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ISO Technical Committee 209 Status Report

Conor Murray
Irish Representative,
ISO TC 209 Committee
Chairman Irish Cleanroom Society

ICCCS

ISO International Organization for Standardization

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ISO TC 209
Cleanrooms and associated controlled environments

Conor Murray Bio

- Conor Murray is a founder member and current Chairman of the Irish Cleanrooms Society, (ICS). The ICS hosted the biennial International Confederation of Contamination Control Societies, (ICCCS) Symposium in September 2008 and Conor was Chairman of the ICCCS that year.
- Conor is the inaugural Chairman of the International Cleanroom Education Board (ICEB), a major initiative of the ICCCS to promote the harmonisation and accreditation of internationally recognised educational courses in cleanrooms.
- Conor graduated in 1978 with an honours degree in Electrical Engineering and has been involved in the cleanroom industry since the early 1980s.
- Conor is the principal in 3dimension, a company specialising in cleanroom Design and Construct. Conor acts as an independent Technical Expert and Advisor on GMP Cleanrooms and Biosafety Labs. Conor is also a principal in the C6 Cleanroom Network which is an international network of technical experts, advisors and specialists in cleanrooms providing advice and expertise to government health departments, institutions, and companies.
- Conor is a technical expert and advisor on a number of Irish Government technical advisory committees including the Healthcare Standards Consultative Committee and supported the introduction of the recent EU Blood and EU Tissue Directives.
- Conor is on the editorial boards of a number of cleanroom magazines and lectures internationally on a range of specilaist topics associated with cleanroom standards, modular Design & Build, clean build protocols in Cleanrooms and Biosafety Labs.
- Conor represents the National Standards Autority of Ireland (NSAI) at ISO level on cleanroom standardisation internationally and is currently on WG1 of ISO TC 209.

ICCCS

ISO International Organization for Standardization

Presentation Structure

- Part I is an overview of the last ISO TC 209 Committee meeting in Ireland
- Part II deals specifically with WG1 and revisions to ISO 14644-1 & 2
- Part III deals with ISO 14644 and the new revision to the EMEA's Annex 1 re sterile processing, effective 1-3-'09

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ISO TC 209
Cleanrooms and associated controlled environments

The last meeting was held in Cork, Ireland on 14-15 September 2008 - 28 attendees from 17 countries

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Part I - Progress of ISO TC 209 Committee Work Items

Published Documents

ISO Document	Title	Status
ISO-14644-1	Classification of Air Cleanliness	1999-WG1
ISO-14644-2	Specification of Testing for Continued Compliance to -1	2000-WG1
ISO-14644-3	Test Methods & Metrology	2005
ISO-14644-4	Design, Construction & Start Up	2001
ISO-14644-5	Cleanroom Operations	2004
ISO-14644-6	Terminology	2007 - SG6
ISO-14644-7	Separative Enclosures	2004
ISO-14644-8	Classification of Airborne Molecular Contamination	2007
ISO-14698-1	Biocontamination: General Principles	2003-WG2
ISO-14698-2	Biocontamination: Evaluation & Interpretation of Data	2003-WG2

21 Participating (P) Member Countries

- Australia
- ***Belgium***
- ***Brazil***
- ***China***
- ***Denmark***
- ***Finland***
- ***France***
- ***Germany***
- ***Ireland***
- ***Italy***
- ***Japan***
- ***Kenya***
- ***Korea, Rep***
- ***Netherlands***
- ***Norway***
- Portugal
- ***Russian Federation***
- ***Sweden***
- ***Switzerland***
- ***United Kingdom***
- ***United States***

21 Observer (O) Member Countries

- Argentina
- Barbados
- Bosnia & Herz
- Bulgaria
- Cuba
- Czech Republic
- Egypt
- Hungary
- India
- Iran
- Jamaica
- Malaysia
- Mexico
- Philippines
- Poland
- Saudi Arabia
- Serbia
- South Africa
- Thailand
- Turkey
- Ukraine

Liaison (L) Members

1. ISO committees in liaison
2. **ISO/TC 24/SC 4,** Sizing by methods other than sieving/Particle characterisation
3. **ISO/TC 146**, Air quality
4. **ISO/TC 198**, Sterilisation of health care products
5. **ISO/TC 210**, Quality management and corresponding general aspects for medical devices
6. **ISO/TC 229**, Nanotechnology

Liaison (L) Members

<u>CEN committees in liaison</u>

CEN/TC 243, Cleanrooms

<u>Organisations in liaison</u>

ICCCS, International Confederation of Contamination Control Societies

Secretariat - US (ANSI/ IEST)

Chairman – Mr. David Brande
E-mail: **davidbrande@earthlink.net**
Secretary – Mr. Robert Mielke
E-mail: **robert.mielke@abbott.com**
Secretariat Coordinator – Mrs. Linda Gajda
E-mail: **gajda@iest.org**

Standard ISO Document Stages

- FDIS - Final Draft International Standard
- DIS - Draft International Standard
- CD - Committee Draft
- Note Working Groups and Study Groups, formed as subcommittees with Conveners, are used to focus on specific work items in support of the committee eg WG 1 & SG6

Current ISO 14644 Series Document Status

- Documents in the Final Draft International Standards (FDIS) Stage
  - **None**
- Documents in the Draft International Standards (DIS) Stage
  - **ISO/DIS 14644-9 returned 19-3-'09**
- Documents in the Committee Draft (CD) Stage
  - **ISO 14644-1 returned 16-4-'09**
  - **ISO 14644-2 returned 16-4-'09**

Systematic Review of Documents

Periodic reviews completed in the last year

- ISO 14644-5:2004 – Confirmed December 2007
- ISO 14644-7:2004 – Confirmed March 2008

Periodic reviews currently underway

- ISO 14698-1

Active ISO 14644 Documents

- WG 1 – Air cleanliness
- WG 2 – Biocontamination
- SG 6 – Terms and definitions
- WG 8 – Chemical contamination
- WG 9 – Clean surfaces

Working Group 1 - Air Cleanliness

- **ISO 14644-1**, Classification of air cleanliness
- **ISO 14644-2**, Specifications for testing and monitoring to prove continued compliance with ISO 14644-1

Working Group 2 - Biocontamination

Working Group 2 will work on two documents:

1. Classification of airborne biocontamination in cleanrooms, including methods of measurement and their validation
2. Classification of surface biocontamination in cleanrooms, including methods of measurement and their validation

A new convener for WG 2 has not been chosen

Study Group 6 — *ISO 14644 Part 6, Terms and definitions*

- ISO 14644-6 was published in 2007
- A *Vocabulary Group* is still active to harmonize terms and definitions

Working Group 8 — Chemical contamination

- Working Group 8 has written a Working draft on the subject of "*Classification of surface chemical cleanliness*" which will become ISO 14644-10 in the future

Working Group 9 — Clean Surfaces

- A Draft International Standard (DIS) titled ***ISO/DIS 14644 Part 9, Classification of surface particle cleanliness*** was out for vote, is now returned and comments will be reviewed by WG9
- Working Group 9 proposed that a new standard be written to address the subject of '*Decontamination of Surfaces*'

Working Group 9 — Clean surfaces

- *ISO/DIS 14644 Part 9, Classification of surface particle cleanliness* describes the classification of physical contamination level of surfaces in cleanrooms
- Eight surface particle cleanliness (SPC) classes
- Particle sizes range from 0.05 μm to 500 μm
- Provides recommendations on measuring methods - scattered light method, light-optical microscope & electron microscopy

Published Documents

ISO Document	Title	Status
ISO-14644-1	Classification of Air Cleanliness	1999-WG1
ISO-14644-2	Specification of Testing for Continued Compliance to -1	2000-WG1
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ISO-14644-4	Design, Construction & Start Up	2001
ISO-14644-5	Cleanroom Operations	2004
ISO-14644-6	Terminology	2007 - SG6
ISO-14644-7	Separative Enclosures	2004
ISO-14644-8	Classification of Airborne Molecular Contamination	2007
ISO-14698-1		
ISO-14698-2		

2 new standards under development to cover SPC via WG9 & DIS -9 and SCC via WG8 & -10

Resolutions from Sept 2008 meeting

- Resolution #1

  ISO/TC 209 resolves to seek a formal liaison with ISO/TC 142 "Cleaning Equipment for air and other gases"

Resolutions from Sept 2008 meeting

- Resolution #2

  ISO/TC 209 resolves that a formal NWIP be prepared by Egon Hollaender on behalf of WG 9 and voted on by the next ISO/TC 209 meeting. The NWIP shall be based on the earlier poll and subsequent discussion on "decontamination of surfaces" during the meeting of ISO/TC 209 held on 14th & 15th September 2008.

Resolutions from Sept 2008 meeting

- Resolution #3

  ISO/TC 209 approves the addition of a new work item "ISO 14644-1 *Cleanrooms and associated controlled environments, Part 1 Classification of airborne particulate cleanliness"* (revision of ISO 14644-1:1999) to the TC 209 work programme and assigns it to ISO/TC209 WG 1. The latest draft of this revision shall be issued as a Committee Draft for vote.

Resolutions from Sept 2008 meeting

- Resolution #4

  ISO/TC 209 approves the addition of new work item "ISO 14644-2 *Cleanrooms and associated controlled environments, Part 2 Monitoring for Continued Compliance"* (revison of ISO 14644-2:2000)" to the TC 209 work programme and assigns it to ISO/TC 209 WG 1. The latest draft of this revision shall be issued as a Committee Draft for vote.

Resolutions from Sept 2008 meeting

- Resolution #5

  ISO/TC 209 approves the addition of new work item "ISO 14644-10 *Cleanrooms and associated controlled environments, Part 10 Classification of surface chemical cleanliness*" to the TC 209 work programme and assigns it to ISO/TC 209 WG 8. The draft finalized by WG 8 at their meeting on 16th September 2008 shall be issued as a Committee Draft for vote.

Resolutions from Sept 2008 meeting

- ## Resolution #6

ISO/TC 209 notes that a single clean zone may have multiple cleanliness classifications for different attributes. TC 209 resolves that TC members and WGs 1, 2, 8, and 9 consider the proposal that individual classification shall be unambiguously identified as relating to:
APC – Airborne Particulate Cleanliness
SPC – Surface Particulate Cleanliness
AMC – Airborne (Chemical) Molecular Cleanliness
SCC – Surface Chemical Cleanliness
AVC – Airborne Viable Cleanliness
SVC – Surface Viable Cleanliness,
and submit written comments 90 days in advance of the next meeting of ISO TC209.

Resolutions from Sept 2008 meeting

- Resolution #7

ISO/TC 209 thanks the ad hoc group on contamination control in nano-technologies for its report and accepts its recommendation for a working group to be established to develop a standard(s) in this area. ISO/TC 209 WG 10 shall be created for this purpose and shall be convened by the United States with Secretariat support from the UK.

The WG shall prepare text for a NWIP for presentation to TC 209 at or before the next meeting. The TC 209 Secretariat is instructed to request the nomination of experts to this group by 31st January 2009 in order that the first meeting of the Working Group can take place during May 2009 at Seattle in conjunction with ISO/TC 229. The nomination of experts shall also be extended to the members of ISO/TC 229.

Part II - Update on Revision to ISO 14644-1&2 - April 2009

Important Notes re ISO 14644-1&2 Revisions

- The information is for discussion only
- **CANNOT** be used for classification or monitoring of cleanrooms until ……
- EN/ISO 14644-1:1999 & 14644-2:2000 remain the applicable standard for classification by airborne particles.
- CD comments and vote back 16-4-'09

Revision to ISO 14644-1 & 2

- ISO TC 209 WG 1 was reconvened to look at the issues and report to TC209 in Moscow in September 2005
- ISO TC 209 resolved that revision of 14644-1 & 2 **should commence immediately**
- The last meeting of ISO TC 209 WG1 was in London in May 2008
- ISO TC 209 agreed to issue CD for vote at meeting in Cork in September 2008
- ISO/ CD 14644-1 & 2 revisions posted January 09
- Review, comments & vote 90 days closes 15-4-'09
- ISO TC 209 WG1 will meet to consider comments
- If vote is +ve DIS Enquiry will be issued July 09
- Means possible revised standards could be in **2010**

The Key Issues and Impact on Industry

- The basis for classification
- The 95% Upper Confidence Limit, (UCL) evaluation
- The statistical issue resolution
- The number of sample locations
- Annex F sequential sampling
- Table of Test Frequencies
- Real-time monitoring systems

The Basis for Classification

ISO 14644-1

ISO Issue

- Proposed change from Classification by Formula + Table for Illustration → → Classification by Table + Formula for Intermediate Classes

Impact

- Not a major impact on the principle of classification if this were to change
- Helps prevent poor selection of size vs class

The ISO 14644-1 Formula

- ISO $C_n = \left(\frac{0.1}{D}\right)^{2.08} \times 10^{N(class)}$
- Retained for the decimal classes only

ISO 146441:1999 Classification by Particles

The formula illustrated by a Table

Table 1 Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with 3.2)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

NOTE: Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level.

US Fed Std 209 Classification by Table (Particles)

Class Name**		Class limits									
		0.1 μm		0.2 μm		0.3 μm		0.5 μm		5 μm	
		Volume units		Volume units		Volume units		Volume units		Volume units	
SI	English***	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)
M 1		350	9.91	75.7	2.14	30.9	0.875	10.0	0.283	--	--
M 1.5	1	1 240	35.0	265	7.50	106	3.00	35.3	1.00	--	--
M 2		3 500	99.1	757	21.4	309	8.75	100	2.83	--	--
M 2.5	10	12 400	350	2 650	75.0	1 060	30.0	353	10.0	--	--
M 3		35 000	991	7 570	214	3 090	87.5	1 000	28.3	--	--
M 3.5	100	--	--	26 500	750	10 600	300	3 530	100	--	--
M 4		--	--	75 700	2140	30 900	875	10 000		--	--
M 4.5	1 000	--	--			--	--		1 000	247	7.00
M 5		--	--					100 000	2 830	618	17.5
M 5.5	10 000	--	--			--	--	353 000	10 000	2 470	70.0
M 6		--	--			--	--	1 000 000	28 300	6 180	175
M6.5	100 000	--	--			--	--	3 530 000	100 000	24 700	700
M 7		--	--			--	--	10 000 000	283 000	61 800	1 750

No 5.0μm in these classes

ISO 14644-1 Formula

Low values have sample size warning

Inappropriate values deleted

Annex 1 EU GMP = 20

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (*N*)	Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below [concentration limits are calculated in accordance with equation (1) in 3.2]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10					
ISO Class 2	100	24	10			
ISO Class 3	1 000	237	102	35		
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level

The 95% UCL Evaluation

ISO 14644-1

ISO Issue

- B5.2 There is major problem with this statistical approach in that it assumes an even distribution of contamination in a cleanroom. This may not be the case, particularly for Non-UDAF cleanrooms in the 'In Operation' state

Impact

- Not a major impact on the principle of classification if this were to change.
- Firms might have to redefine their classification sampling & data evaluation.
- Does not affect **Real-time monitoring**

The Statistical Issue Resolution

- All numbers of locations to be dealt with evenly
- No standard statistical distribution assumed (e.g. normal)
- Must not be sensitive to unusually low values
- Should be presented in tabular form for convenience of use

The Statistical Issue Resolution

- Provides the chosen level of confidence for all room sizes.
- Means: Provides 95% confidence that at least 90% of all locations (within the zone) do not exceed the class limits.
  - This means that if 10% of the locations exceed class limits, 95% of the time we will discover at least 1 non-conforming location.
  - This is a significant improvement in confidence compared to ISO 14644-1:1999.

How to Treat the Number of Sample Locations

ISO 14644-1

ISO Issue

- The current number of sample locations is not class or statistically sensitive:

$$N_L = \sqrt{A}$$

- This may change in order to improve confidence at each location

Impact

- Would require a new classification of existing areas
- Does not affect Real-time monitoring
- Following tables illustrate the changes & compare to the OLD Fed Std 209

ISO TC 209
Cleanrooms and associated controlled environments

Room Size (m^2)	ISO 14644-1: 1999	**ISO 14644-1: 2012 (95,90 CL)**	FS209E UDAF (all classes)	FS209E Turbulent Class 1000	FS209E Turbulent Class 10K	FS209E Turbulent Class 100K
2	**2**	**1**	2	2	2	2
4	**2**	**2**	2	2	2	2
6	**3**	**3**	3	3	2	2
8	**3**	**4**	4	3	2	2
10	**4**	**5**	5	4	2	2
12	**4**	**6**	6	5	2	2
14	**4**	**7**	7	5	2	2
16	**4**	**8**	7	6	2	2
18	**5**	**9**	8	7	2	2
26	**6**	**10**	12	9	3	2
28	**6**	**11**	13	10	4	2
32	**6**	**12**	14	11	4	2
34	**6**	**13**	15	12	4	2
36	**6**	**14**	16	13	4	2
38	**7**	**15**	17	13	5	2

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ISO TC 209
Cleanrooms and associated controlled environments

Room Size (m^2)	ISO 14644-1: 1999	**ISO 14644-1: 2012 (95,90 CL)**	FS209E UDAF (all classes)	FS209E Turbulent Class 1000	FS209E Turbulent Class 10K	FS209E Turbulent Class 100K
52	**8**	**16**	23	18	6	2
54	**8**	**17**	24	19	6	2
58	**8**	**18**	25	20	7	2
74	**9**	**19**	32	26	8	3
78	**9**	**20**	34	27	9	3
96	**10**	**21**	42	33	11	4
116	**11**	**22**	50	40	13	4
138	**12**	**23**	60	47	15	5
176	**14**	**24**	76	60	19	6
200	**15**	**25**	87	69	22	7
300	**18**	**26**	130	103	33	11
500	**23**	**27**	216	171	54	18
1000	**32**	**28**	431	341	108	35
2000	**45**	**29**	862	681	216	69
5000	**71**	**29**	2153	1702	539	171
10000	**100**	**29**	4306	3404	1077	341
>10000		**29**				

Annex F Sequential Sampling

ISO 14644-1

ISO Issue

- This procedure is still effective but the specification in Annex F is difficult to follow and has improved presentation

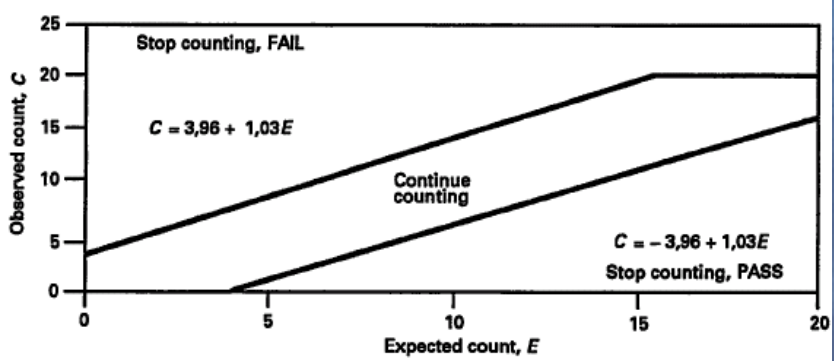

Figure F.1 — Boundaries for pass or fail by the sequential sampling procedure

Impact

- The clarified specification of sequential sampling would assist its use for classification of clean-zones with low particle concentrations limits
- It can also be applied to real-time monitoring when limits are low levels

Table of Test Frequencies

ISO 14644-1

ISO Issue

- The normative section is unclear currently and some parties don't agree with the frequencies
- Possibly will be expanded and placed in an informative annex

Impact

- This change will make it easier to use RISK BASED decision making about testing frequency
- Means if GMPs need to be specific, they can in the context of the ISO guidance
- e.g. FDA's 6 monthly leak testing of HEPA filters in the aseptic core

Real-time Monitoring Systems

ISO 14644-1

ISO Issue

- A new section to specify the essential requirements of such systems that should be considered

Impact

- Both FDA's Aseptic Guidance and Annex 1 require use of real-time particle monitoring systems for critical areas

BUT

- There is no guidance or standard for such systems
- This change will be useful to GMPs + current GMP will influence ISO drafting

Part III - Changes to EMEA Annex 1 re Sterile Processing - effective March 1st 2009

Background to Annex 1 Changes

The revision of Annex 1 was necessary in particular to align the classification table for environmental cleanliness of clean rooms with the ISO standards 14644 series. The revised Annex 1 provides supplementary guidance on the application of the principles and guidelines of GMP to sterile medicinal products.

The guidance has been updated in four main areas:

- Classification table for environmental cleanliness of clean rooms and associated text
- Guidance on media simulations
- Guidance on bioburden monitoring
- Guidance on capping of freeze-dried vials

The new Annex is effective from March 01, 2009 except for the provisions on capping of freeze-dried vials, which come into effect on March 01, 2010. Further info can be found at: http://www.emea.europa.eu/Inspections/WhatsNew.html

Background to Annex 1 & ISO 14644

The revision of the Annex 1 was necessary to align the classification table for environmental cleanliness of clean rooms with ISO standards 14644 series and gives clear guidance with inaccurate and loose terms removed.

- Class limits align with ISO 14644-1 at 0.5um and greater particle sizes
- Class limits align nearly with ISO 14644-1 at 5um and greater particle sizes
- Grade A is 20 instead of ISO recommended 29 in ISO 14644-1 but is close enough!
-Grade B is 29 and aligns with ISO 14644-1
- Minimum 1m3 sample volume per location, (was minimum total sample of 1m3)
- Gives better and clearer text on definitions and use of terms, eg unidirectional flow vs laminar flow.

Old Annex 1 - May '03

	At Rest		In Operation			
Grade	Max Particles greater than or equal to the stated sizes				Microbiological	
	0.5µ	5.0µ	0.5µ	5.0µ	Air sample cfu/m³	90mm settle plate cfu/4hr
A	3 500	1	3 500	1	<1	<1
B	3 500	1	350 000	2 000	10	5
C	350 000	2 000	3 500 000	20 000	100	50
D	3 500 000	20 000	Not defined	Not defined	200	100

5um Particle Size in New Annex 1

	May '03		March 1 '09	
Grade	At Rest	Operational	At Rest	Operational
A	1	1	20	20
B	1	2000	29	2900

The 20 vs 29 number nearly aligns ISO 1464-1 but is close enough.

New Annex 1 - March 1st '09

	At Rest		In Operation			
Grade	Max Particles greater than or equal to the stated sizes				Microbiological	
	0.5µ	5.0µ	0.5µ	5.0µ	Air sample cfu/m³	90mm settle plate cfu/4hr
A	3 500	20	3 500	20	<1	<1
B	3 500	29	350 000	2 900	10	5
C	350 000	2 000	3 500 000	20 000	100	50
D	3 500 000	20 000	Not defined	Not defined	200	100

Thank you for your attention

This presentation has been prepared with the co-operation of:

- David Brande, Chairman ISO TC209
- Bob Mielke, Secretary ISO TC 209
- Gordon Farquharson, Convener WG 1

The next ISO/ TC209 meeting is planned for Washington, DC, USA, 11-13th September 2009