daily Dose

Element	Instrumental Detection Limit (ng/mL)	Method Detection Limit (µg/g)	Concentration Limit Max. Daily Dose of 10 g/day (µg/g)
Cadmium	0.0001	0.0001	0.5
Lead	0.0005	0.0005	0.5
Inorganic arsenic	0.0005	0.0005	1.5
Inorganic mercury	0.003	0.003	1.5
Iridium	0.002	0.002	10
Osmium	0.0006	0.0006	10
Palladium	0.0008	0.0008	10
Platinum	0.0005	0.0005	10
Rhodium	0.0007	0.0007	10
Ruthenium	0.001	0.001	10
Molybdenum	0.003	0.003	18
Nickel	0.003	0.003	60
Vanadium	0.006	0.006	12
Copper	0.009	0.009	130

Arsenic measurement in the presence of cobalt with iCAP TQ ICP-MS

- Determination of elemental impurities in Vitamin B12
- Vitamin B12 contains Co (approx. 4% (w/w))
- Elements to be measured As, Cd, Pb and Hg the so-called 'Big Four' in pharmaceutical analysis
- Digest sample in nitric acid
- Run all elements in SQ-KED mode and also As in TQ-O₂ mode (as ⁷⁵As¹⁶O)

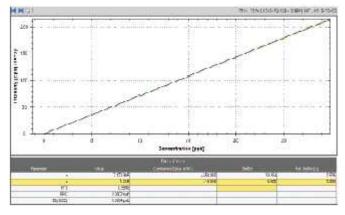


Performance in SQ and TQ modes

Concentration Vitamin B12	Signal at m/z=59 (SQ-KED) [CPS]	Signal at <i>m/z=</i> 75 (SQ-KED) [CPS]	BEC in SQ- KED mode [ng·g ⁻¹]	Signal at <i>m/z=</i> 75 (TQ-O ₂)	BEC in TQ-O ₂ mode [ng·g ⁻¹]	Spike recovery In TQ-O ₂ mode [%]
BLK	73	2	8000.0	4	0.0007	N/A
0.0001 mg-mL*	202,455	13	0.003	9	0.001	100.1
0.001 mg mL1	2,174,144	83	0.02	10	0.001	99.5
0.01 mg·mL1	24,003,087	852	0.21	8	0.001	101.6
0.1 mg-mL ¹	243,093,619	8744	2.47	18	0.002	106.4

- SQ-KED mode elevated BEC due to CoO contribution that cannot be suppressed with He KED.
- TQ-O₂ mode measure AsO at m/z 91 free from CoO interference
- Accurate spike recovery (1 ng/g As) achieved with increasing concentrations of Vitamin B12 in TQ-O₂ mode

Calibration and results for a Vitamin B12 supplement



- Sample prepared according to manufacturers instructions, then diluted 1:100 for analysis
- Sensitivity 7000 cps/ppb
- BEC 0.0002 ppb
- Spike recovery determined (at 10 ng/g As)
- Recovery compared with and without butanol addition to the diluent

Element	Mode	Result [ng·g ⁻¹]	Spiked concentration [ng·g ⁻¹]	Recovery [%]	Recovery with butanol [%]
As	TC-0,	0.019	9.87	179	99
As	SQ-KED	0.150	9.87	1/1	100
Gd	SQ-KED	Below IDL	3.29	97	98
Hg	SQ-KED	0.05	1.32	9a	98
Pb	SQ-KED	0.1	6.58	105	107





Elemental analysis of food samples

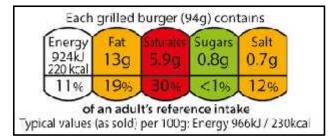
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Country/Region Specific Legislation for Food

Gov. body/directive	Matrix	Elements
US FDA 21 CFR	•107 Infant Formula	•Fe, I, Na, K (chloride)
	 136 Bakery Products 	•Bromate, Ca, Fe
	•137 Cereal Flours	•Bromate, Ca, Fe
	 165 Bottled water 	•Fe, Mn, Zn, As, Sb, Ba, Be, Cd, Cr, Cu, Pb, Hg, Ni, Se, Tl, U
	•172 Bakers yeast	•Zn, As, Cd, Se, Pb
	•573 Animal feeds	•Se (IV, VI and yeast)
US FDA:		
Guidance for Industry	•Candy	•Pb
Guidance docs	 Shellfish (crustacean, molluscs) 	•As, Cd, Cr, Pb, Ni
	•Fish	•Hg (<i>MeHg</i>)
Recommendations	•Fish, wheat	•Hg
Action levels	Pottery leachate	•Cd, Pb
EU 1881/2006 EC	 Variety defined foodstuffs 	•Pb, Cd, Hg, inorganic Sn
WHO/FAO, JEFCA	 Acceptable DIs Food Additives 	•As, Cd, Hg, Pb
FSANZ	Reporting limits	•As, Sb, Cd, Cu, Pb, Hg, Se, Sn, Zn
Hong Kong Food Adulteration Legislations	 Variety defined foodstuffs 	•As, Sb, Cd, Cr, Pb, Hg, Sn
Japan	Potable and Drinking Waters	•Cr(VI), Cd, Hg, Pb, As, P, Zn, Fe, Cu, Mn, Ca, Mg, Se, B
	Plastics for milk storage	•As, heavy metals (Cd and Pb) Sb, Ge, <i>dibutyltin</i>

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Food labelling information



Nutrition Facts

Serving Size 1 cup (228g) Servings per Container 2

Amount Per Servin	g		
Calories 280		Calories fr	om Fat 120
		% Da	aily Value*
Total Fat 13g			20%
Saturated Fat 5g			25%
Trans Fat 2g			
Cholesterol 2mg			10%
No. And Anna			28%
Total Carbohydrate	31g		10%
Dietary Fiber 3g			0%
Sugars 5g			
Protein 5g			
Vitamin A 4%		Vit	amin C 2%
Calcium 15%		Inc	on 4%
Percent Doly Values are be be higher or lower depende			ity values may
	Calories:	2,000	2,500
Total Fat	Less than	65g	8Cq
Sat Fat	Less than	200	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Fiber		25g	30g
Calories per gram: Fat 9	Carbohydrate	4.	Protein 4





Analysis of elements in food stuff by ICP-OES

- ICP-OES is ideal for analysis of trace elements from sub ppm to % (in solid samples)
- Ideally use Duo view instrument iCAP 7400 ICP-OES Duo
 - Axial view allows the lowest detection limits whilst radial view allows analysis of higher concentrations
 - Total dissolved solids is relatively low (1%)
- Samples prepared by microwave assisted acid digestion and diluted to 0.5% HNO₃ with DI water
- Creation of method using the standard sample introduction kit

Parameter	Setting	
Pump Tubing (Standard)	Sample Tygon ^e orange/white Drain Tygon ^e white/white	
Spraychamber	Glass cyclonic	
Nebulizer	Glass concentric	
Center Tube	2.0 mm	
Pump Speed	50 rpm	
Nebulizer Gas Flow	0.6 L-min *	
Auxiliary Gas Flow	0.5 Lmin ⁴	
Coolant Gas Flow	12 Limin ⁻¹	
RF Power	1150 W	
Exposure Time	UV 15 s, Vis 5 s	

Element	Wavelength (nm)	View
Ca	317.933	Radial
Cu	327.396	Axial
Fe	274.932	Radial
Mg	285.213	Radial
Mn	257.61	Axial
NI	231.604	Axial
р	178.284	Axiai
Zn	206.2	Axial

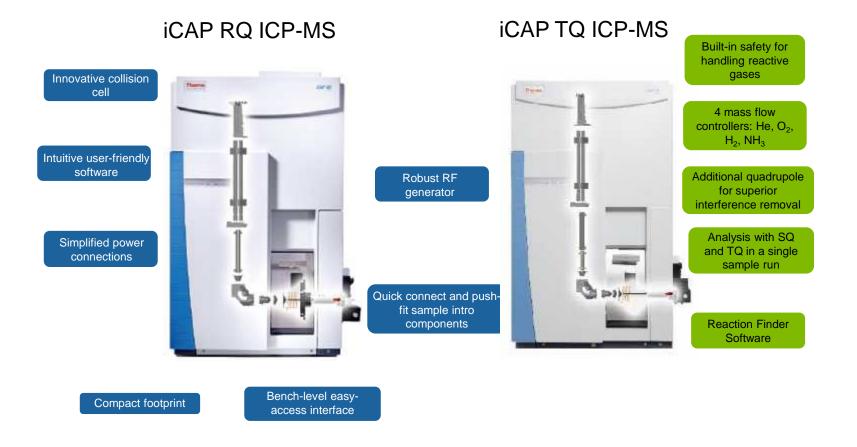
Analysis of elements in food stuff by ICP-OES Results

- MDLs sub ppm in solid & IDLs of sub ppb (Dilution factor of 100)
- Ability to analyze over a wide concertation range
- A simple method of analysis after a digestion
- All results in mg·kg⁻¹. Total Diet (ARC182), Wheat Flour (NBS1567), Bovine Liver (NBS1577a).

-	N	'a	N	7	4	MDL				
Element	Found in solid	CRM	Recovery (%)	Found in solid	CRM	Recovery (%)	Found in solid	CRM	Recovery (%)	in solid
Ca	133.6	120	111.33	195	190	102.63	2670	2860	93.36	0.99
Cu	153.3	158	97.03	2.105	2	105.25	N/A	N/A	N/A	0.16
Fe	192.9	194	99.43	18.86	18.3	103.06	N/A	N/A	N/A	4.3
Mg	576.5	600	96.08	N/A	N/A	N/A	719.2	785	91.62	0.46
Mn	10.14	9.9	102.42	8.634	8.5	101.58	12.98	12.9	100.62	0.01
Ni	N/A	N/A	N/A	0.1719	0.18	95.5	0.2863	0.271	105.65	0.03
Р	11490	11100	103.51	N/A	N/A	N/A	N/A	N/A	N/A	0.24
Zn	122.2	123	99.35	10.96	10.6	103.4	29.16	28.9	100.9	0.03



ICP-MS Overview: Single and Triple Quadrupole ICP-MS



Elemental impurities in Food by ICP-MS

- iCAP RQ ICP-MS using single He KED mode for analysis of all analytes regardless of concertation
 - Li, 0-100 μg·L⁻¹ and Na, 0-100 mg·L⁻¹
- Samples prepared by microwave assisted acid digestion (0.5g sample → 50ml)

Parameter	Value
Forward Power	1500 W
Nebulizer Gas	0.9 L-min ⁺
Auxiliary Gas	0.8 L-min ⁻¹
Cool Gas Flow	14.0 L-min-1
CRC Conditions	4.5 mL·min ⁻¹ at He, 3V KED
Sample Uptake/Wash Time	45 s each
Dwell Times	Optimized per analyte
Total Acquisition Time	3 min

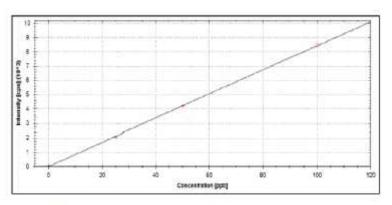


Figure 1. Calibration curve for 7Li in He KED mode.

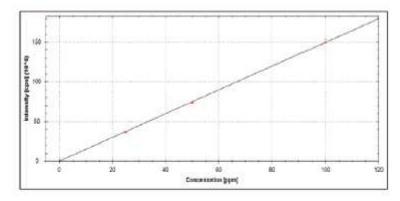


Figure 2. Calibration curve for ²³Na in He KED mode.

Elemental impurities in Food by ICP-MS Results

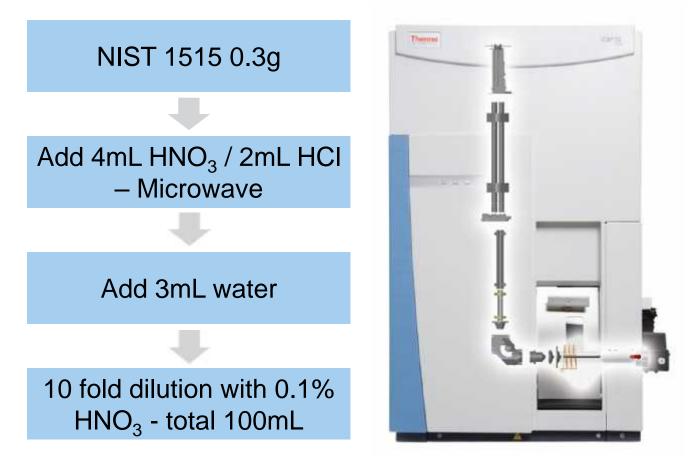
- MDL are orders magnitude lower than ICP-OES
- Ability to measure trace and major in one analysis
- Simple analysis using one analysis mode He KED

• All results in µg·L⁻¹

Isotope	Method detection		RMM-804 Rice		NCS ZC73016 Chicken					
	limit (MDL)	Measured	Certified	% RSD	Measured	Certified	% RSD			
บ	3	•	-	-	28 ± 1	34 ± 7	1.9			
**B	10	-			730 ± 23	760 ± 130	1.9			
²³ Na	0.3 (mg-L')	1	G	100	1310 ± 25	1440 ± 90	1.3			
^{ss} Mg	0.01 (mg·L [*])	9			1200 ± 22	1280 ± 100	1.1			
^н Р	0.6 (mg-L*)	-	-	2	8950 ± 220	9600 ± 800	1.7			
³⁴ S	9 (mg-L*)	*	34	1	8310 ± 220	8600 ± 500	1.9			
³⁸ K	0.5 (mg-L)	2	-	2	14000 ± 480	14600 ± 700	1.8			
"Ca	0.2 (mg·L')	+	21		200 ± 4	220 ± 20	1.7			
PCr	0.2	*			450 ± 10	590 ± 110	0.0			
^{ss} Mn	1	35800 ± 470	34200 ± 2300	0.5	1640 ± 20	1650 ± 70	8.0			
⁶⁶ Fe	-4	+	-		32700 ± 260	31300 ± 3000	0.7			
^{co} Ni	2				163 ± 2	150 ± 30	0.8			
#Cu	0.8	2650 ± 30	2740 ± 240	0.4	1350 ± 11	1460 ± 120	0.7			
°°Zn	2	23100 ± 270	23100 ± 1900	0.7	25300 ± 220	26000 ± 1000	0.6			
⁷⁶ As	0.2	52.3 ± 0.8	49 ± 4	1,4	115 ± 1	109 ± 13	0.9			
78Se	1	35.1 ± 1.0	38 (Reference value)	1.3	549 ± 11	490 ± 60	1.8			
#Sr	0.1	-	1	2	611 ± 11	640 ± 80	1.6			
"Mo	1				112 ± 1	110 ± 10	1.9			
^{##} Cd	0.3	1620±9	1610 ± 70	0.7			-			
ⁱⁿ Ba	0.3	-		1	1610 ± 16	1500 ± 400	1.4			
^{un} Pr	0.02			3	2.6 ± 0.1	2.8 ± 0.6	1.6			
==Pb	0.1	460 ± 8	420 ± 70	0.8	90.7 ± 2.0	110 ± 20	1.0			

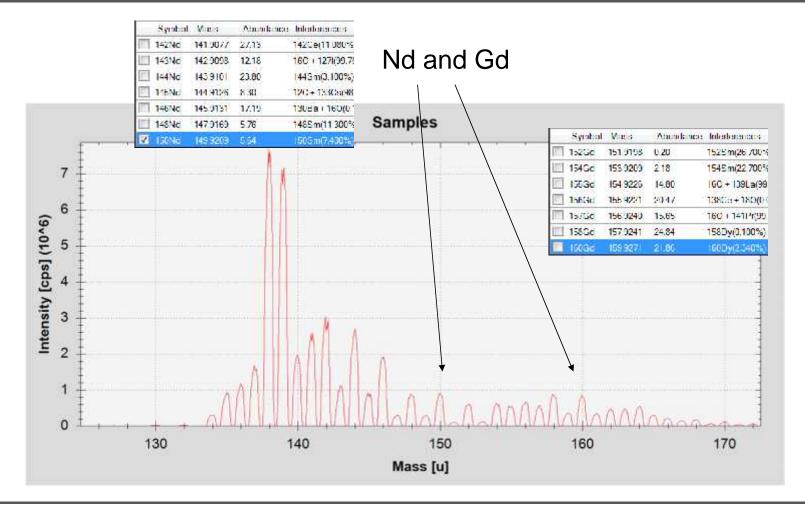


iCAP TQ ICP-MS - Food CRM NIST 1515 Apple leaves

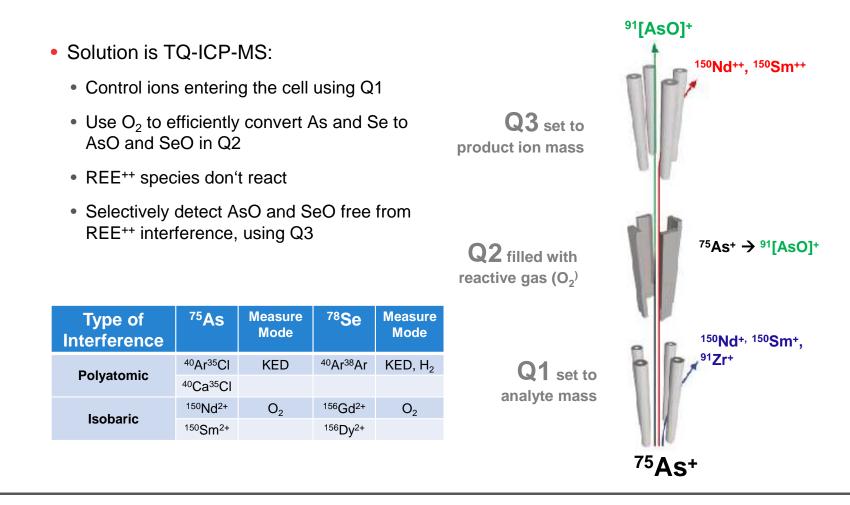


Parameter	Value
Spray chamber	PFA cyclonic spray chamber cooled at 3°C
Nebulizer	100µL PFA nebulizer
Injector	2.0 mm Sapphire injector
Interface	Ni sampler and Ni skimmer with 2.8mm insert
TQ-O ₂ Mass shift mode	Pure Oxygen 0.3mL/min
Dwell time	0.3 sec, 5 sweeps

Apple Leaves survey result



Accurate Analysis of Arsenic and Selenium in REE Matrix

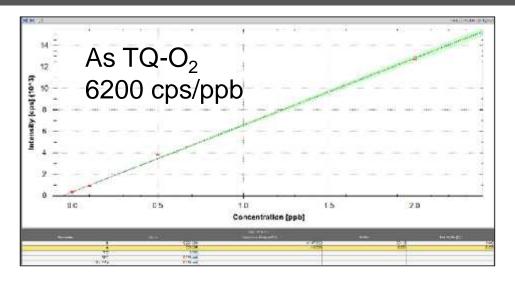


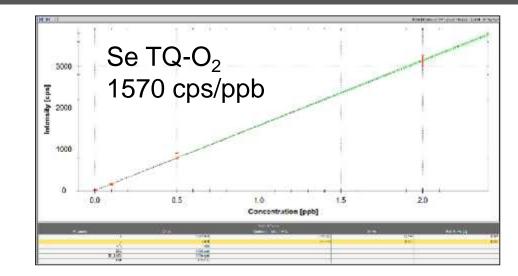
Analysis Se and As result of Apple leaves NIST 1515

Qu	antification													No.					
四.	Use Quality Control													1					
Ans	ilyte	Measu	rement	Mode	Qua	intify			Interna	Stand	ard	Fit	Type	1					
	75As 75As.160	M-TQ-	TQ-02 Yes		Yes						Line	Linear		1				He	
	80Se 80Se.16O	M-TQ-	02		Yes				l			Line	Linear 🦼		-				
	115In (M-TQ-O2)	M-TQ-	02		Ne				Use as Internal Stand			Line	Linear S		C	N	0	F	Ne
														5	Si	P	S	CI	Ar
_	attained path	-	haff.		100		-		-			es tempte		1	-	•		-	
-		K	Ca	SC	TI	V	Cr	Mn	Fe	Co		Cu	Zn	Ga	Ge	As	Se	Br	Kr
		Rb	SI	Y	Zı	Nb	Mo	To	Ru	Rh	Pd	Ag	Cd	In	SI	SD	Te	1	Xe
		Cs.	3.	La	Hſ	Ta	W	Re	Os	h	Pt	Au	Hg	TI	Ρb	Bi	Pu	At	Rn
		Fr	Ra	Ac		1.1.	11-11-												
					Cə	Pr	No	Pm	Sm		Gd	Τb	Dy	Но	Er	Tm	Yb	La	
					Th	Pa	U	Np	Sec. 1	Am	Cm	Bk	CI	Es	Fm	Md	No	Lr	

Reaction finder choose the analysis mode automatically – improve *Ease of use* and *Productivity* (minimum method developing time)

As and Se result KED vs TQ-O₂





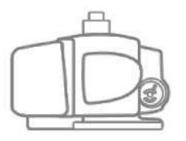
	Reference value mg/kg	SQ KED mode mg/kg	TQ-O2 mode mg/kg
As	0.038	1730	0.037
Se	0.050	4800	0.049

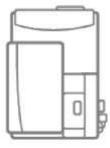
Conclusions

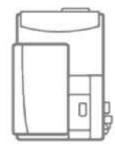
- ICP-OES
 - Fast multi element analysis
 - Detection limits in ppb range and below
 - For laboratories with low and high sample throughput

SQ-ICP-MS

- Detection limits in the ppt range
- Wide quantification range ideal for many different sample types
- Single mode He KED with low mass cut off
- TQ-ICP-MS
 - Detection limits in the ppt range
 - Enhanced interference removal for challenging samples (TQ-ICP-MS)









Thank You! Questions?

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