

The Future of Reference Materials
IRMM, Geel, Belgium
23-25 Nov. 2010.

Smart Calibration of Organic Standards

-Proton Based Calibration System by qNMR-

*National Metrology Institute of
Japan*

Koichi Chiba

Growing Demands for Reference Materials in Food Safety

Waterworks Law (amended in 2003)

- 50 items to be regulated
- 27 items to be monitored
including **102 pesticides**



Regulation of residual

pesticides (amended in 2006)

- shifted to a positive-list system
from a negative-list system
- about **800 pesticides** with
an uniform limited value (**0.01 ppm**)



Reference Materials for Waterworks Law

	Regulated Itme	Regulatory limit	CRM	RM		Regulated Itme	Regulatory limit	CRM	RM
1	bacillus (colony)	100>			26	Trihalomethane	0.1 mg/ L	JCSS	
2	colon bacillus	n.d.			27	Trichloromethane	0.2 mg/ L	X	Commecial
3	Cd and its compounds	0.01 mg/ L	JCSS		28	bromdichloromethane	0.03 mg/ L	JCSS	
4	Hg and its compounds	0.0005 mg/ L	JCSS		29	bromoform	0.09 mg/ L	JCSS	
5	Se and its compounds	0.01 mg/ L	JCSS		30	formaldehyde	0.08 mg/ L	JCSS	
6	Pb and its compounds	0.01 mg/ L	JCSS		31	Zn and its compounds	1.0 mg/ L	JCSS	
7	As and its compounds	0.01 mg/ L	JCSS		32	Al and its compounds	0.2 mg/ L	JCSS	
8	Cr(VI) compounds	0.05 mg/ L	JCSS		33	Fe and its compounds	0.3 mg/ L	JCSS	
9	CN ⁻ compounds & CN chlorides	0.01 mg/ L	X	Self prep.	34	Cu and its compounds	1.0 mg/ L	JCSS	
10	nitric oxide & nitous oxide	10 mg/ L	JCSS		35	Na and its compounds	200 mg/ L	JCSS	
11	F and its compounds	0.8 mg/ L	JCSS		36	Ma and its compounds	0.05 mg/ L	JCSS	
12	B and its compounds	1.0 mg/ L	JCSS		37	chloride ions	200 mg/ L	JCSS	
13	tetrachloromethane	0.002 mg/ L	JCSS		38	Ca, Mg, etc (Water Hardness)	300 mg/ L	JCSS	
14	1,4- dioxane	0.05 mg/ L	X	Commecial	39	ignition residue	500 mg/ L		---
15	1,1- dichloroethylene	0.02 mg/ L	JCSS		40	anionic surfactant	0.2 mg/ L		Commecial
16	cis- 1,2- dichloroethylene	0.04 mg/ L	JCSS		41	musty odorsubstances	0.00001 mg/ L		Commecial
17	dichloromethylene	0.02 mg/ L	JCSS		42	2- MIB	0.00001 mg/ L		Commecial
18	tetrachloroethylene	0.01 mg/ L	JCSS		43	nonionic water soluble surfactant	0.02 mg/ L		Commecial
19	trichloroethylene	0.03 mg/ L	JCSS		44	phenol	0.005 mg/ L		Commecial
20	benzene	0.01 mg/ L	JCSS		45	TOC	5 mg/ L		Self prep.
21	chloroactic acid	0.02 mg/ L	X	Commecial	46	pH	5.8 - 8.6	JCSS	
22	chloroform	0.06 mg/ L	JCSS		47	taste	nomarl		---
23	dichloroacetic acid	0.04 mg/ L	X	Commecial	48	smell	nomarl		---
24	dibromochloromethane	0.1 mg/ L	JCSS		49	color	5 degree		Self prep.
25	bromic acid	0.01 mg/ L		Commecial	50	tirbidity	2 degree		Commecial

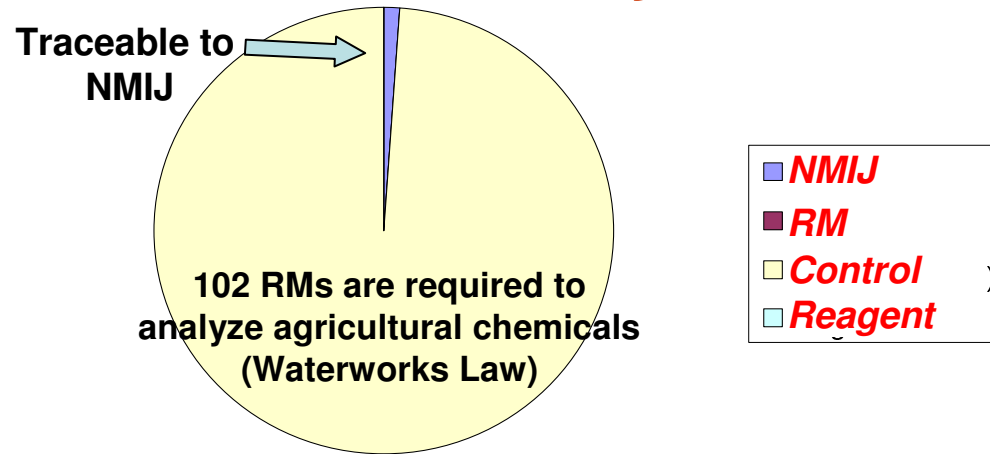
JCSS: Japan Calibration Service system

Inorganic substance

Organic substance

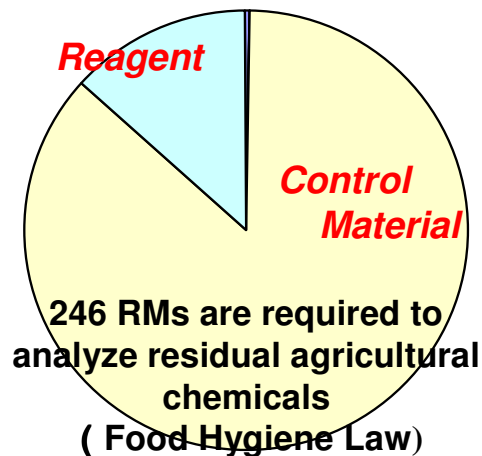
Reference Materials Used in Japan

Environmental analysis

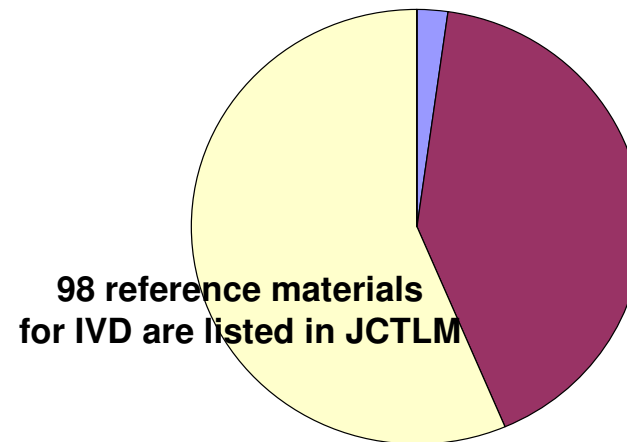


*A vast number of reference materials are demanded in the fields of **environmental protection, food safety and clinical analyses.***

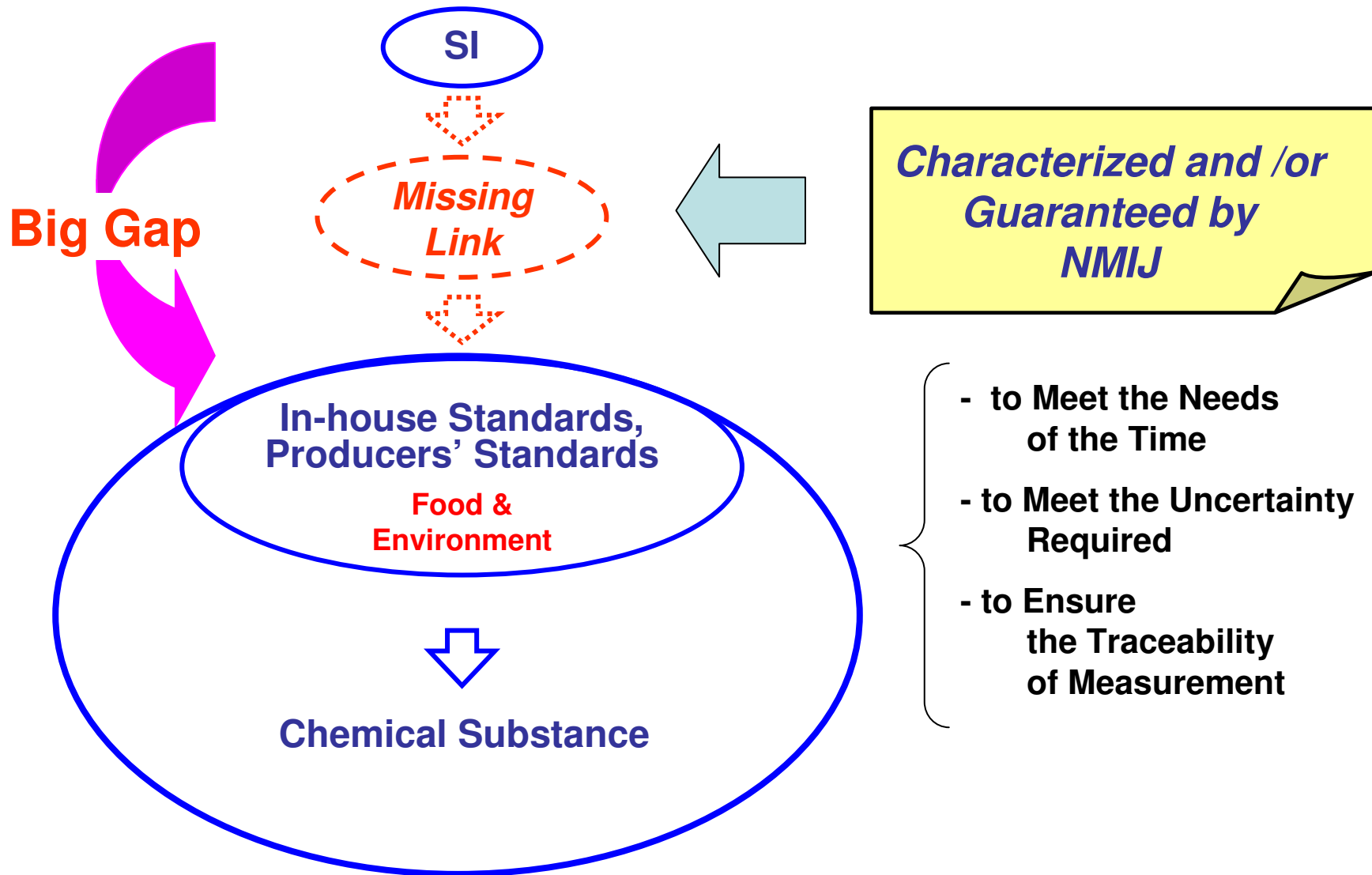
Food analysis



Clinical laboratory testing



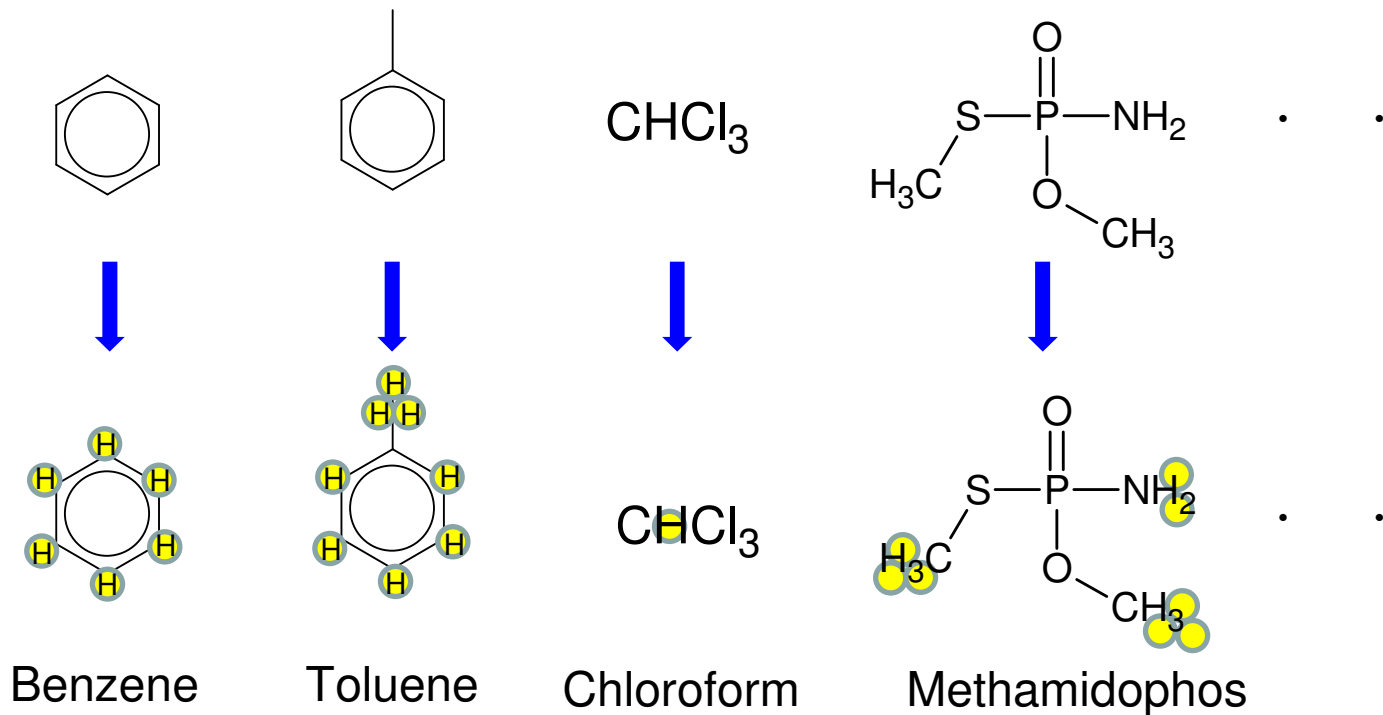
New Dissemination System for Metrological Standards of Organic Substances



Smart Calibration by Quantitative NMR

Conventional Calibration

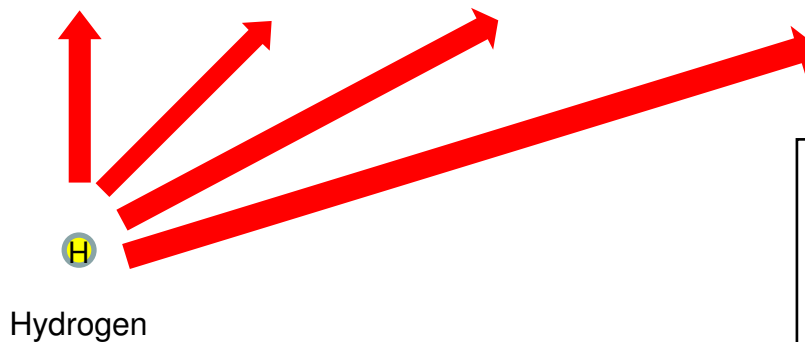
"Substance to Substance" Calibration



Working Std.

Proton Based Calibration

Hydrogen basis of Universal Calibration

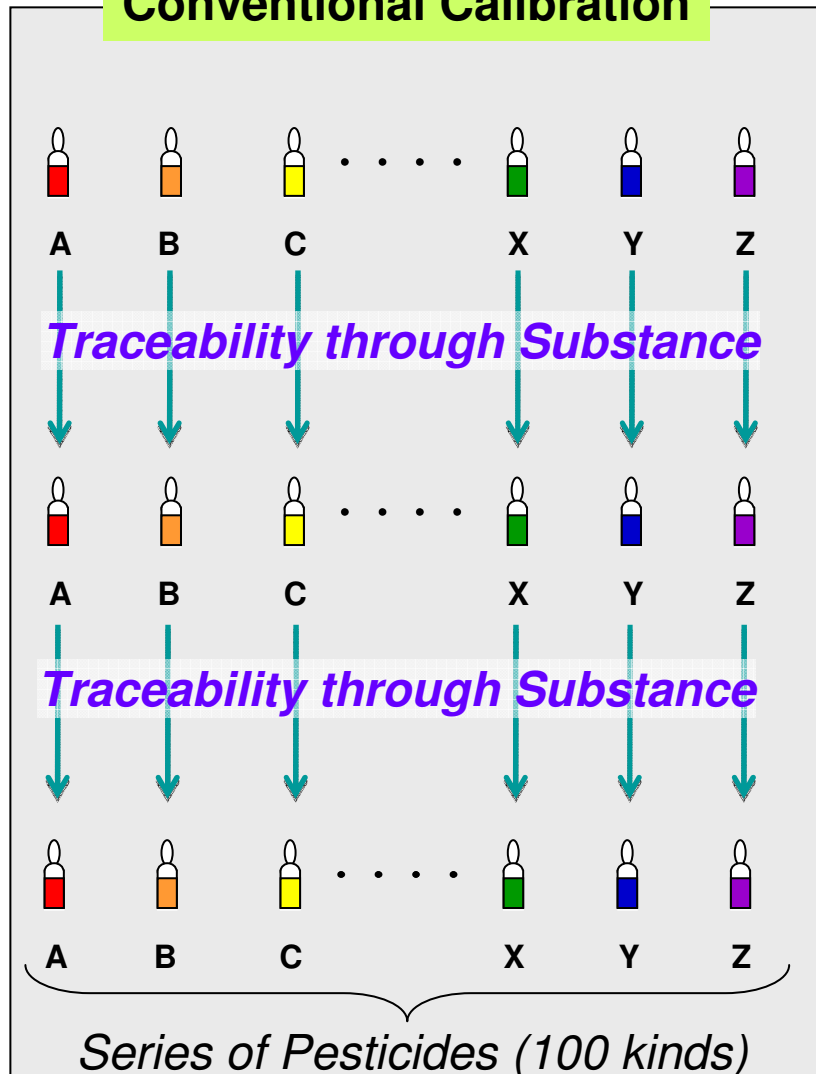


【qNMR】

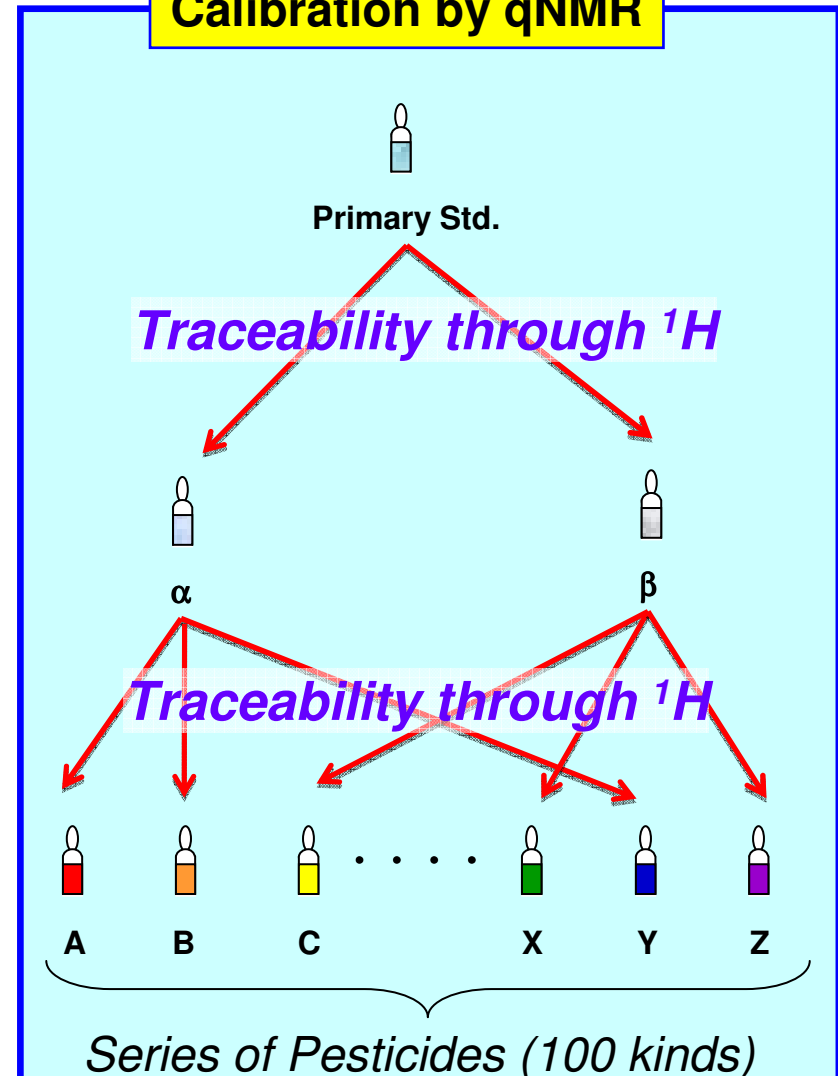
To calibrate the amount of a substance by measuring the amount of hydrogen containing in the substance .

Innovation in Dissemination of Chemical Standards

Conventional Calibration



Calibration by qNMR



National Std. (NMIJ CRM)

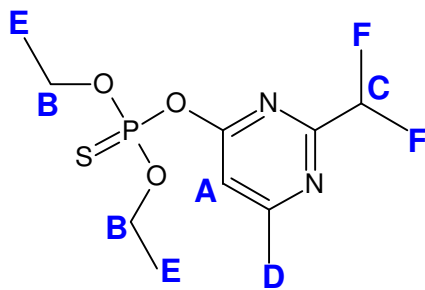


Secondary Std.

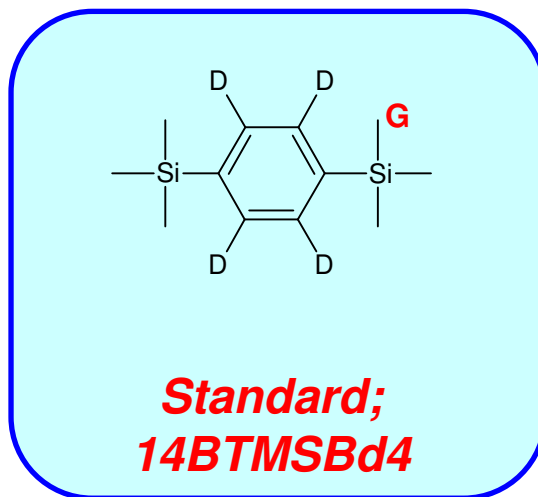


Working Std.

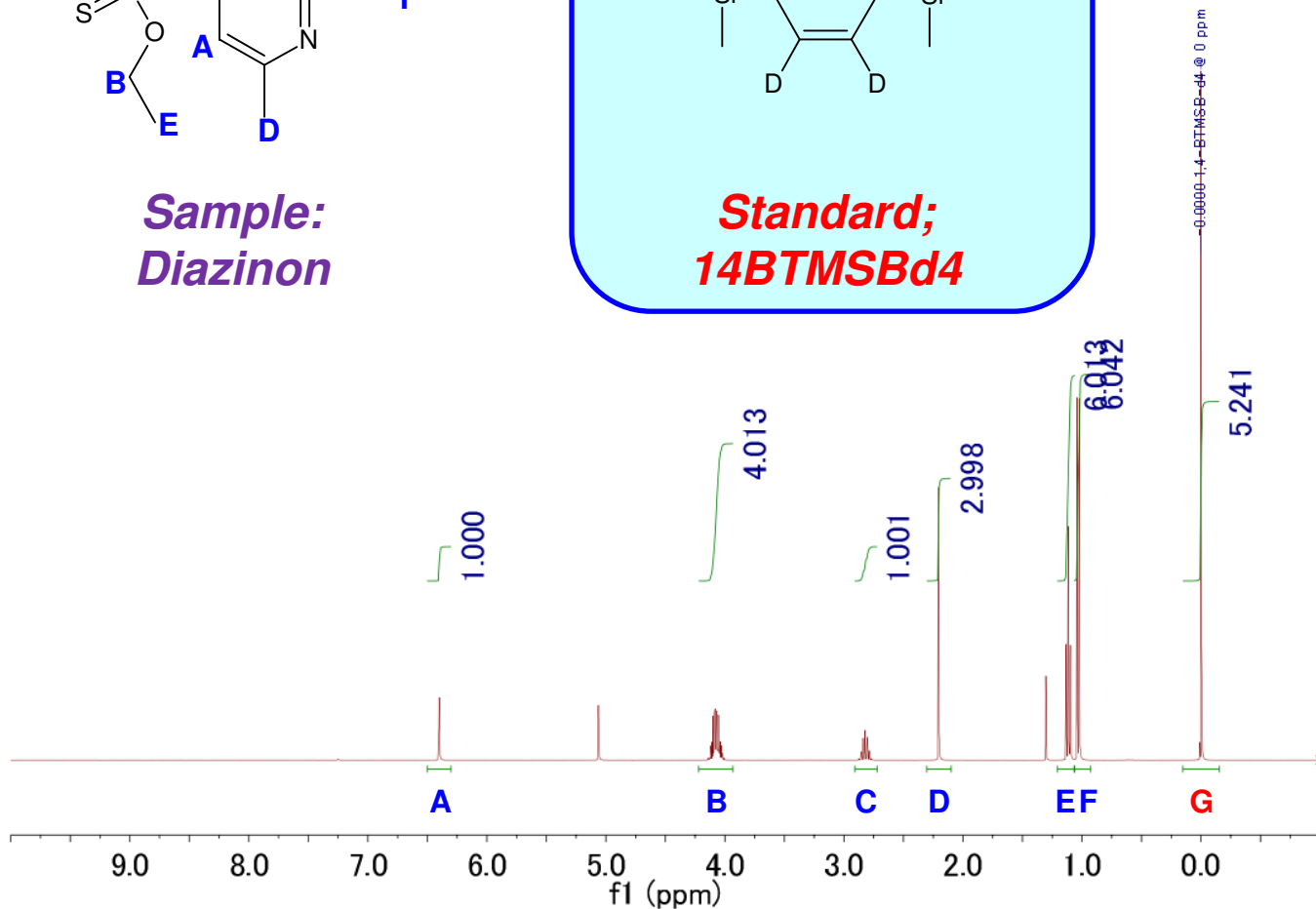
NMR spectrum of Diazinon and 14BTMSBd4



Sample:
Diazinon



Standard;
14BTMSBd4



Parameter	Value
Comment	Diazinon-14BTMSBd4-CD2Cl2_run11
Spectrometer	ECS 400
Solvent	CD2Cl2
Temperature	25
Pulse Sequence	single_pulse_qua
Number of Scans	32
Receiver Gain	34
Relaxation Delay	60
Pulse Width	10
Acquisition Time	3.9999
Acquisition Date	2010/3/7
Spectrometer Frequency	398.78
Spectral Width	39904.2
Nucleus	1H
Acquired Size	159613
Spectral Size	524288

Uncertainty Budget of q-NMR Measurement

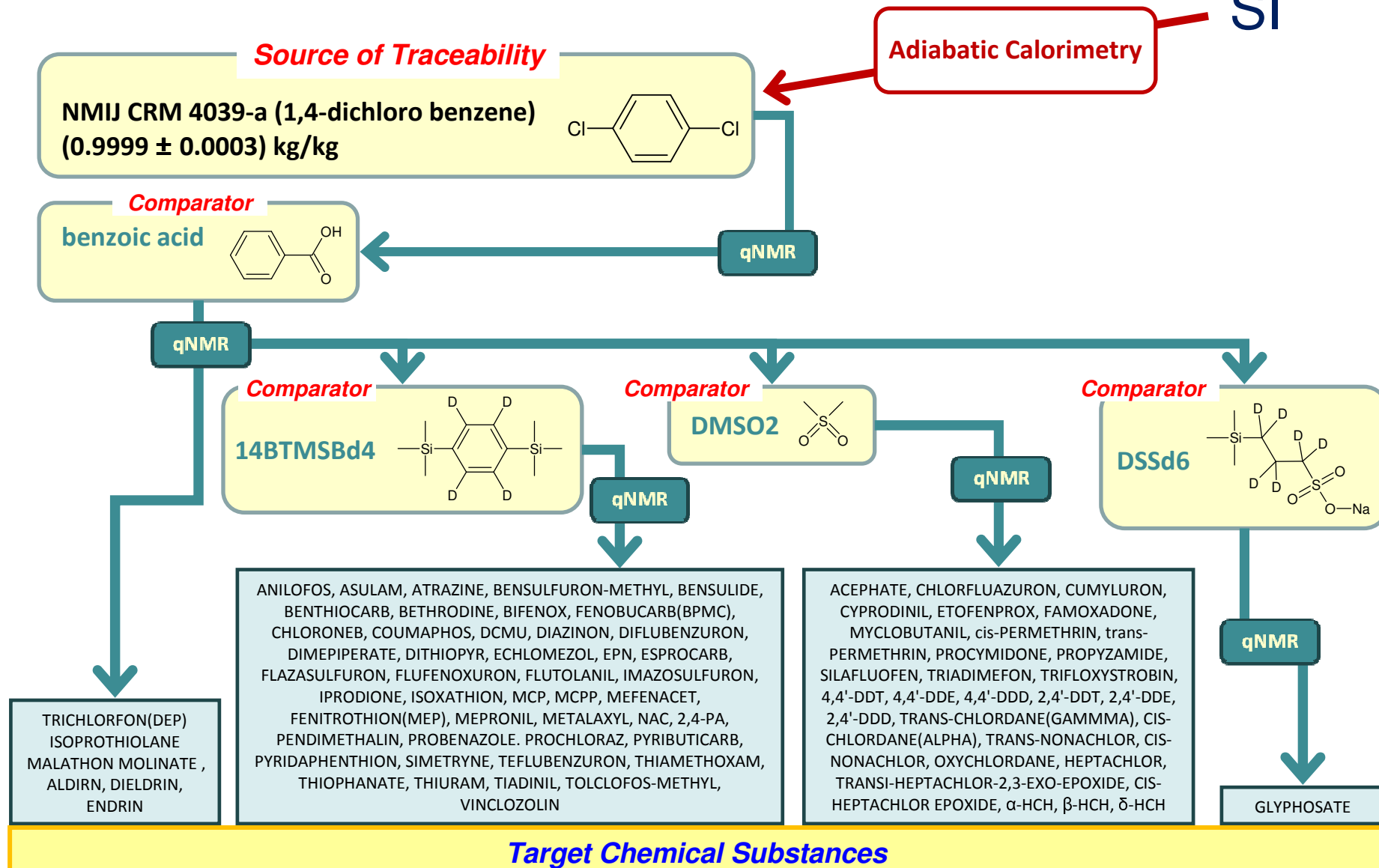
Quantity	Symbol	Uncertainty component	x_i	$u(x_i)$	$\left \frac{\partial f}{\partial x_i} \right $	$\left \frac{\partial f}{\partial x_i} \right u(x_i)$	Type	Degree of freedom, f
Main Uncertainty Component								
NMR experiments, g		ANOVA	0.9956	6.3753E-04	-1	6.3753E-04	A	3
		peak & sample		5.4236E-04				3
		measurement			3.3509E-04			44
Balance	m_{VTx}	Mass of the sample + blank1	41.8581 mg	1.9039E-04 mg	0.0904 mg ⁻¹	1.7216E-05	B	Large
Balance	m_{VTs}	Mass of the reference + blank2	33.5779 mg	1.7557E-04 mg	0.3611 mg ⁻¹	6.3397E-05	B	Large
Balance	m_{Vx}	Mass of the blank1	30.8486 mg	1.7068E-04 mg	0.0904 mg ⁻¹	1.5435E-05	B	Large
Balance	m_{Vs}	Mass of the blank2	30.8209 mg	1.7063E-04 mg	0.3611 mg ⁻¹	6.1615E-05	B	Large
NMR, theoretical	S	Peak saturation	0.9956	2.8868E-05	1.0000	2.8868E-05	B	Large
NMR, instrumental	S	NMR signal intensity	0.9956	2.0000E-03	1.0000	2.0000E-03	B	Large
The number of ¹ H nuclear	n_a	¹ H natural abundance for the sample	9	8.9917E-05	0.1106	9.9465E-06	B	Large
The number of ¹ H nuclear	n_s	¹ H natural abundance for the reference sample	18	8.9917E-05	0.055310	4.9733E-06	B	Large
Molecular weight	M_a	Molecular weight of the sample	304.345502 g·mol ⁻¹	3.1661E-03 g·mol ⁻¹	0.0033 mol·g ⁻¹	1.0357E-05	B	Large
Molecular weight	M_s	Molecular weight of the reference sample	226.4391555 g·mol ⁻¹	4.4905E-03 g·mol ⁻¹	0.0044 mol·g ⁻¹	1.9743E-05	B	Large
Purity	P_s	Internal reference material for this study	0.9975 kg·kg ⁻¹	0.0032 kg·kg ⁻¹	0.99811 kg·kg ⁻¹	3.2131E-03	B	39

Analytical Performance of q-NMR

Compound	q-NMR		DSC		GC
	Purity (%)	Uncertainty (% , $k=2$)	Purity (%)	Uncertainty (% , $k=2$)	Purity (%)
4,4'-DDT	99.9	1.1	99.6	0.3	99.5
4,4'-DDE	99.8	0.6	99.7	0.3	99.6
4,4'-DDD	99.9	0.5	99.8	0.2	99.6
Endrin	99.2	0.9	99.7	0.2	97.7
<i>trans</i> -Chlordane	99.5	0.6	99.8	0.2	99.6
<i>cis</i> -Chlordane	99.1	0.5	99.7	0.4	99.7
<i>trans</i> -Nonachlor	99.5	0.6	99.7	0.2	99.0
<i>cis</i> -Nonachlor	99.9	0.5	99.8	0.2	99.8
Oxychlordane	99.3	0.5	99.9	0.1	99.6
Heptachlor	99.3	0.3	99.7	0.3	99.3
α -HCH	99.2	0.6	99.6	0.3	99.2
δ -HCH	99.0	0.6	99.9	0.1	99.2
Trichlorfon(DEP)	99.6	0.5	99.7	0.3	100.0
Propyzamide	99.1	0.6	99.8	0.8	99.7

Traceability of q-NMR Calibration

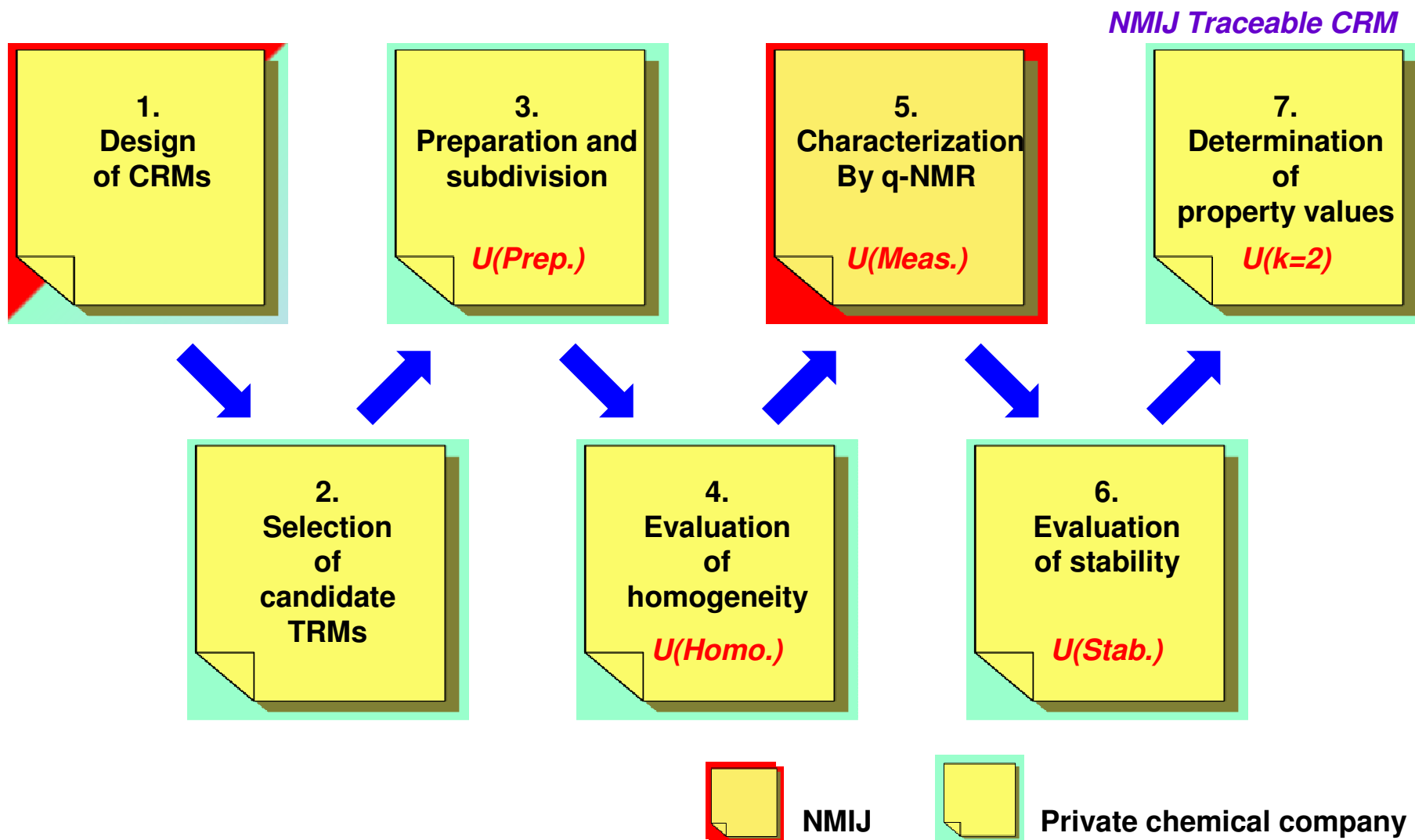
SI



<Pesticide>

No.	Compound	Calibration Method				No.	Compound	Calibration Method			
		NMR	DSC	GC	HPLC			NMR	DSC	GC	HPLC
1	Trichlorfon(DEP)	•	•	•		43	Glyphosate	•			•
2	Procymidone	•	•	•		44	Pyributicarb	•		•	
3	EPN	•		•		45	<i>trans</i> -Permethrin	•		•	
4	Etofenprox	•			•	46	Flufenoxuron	•			•
5	Propyzamide	•	•	•		47	NAC	•			•
6	Benthiocarb	•	•	•		48	Bensulide	•			•
7	Malathion	•		•		49	Chlorfluazuron	•			•
8	Fenobucarb(BPMC)	•	•	•		50	Silafluofen	•			•
9	Atrazine	•			•	51	Isoxathion	•		•	
10	Echloomezol	•	•	•		52	Coumaphos	•	•	•	
11	Pendimethalin	•	•	•		53	MCP	•	•		•
12	Bethrodine	•	•	•		54	Prochloraz	•		•	
13	Chloroneb	•	•	•		55	Triadimefon	•	•	•	
14	Simetryne	•	•	•		56	Diazinon	•		•	
15	Thiuram	•			•	57	Flazasulfuron	•			•
16	Isoprothiolane	•	•	•		58	Imazosulfuron	•			•
17	Bifenox	•		•		59	Cyprodinil	•			•
18	Probenazole	•			•	60	Diflubenzuron	•			•
19	Pyridaphenthion	•		•		61	Famoxadone	•	•		•
20	2,4-PA	•	•		•	62	Trifloxystrobin	•			•
21	DCMU	•	•	•	•	63	Tiadinil	•	•	•	
22	Iprodione	•	•	•	•	64	Acephate	•	•	•	
23	MCPP	•	•	•	•	65	Thiamethoxam	•			•
24	1,4-BTMSB- <i>d</i> ₄	•	•	•		66	Tolclofos-methyl	•	•	•	
25	Fenitrothion(MEP)	•	•	•		67	Warfarin	•			•
26	Dithiopyr	•	•	•		68	Teflubenzuron	•			•
27	Mefenacet	•	•	•		69	Linuron	•	•	•	•
28	Bensulfuron-methyl	•	•	•	•	70	Flusulfamide	•	•	•	•
29	Esprocarb	•		•		71	DSS- <i>d</i> ₆	•			•
30	Mepronil	•		•		72	Cymoxanil	•			•
31	Thiophanate	•		•	•	73	Indanofan	•			•
32	Metalaxyl	•		•		74	Pyrazoxyfen	•			•
33	Vinclozoline	•	•		•	75	Thiacloprid	•	•		•
34	Asulam	•			•	76	Chlorfenapyr	•	•	•	
35	Flutolanil	•	•	•		77	CNP-amino	•	•	•	
36	Dimepiperate	•	•	•		78	Chloro IPC	•	•	•	
37	Molinatate	•		•		79	Methyl Thioacetohydroxamate	•		•	
38	Cumyluron	•	•	•	•	80	Pyrimethanil	•	•	•	
39	<i>cis</i> -Permethrin	•		•		81	Phosalone	•		•	
40	Anilofos	•			•	82	XMC	•	•	•	
41	PCP	•	•	•		83	Bifenthrin	•		•	
42	Myclobutanil	•		•		84	Daminozide	•			•

NMIJ Traceable CRM Production Process



Reference Materials Traceable to NMIJ

<Pesticide>

Calibrated through smart calibration system by q-NMR

No.	Compound	Purity (%)	Uncertainty (% $, k=2$)	No.	Compound	Purity (%)	Uncertainty (% $, k=2$)
1	Trichlorfon(DEP)	99.6	0.5	25	Benthiocarb	99.1	0.7
2	Aldrin	98.7	0.5	26	Malathon	99.4	0.4
3	Dieldrin	97.8	1.0	27	Fenobucarb(BPMC)	99.8	0.7
4	Endrin	99.2	0.8	28	Atrazine	99.5	0.7
5	4,4'-DDT	99.9	1.2	29	Echlomezol	99.2	0.6
6	4,4'-DDE	99.8	0.7	30	Pendimethalin	99.5	0.6
7	4,4'-DDD	99.9	0.6	31	Bethrodine	99.8	0.6
8	2,4'-DDT	99.9	0.5	32	Chloroneb	99.7	0.6
9	2,4'-DDE	100.0	0.6	33	Simetryne	100.0	0.6
10	2,4'-DDD	100.0	0.8	34	Thiuram	99.8	0.6
11	<i>trans</i> -Chlordane	99.5	0.6	35	Isoprothiolane	99.8	0.5
12	<i>cis</i> -Chlordane	99.1	0.5	36	Bifenox	99.5	0.6
13	<i>trans</i> -nonachlor	99.5	0.6	37	Probenazole	99.0	0.6
14	<i>cis</i> -Nonachlor	99.9	0.5	38	Pyridaphenthion	99.7	0.6
15	Oxychlordane	99.3	0.5	39	2,4-PA	99.5	0.6
16	Heptachlor	99.3	0.3	40	DCMU	99.7	0.6
17	<i>cis</i> -Heptachlor epoxide	97.5	0.4	41	Iprodione	99.6	0.6
18	α -HCH	99.2	0.6	42	MCPP	99.8	0.6
19	β -HCH	99.5	0.3	43	Fenitrothion(MEP)	99.4	0.5
20	δ -HCH	99.0	0.7	44	Dithiopyr	98.6	0.6
21	Procymidone	99.3	0.5	45	Mefenacet	99.3	0.5
22	EPN	99.4	0.7	46	Bensulfuron-methyl	98.9	0.9
23	Etofenprox	99.5	0.5	47	Esprocarb	99.8	0.7
24	Propyzamide	99.1	0.6	48	Mepronil	99.2	0.8

Disseminated by Private Chemical Companies

Reference Materials Traceable to NMIJ

<Pesticide>

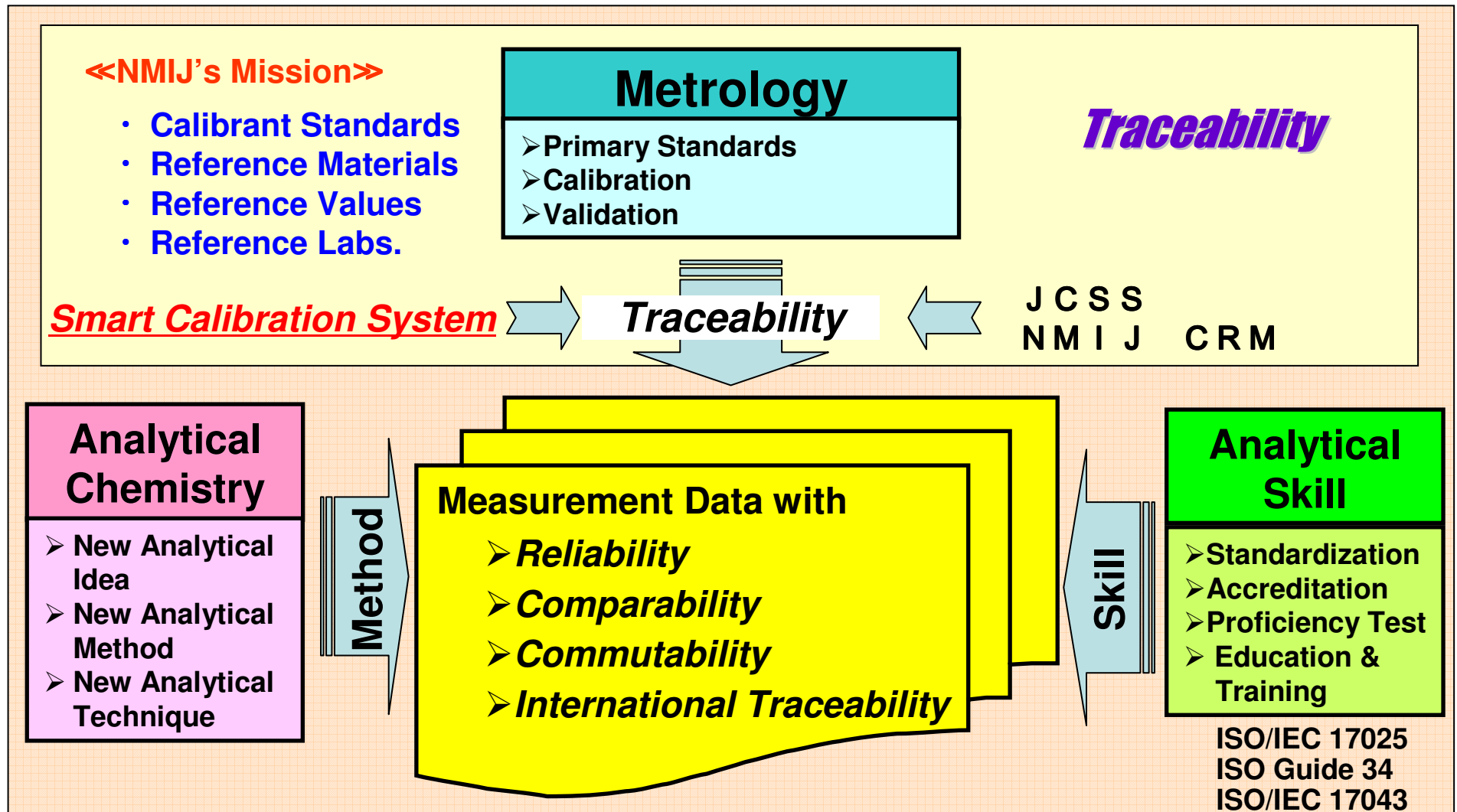
Calibrated through smart calibration system by q-NMR

No.	Compound	Purity (%)	Uncertainty (% $, k=2$)	No.	Compound	Purity (%)	Uncertainty (% $, k=2$)
49	Thiophanate	99.8	0.7	72	Triadimefon	98.8	0.9
50	Metalaxyl	99.6	0.7	73	Diazinon	99.6	0.8
51	Vinclozoline	99.7	0.8	74	Flazasulfuron	99.2	1.0
52	Asulam	98.4	1.0	75	Imazosulfuron	98.9	0.9
53	Flutolanil	98.3	1.2	76	Cyprodinil	99.7	0.6
54	Dimepiperate	99.5	0.9	77	Diflubenzuron	99.8	0.8
55	Molinate	99.4	0.7	78	Famoxadone	99.2	0.6
56	Cumyluron	99.8	0.7	79	Trifloxystrobin	99.3	0.6
57	<i>cis</i> -Permethrin	99.8	0.7	80	Tiadinil	99.4	0.9
58	Anilofos	98.5	0.8	81	Acephate	98.9	0.7
59	Myclobutanil	99.8	0.7	82	Thiamethoxam	100.0	0.8
60	Glyphosate	97.8	1.1	83	Tolclofos-methyl	99.3	0.8
61	Pyributicarb	99.3	0.9	84	Warfarin	99.9	0.8
62	<i>trans</i> -Permethrin	99.6	0.6	85	Teflubenzuron	99.9	0.9
63	Flufenoxuron	99.0	0.9	86	Linuron	99.6	1.0
64	NAC	99.8	0.8	87	Flusulfamide	99.3	0.8
65	Bensulide	99.5	0.8	88	Cymoxanil	99.9	0.8
66	Chlorfluazuron	99.6	0.6	89	Indanofan	99.7	0.8
67	Silafluofen	99.5	0.6	90	Pyrazoxyfen	99.8	0.6
68	Isoxathion	98.4	0.9	91	Thiacloprid	98.2	0.9
69	Coumaphos	99.5	0.8	92	Chlorfenapyr	99.7	0.7
70	MCP	99.5	0.8	93	CNP-amino	99.0	0.7
71	Prochloraz	99.0	1.0	94	Chlor IPC	99.9	0.6

Disseminated by Private Chemical Companies

Development of Standards for Safety and Security

Comparability and Reliability of Measurement Data



New Horizon in Metrology

- Traceability in Chemical Metrology -



Thank you for your attention!



Himeji Castle 2010.3.