TECHNICAL PAPER

Impaction Technology and ISO 14698

Selection of Portable and Automated
Air Sampler Systems to meet cGMP

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01. Rev 01. 02/24/2017

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Impaction Technology and ISO 14698 – Selection of Portable and Automated Air Sampler systems to meet cGMP.

PIC/s Annex 1 was recently updated in Jan 2017 and under the Clean Room and Clean Air Device Monitoring section the recommended limits for microbial monitoring of clean areas during operation have remained intact since 2003. A one cubic meter sample volume is still required using an air sampling instrument for active air sampling.

	Recommended limits for microbial contamination [a]			
Grade	Air sample cfu/m³	Settle plates (diam. 90 mm), cfu/4 hours [b]	Contact plates (diam. 55 mm), cfu/plate	Glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes: [a] These are average values.

[b] Individual settle plates may be exposed for less than 4 hours.

Fig.1 PICs Annex 1 Table for Microbial Contamination recommended limits

Even though these requirements from a GMP point of view have remained the same since 2003 there are still many Companies receiving FDA 483's for lack of microbial monitoring using Air Samplers. This is alarming as CFU results dictate the release/hold decisions of product batches and are a reflection of product quality.

FDA Warning Letter Example (2016)

Air and surface sampling within all classified areas is not adequate based on the following;

1. *Viable particulate sampling was not conducted inside your Ante room, Gowning room, Buffer room and laminar flow hood during certification of these above classified areas.*

FDA Warning Letter Example (2014)

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically, your firm's procedures for monitoring ISO5 hoods are not suitable to ensure the quality of air. For example;

A. *During periods of production, your firm does not conduct viable air monitoring daily.*

There are many more with the same theme and with that in mind it is the authors opinion that this technical article should be dedicated to understanding active air sampling technology to help decision makers make informed decisions when reviewing the many makes and models currently available on the market.

What is Air Sampling Impaction Technology?

Aerosol Impaction Air Samplers are designed to have a sharp cutoff curve [1] and is the process in which particles are removed from an air stream by forcing the gases to make a sharp bend. Particles above a certain size possess so much momentum that they cannot follow the air stream and strike a collection surface such as a media plate which is available for later analysis of composition after an incubation period.

It is important to understand that not all Air Samplers have the same physical abilities in particle impaction capture. We all understand that a Particle Counter used widely in Environmental Monitoring programs has a set resolution based on the smallest particle size it can physically detect. The same holds true for Air Samplers as they have a limitation on the size of particles that will impact on the media. For Air Samplers this resolution is based on many physical factors that we will cover in this article. Let's first look closer at ISO 14698.

Why is ISO 14698 so important?

ISO 14698 Part 1 - Cleanrooms and associated controlled environments – Bio-contamination control - Part 1: General principles and methods was first released in 2003.

One significant part of ISO 14698 Part 1 is in the selection of an appropriate air sampling instrument outlined in Annex A. In Jan 2013 it was voted that this standard including Part 2 were further revised. This is a key indicator as to the importance of this standard to GMP and an indication that it firmly stands as an important GMP guidance document.

The main changes to ISO 14698 under discussion are:

- A new classification system for viable counts, split into surface and air cleanliness
- Guidance for assessing cleanrooms at start-up or after modifications for bio-burden, in a similar way that cleanrooms are currently assessed for particle counts
- Guidance on viable monitoring methods
- Recommendations for data analysis

With these significant revisions under discussion the scope of Air Samplers increases significantly and so it is very important make informed decisions on the selection of the right model for your application something that ISO 14698 Annex A has required since 2003.

Many eager salesmen will tell you that faster air sampling is the best option since it saves you time. But the key question to ask and to verify should be; is that model sufficient for my process?

Two main properties of an Air Sampler effect the instruments ability to capture and assist in incubation of the captured particles on a media plate.

Physical Efficiency [2] is the ability of the Air Sampler to collect various sizes of particles.

This efficiency is the same whether the particle is a micro-organism, carries a microorganism, or is an inanimate particle. Physical efficiency is based on many factors and the sample head geometry and Air Sampler internal design including the media height, even environmental conditions influence physical efficiency.

Biological Efficiency [2] is the efficiency in collecting microbe-carrying particles.

Biological efficiency will be lower than physical efficiency for a number of reasons, such as the survival of the micro-organisms during collection and the ability of the collection medium to support their growth.

According to ISO 14698-1 2003 Annex A.3.2, there are many factors to consider when choosing an Air Sampler. The sampling rate, duration of sample, and type of sampling device can strongly influence the viability of the micro-organisms that are collected. Because of the number and variety of microbial air sampling systems commercially available, the selection for a particular application should consider, as a minimum, the following factors: [2]

- type and size of viable particles to be sampled
- sensitivity of the viable particles to the sampling procedure
- expected concentration of viable particles
- ability to detect high or low levels of bio-contamination
- appropriate culture media
- time and duration of sampling
- ambient conditions in the environment being sampled
- disturbance of unidirectional airflow by sampling apparatus

One of the most fundamental selection CRITERIA in an Air Sampler is the resolution of the Air Sampler which can be equated to what is known as the d50 cutoff point.

We all know with a particle counter in pharmaceutical applications it must count 0.5um and 5.0um particles as a minimum so we make sure whatever particle counter model is selected it meets that requirement. For an Air Sampler and its ability to capture particle sizes of interest especially when we consider single rod bacteria diameters are potentially as low as 0.3um in diameter its becomes such a critical factor to select an air sampler with the right d50 (Resolution) and ability to collect the smallest particle size physically possible, so you are confident in the results obtained and further more confident in product batch released.

The d50 is based on particles greater than a certain aerodynamic size collected on the media plate (normally 90mm diameter plates are used) and particles less than that size passing through the Air Sampler. Fig.2 below provides a good overview of particles entering an impactor (Sample Head of Air Sampler) and the fluid dynamics as well as the flight path of various sizes of particles following the jet stream as it follows the airflow path.

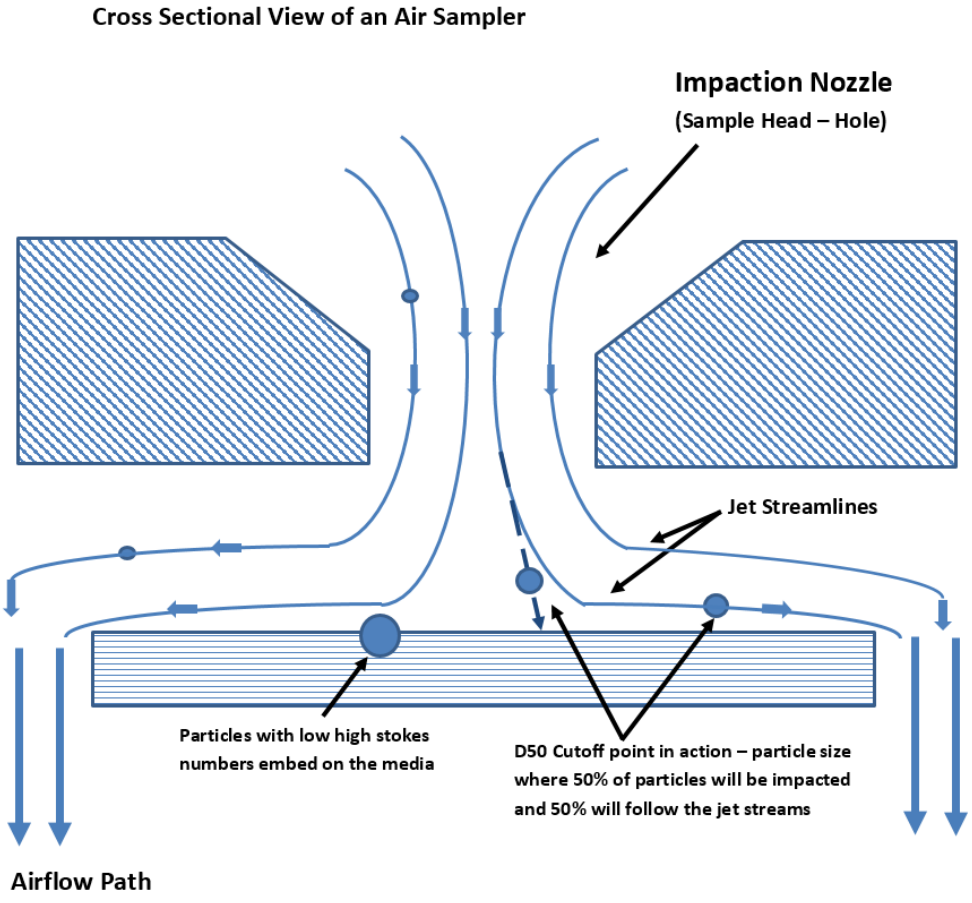


Fig.2 Flight path and jet streamlines of an Impactor head and media plate

With fluid dynamics and Air Sampler impaction technology an indicator of collection efficiency is the Stokes Number. The Stokes number (StK) [1] is a dimensionless number characterizing the behavior of particles suspended in a fluid flow. The stokes number is defined as the ratio of the characteristic time of a particle to a characteristic time of flow or of an obstacle and is based on the following formulae;

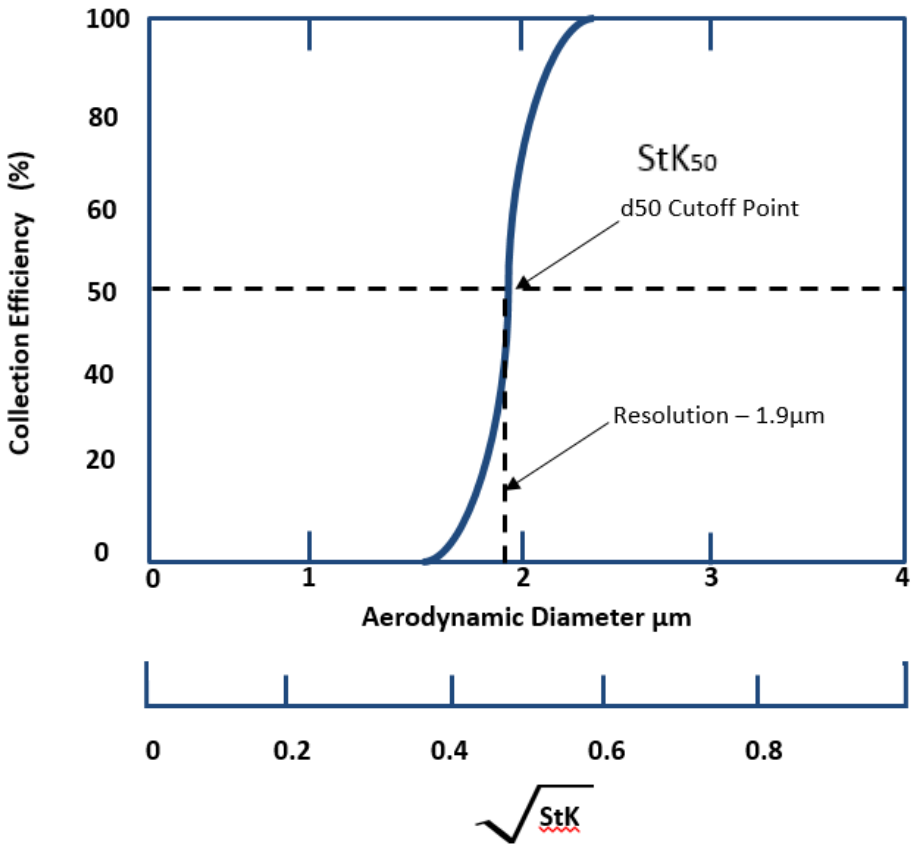
$$\mathrm{Stk} = \frac{t_0\, u_0}{l_0}$$

t_0 = is the relaxation time of the particle (the time constant in the exponential decay of the particle velocity due to drag).

u_0 = is the fluid velocity of the flow well away from the obstacle.

l_0 = is the characteristic dimension of the obstacle (typically its diameter).

Most well designed impactors can be assumed to be ideal and their efficiency curves characterised by a single number StK_{50}, the Stokes number that gives 50% collection efficiency [1]. StK_{50} is the location of the ideal cutoff curve that best fits the actual cutoff curve.



A particle with a low Stokes number follows fluid streamlines, while a particle with a large Stokes number is dominated by its inertia and continues along its initial trajectory.

The d50 is the 50% cutoff particle size where 50% are likely to be impacted and 50% are likely to pass through the Air Sampler. Hence the d50 can be seen as the resolution of the Air Sampler – the smallest particle size that can be physically be captured by the Air Sampler.

For those readers out there with a physics background you will also understand that the Reynolds Number comes into play. Quick reminder the Reynolds number is the ratio of inertial forces to viscous forces within a fluid which is subject to relative internal movement due to different fluid velocities. The physical design and flow rate of the Air Sampler greatly influence the Reynolds number. For impaction technology Air Samplers with a Reynolds number between 500 and 3000 are best suited [1]. (This science is also applied to isokinetic sampling of particles using isokinetic probes).

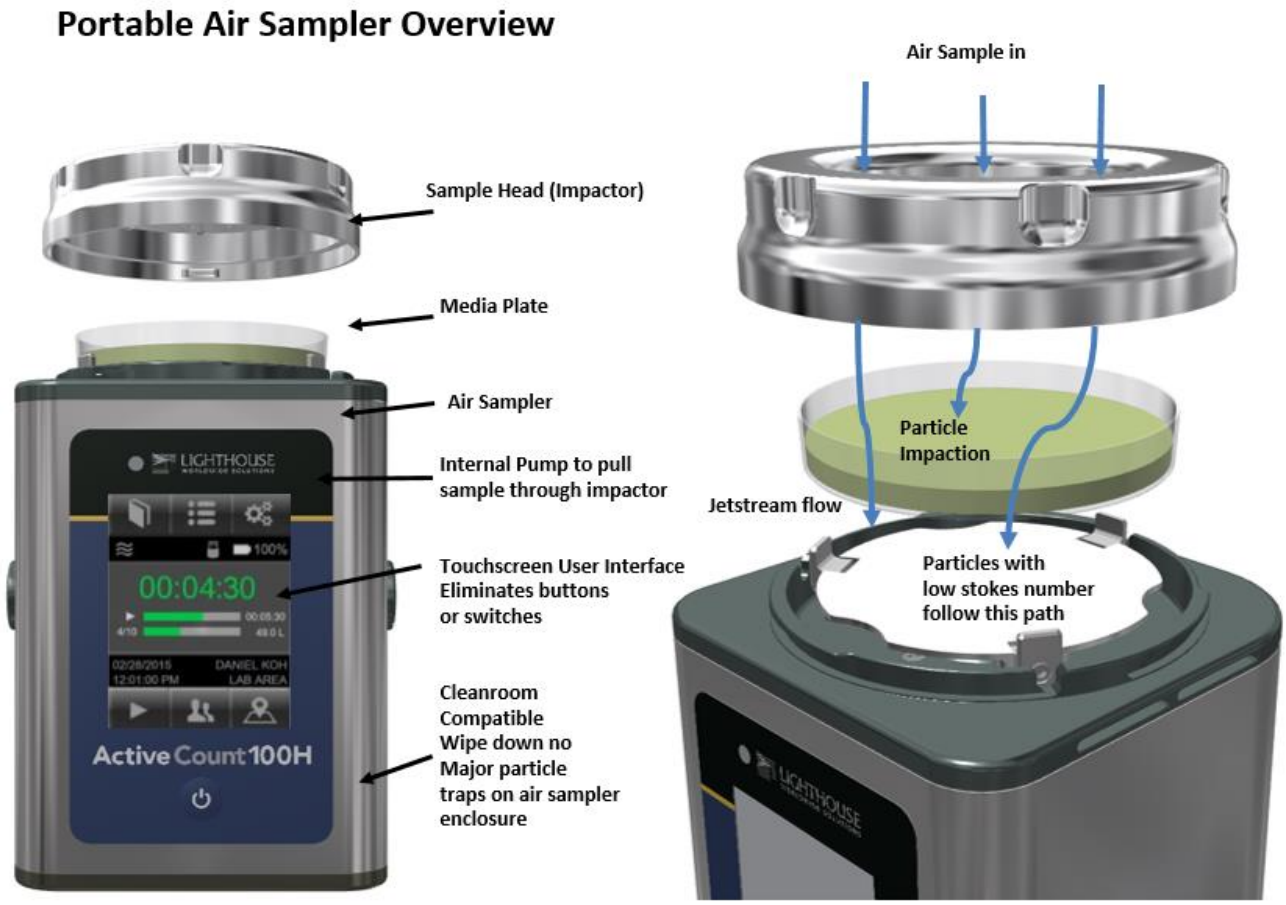


Fig.3 Portable Air Sampler Overview and Jetstream flow between sample head and media plate

Be aware out in the market Air Samplers have varying d50's some as high as 10um – that means anything below 10um is not impacted on the media. Try to explain that to an Auditor who has firm ISO 14698 and bacteria size knowledge.

To put all this into simple terms the sample head must be capable of effectively capturing particles in the air and maintaining uni-flow (laminar) conditions between the sample head and the media where the particles impact. Smaller particles are subject to airflow and larger particles maintain their flight path due to higher inertia. The d50 is the point where 50% off the smallest size particles impact on the media, in other words it's really the resolution of the impactor as the other 50% of these smaller particles will follow the airflow and not impact on the media.

The same holds true for remote sampling heads used in automated systems used in continuous monitoring where a remote vacuum source is controlled using mass flow meters for volume control. Fig.4 below gives more detail on the impaction technology and the collection efficiency of a remote air sampler.

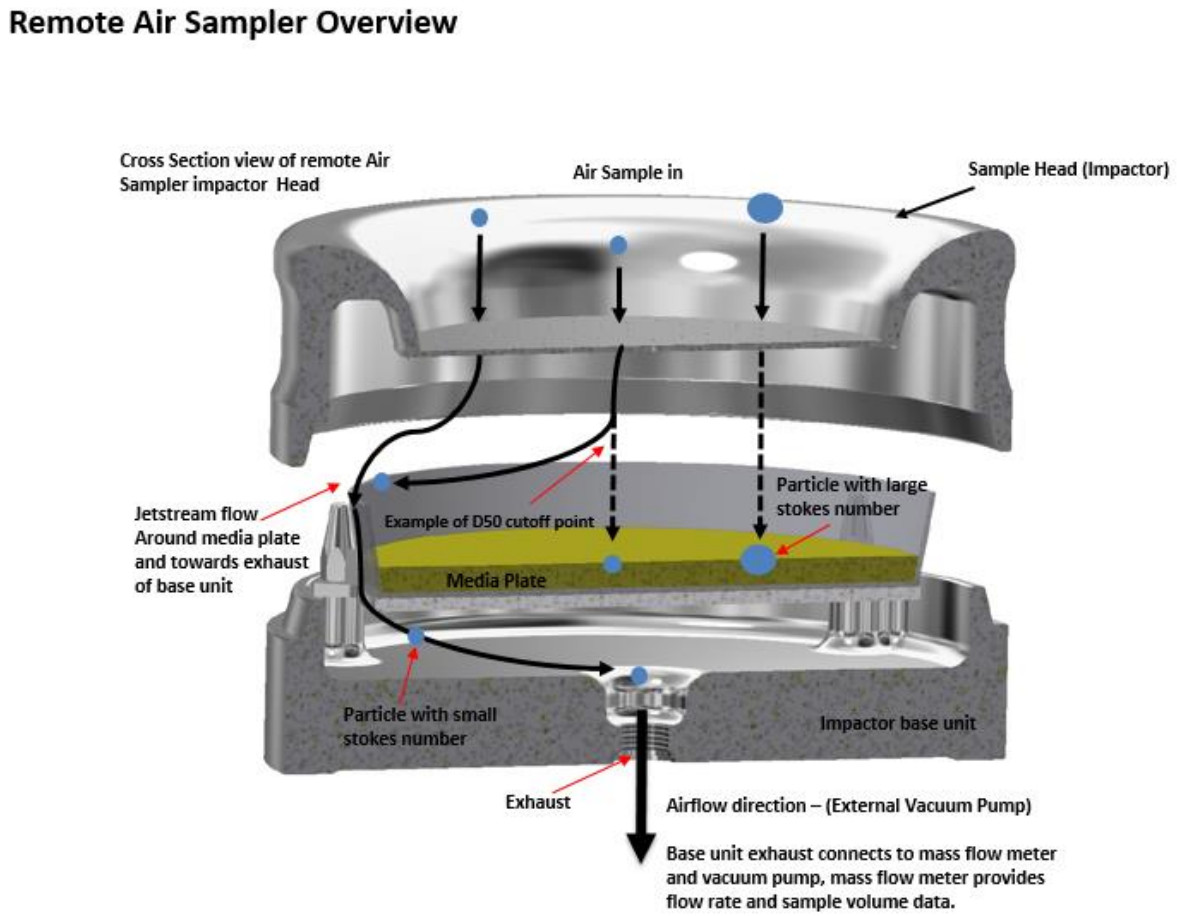


Fig.4 Remote Portable Air Sampler Overview and Jetstream flow between sample head and media plate

Looking at ISO 5 Classification tables in fig.1 we see that very tight limits are set for viable particles effectively expecting an average of zero CFU's over a 1000L of air sampled. It is critical that the device portable or remote air sampler used to sample with has been carefully selected.

Summary

With so many makes and models of Air Samplers on the market it is worth looking deeply into the specifications of each before committing to purchase. ISO 14698 Part 1 Annex A part A.3.4.2 recommends the Air Sampler impact velocity being high enough to allow the entrapment of viable particles down to approximately 1um and being low enough to ensure viability of viable particles as well has having a filtered exhaust.

Following cGMP and ISO 14644-1 the recommended selection criteria below should be used as a guidance in selecting an appropriate Portable Air sampler or Automated Air Sampling system and remember faster flow rate models do not indicate better collection efficiencies the key factor is the d50 and the criteria for active air sampling in sterile applications is for continuous monitoring during that process. Media can dry out faster under higher flow rates which requires more media plate changes.

Air Sampler Attributes

- Physical size – small footprint
- Material of construction of enclosure and sample head – Stainless Steel preferable
- Ability to wipe down easily – no crevices, buttons switches or particle traps
- Media plate holder – easy adjustable holder mechanism media dish diameters vary +/- 1mm to 3mm
- HEPA filtered exhaust - captures viable particles that have not impacted
- Touchscreen Interface - reduces contact and potential particle generation
- Battery Operated for better portability on portable units
- Remote sample options – offer more flexibility
- Gas connector options for testing gases to ISO 8573 requirements
- Local or field calibration options from supplier
- Easily autoclave parts
- Capture particles down to 1um to meet ISO 14698 requirements
- Validated for collection efficiency by third party

References;

[1] Aerosol Technology – Properties, Behavior and Measurement of Airborne Particles Second Edition (1999) William C Hinds, published by John Wiley & Sons.

[2] ISO 14698-1 Cleanrooms and associated controlled environments – Bio-contamination control – Part 1 General Principals and Methods, Annex B Guidance on validating air samplers, First Edition 2003-09-01.

[3] PICs GMP Guide to Good Manufacturing Practice for Medicinal Products – Annexes PE 009-13 (Annexes) 1 Jan 2017 – Annex 1: Manufacture of sterile medicinal products.

[4] Applied and Environmental Microbiology (1996) Evaluation of Three Portable Samplers for Monitoring Airborne Fungi. (Sarish K. Metha, S.K. Mishra and Duane L. Pierson)

[5] Aerosol Research and Exposure Assessment Laboratory, Department of Environmental Health, University of Cincinnati. (1998) Klaus Willeke, Ph.D Professor and Director. Particle Cut Size Evaluation of Air-O-Cell Sampler report.

[6] Investigation of Cut-Off Sizes and Collection Efficiencies of Portable Microbial Samplers. Maosheng Yao and Gediminas Mainelis (2006) published in Aerosol Science and Technology, 40:595-606, 2006.

[7] Collection Efficiencies and design of microbial air samplers, Journal of Aerosol Science, W. Whyte, C. Green and A. Albisu, Department of Mechanical Engineering, University of Glasgow. (2007).

[8] FDA published 483 Warning letters.

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20 Years Upper Management positions in Environmental Monitoring Systems Service, Design, Installation, Validation and ongoing support. Has worked on many Projects for top Life-Science companies assisting in procurement, delivery and compliance to ensure regulatory acceptance. Worked across the World on many projects in the UK, Ireland, Europe, Australia and now resides in Oregon USA. He can be contacted by email on jasonk@golighthouse.com or on LinkedIn and always welcomes queries and questions on Monitoring Systems connected to particle counters or environmental sensors.