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**TOTAL ORGANISMS PER LITER OF AIR
WITH PARTICLE SIZE DISTRIBUTION (TOLAp):
NEW UNIT OF MEASURE FOR THE TEST AND
EVALUATION OF BIODETECTORS**

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PREFACE

The work described in this report was authorized under MIPR Nos. 08-2164M and 09-2509. This work was started in May 2009 and completed in October 2009.

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CONTENTS

1.	BACKGROUND	7
2.	AGENT CONTAINING PARTICLES PER LITER OF AIR (ACPLA): AN IMPERFECT UNIT OF MEASURE	7
3.	BIOLOGICALLY ACTIVE UNITS PER LITER OF AIR (BAULA): AN INFORMATIVE BUT UNWORKABLE UNIT OF MEASURE	9
4.	RATIONAL FOR A NEW UNIT OF MEASURE: TOTAL ORGANISMS PER LITER OF AIR WITH PARTICLE SIZE DISTRIBUTION (TOLAp).....	9
5.	FINDINGS AND RECOMMENDATIONS.....	13
6.	FINAL RECOMMENDATION TO THE JOINT T&E OFFICE	15
	APPENDIX - MEASUREMENT OF TOLAp	17

FIGURES

1. Bioaerosols with the same ACPLA value can be vastly different8
2. Particle size range and distribution “shape” vastly affect detector testing12

TABLE

Simplified Conceptualization of the Calculation of TOLA.....	11
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TOTAL ORGANISMS PER LITER OF AIR
WITH PARTICLE SIZE DISTRIBUTION (TOLAP):
NEW UNIT OF MEASURE FOR THE TEST AND
EVALUATION OF BIODETECTORS

1. BACKGROUND

Detection of biological agents is a complex endeavor, which represents the intersection of the particular detection technology (e.g., PCR, light scatter, immunoassays), the nature of the biological agent (e.g., viral, bacterial, toxin), and the ambient environmental conditions. Therefore, testing and evaluation (T&E) of prototype biodetectors is complicated by the need to consider these variables and to carefully control testing conditions. These considerations can be further complicated, depending on the question of application of the data; that is, whether one is conducting a straight forward T&E assessment of competing biodetection technologies to determine their relative capabilities, or using the data to assess health effects and guide subsequent operational decisions. Ideally, a standard unit of measure for a bioaerosol challenge should be applicable to point and standoff detectors, and should be able to be translated into operational decisions.

2. AGENT CONTAINING PARTICLES PER LITER OF AIR (ACPLA):
AN IMPERFECT UNIT OF MEASURE

One historical unit of measure is Agent Containing Particles per Liter of Air (ACPLA). ACPLA can be easily measured for such biological agents as bacterial spores, which are robust enough to survive environmental and collection conditions, and can be cultured using standard laboratory methods. One can calculate the number of particles, which contain agent (i.e., organism or toxin); but, it is impossible to know how many organisms are present, because one particle could contain either one or thousands of organisms. For this reason, two aerosols that both have an ACPLA measure of, for example, 1 may pose vastly different threats (See Figure 1).

The ambiguity in a unit of measure such as ACPLA clearly poses a problem for operational decision making because it provides very little useful information about the total amount of agent present in the environment. From a solely T&E perspective, ACPLA provides a false sense of accuracy and prevents accurate comparisons between detector technologies. For example, suppose there are two competing technologies, Alpha, that can detect as few as 10 organisms, and Beta, that can detect a single organism. In this theoretical example, it is clear that Beta has 10 times the sensitivity of Alpha. However, using a unit of measure such as ACPLA, it is absolutely possible that Alpha and Beta could test identically, or that Alpha could actually test as the *better* technology. Using the same aerosols in Figure 1, Alpha and Beta would register as capable of detecting 1 ACPLA, hence test with equivalent sensitivity, if Alpha is presented with the 1 ACPLA aerosol that actually contains 10 agents. It is important to note that this inaccuracy is not just a theoretical concern. T&E personnel from multiple facilities

informed the Joint Independent Science Panel (JISP) that these types of inaccuracies do occur to some extent during detector testing.

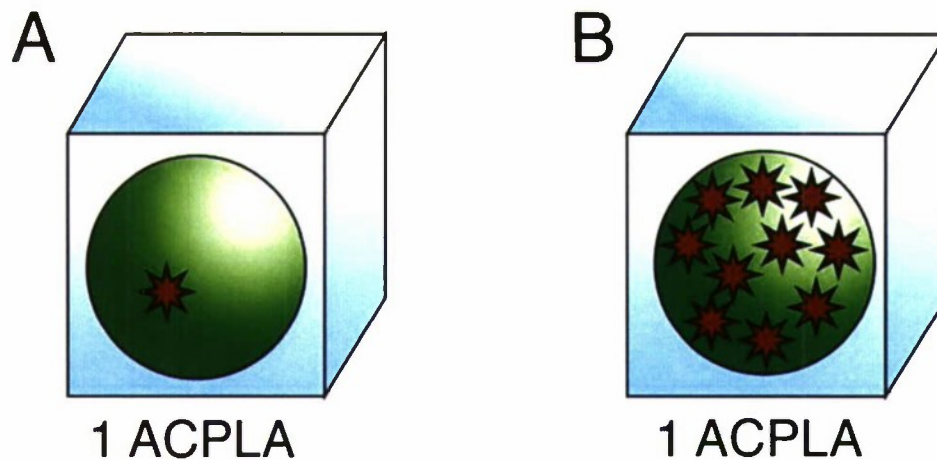


Figure 1. Bioaerosols with the same ACPLA value can be vastly different.

Both aerosol particles depicted above share an ACPLA value of 1; that is, there is one agent containing particle in the surrounding liter of air. However, the threat posed by the aerosol on the right [B] is substantially greater, as it contains 10 times as many biological agents as the aerosol on the left [A]. ACPLA contains no measurement of the total number of agents present, and hence provides very little information about the aerosols being detected.

Problems with ACPLA are further complicated by the fact that the size of the “agent containing particles” is not captured by the unit of measure. A bioaerosol with particles the size of peas poses a relatively low threat because the particles will settle to the ground quickly and can not be readily inhaled. Although this example is obviously extreme, the size of particles is important because particles beyond 10 microns in diameter tend to settle rather quickly and are not efficiently retained in the respiratory tract. This problem is additionally complicated because even in the sub 10 micron range particle size has a very measurable effect on infectivity and presentation of the disease by determining where in the airway – sinuses, throat, or deep bronchi, for example – the organisms are deposited. Furthermore, many standoff detection systems are very sensitive to particle size. Even if the total number of particles is the same (1000 per liter of air), a detector will react differently if those particles are 1 or 5 microns in diameter. Thus, if a particle size distribution (PSD) is not specified within the unit of measure, standoff detector technologies can not be properly assessed, compared, or evaluated. In summary, ACPLA contains very little useful information that describes the bioaerosol, no information about the total amount of agent or whether it is alive or dead, and can be very difficult to measure for agents other than bacterial spores.

3. BIOLOGICALLY ACTIVE UNITS PER LITER OF AIR (BAULA):
AN INFORMATIVE BUT UNWORKABLE UNIT OF MEASURE

A new unit of measure, Biologically Active Units per Liter of Air (BAULA), was recommended by a recent National Research Council (NRC) study. This study also recommended that an additional unit, *Bae*, representing the aerodynamic efficiency of bioaerosol particles, be added to the calculation. In theory, BAULA and *Bae* together provide a single unit of measure that is normalized to health effects, and thus is a useful unit with which to make operational decisions. For example, an arbitrary score of "10" for tularemia would indicate the same health hazard as would a score of "10" for anthrax, even though the number of pathogens and their PSD differed. Such a metric would address the deficiencies of ACPLA by considering the amount of biologically active agent, the agent's PSD, and the infectivity of any given biological agent.

However, in practice, BAULA is virtually impossible to calculate for several reasons. First, the infectivity of most List A biological agents is not known, nor is it likely to be known without enormous investments in developing new animal models for these diseases. Second, there is no legitimate way to calculate the viability of the biological agent once it has been distributed as an aerosol. Most agents other than anthrax spores are very labile in the environment and prone to inactivation as a result of temperature, humidity, ultraviolet radiation, dissemination technique, collection technique, and other environmental factors. Moreover, biodetectors based on immunological, nucleic acid, or light scattering detection cannot discriminate active from inactive agent and thus would be incapable of outputting a measurement in BAULA. Third, the effects of PSD, represented by *Bae*, on disposition of biological agents within the human target cannot be reliably estimated. Indeed, calculating health effects based on different particle sizes, as BAULA requires, is arguably impossible as sites of deposition, immune response, and breathing rates will likely vary between human and animal models and, indeed, between individuals. In addition, particle size calculations are readily achievable in a pristine laboratory environment, but are extremely difficult in the field where background particulates make up the majority of the sample. In summary, BAULA is a theoretically sound, but practically insolvable, unit of measure that oversteps the requirements of the T&E process.

4. RATIONAL FOR A NEW UNIT OF MEASURE: TOTAL ORGANISMS
PER LITER OF AIR WITH PARTICLE SIZE DISTRIBUTION (TOLAP)

With ACPLA insufficient, and BAULA/*Bae* impractical, a new unit of measure is clearly needed for T&E protocols. From a T&E perspective, viability of the biological agent in an aerosol is not a concern because the systems being tested detect only presence of an agent and can not discriminate dead from live agent. From the operational perspective, viability of a biological agent could be useful information; however, given that detection systems can not determine viability, all commanders will put their troops into a protective posture if any biological agent, living or dead, is detected. Therefore, the new measure should not consider the viability of the biological agent, i.e., live or dead is not an issue. The most important factor in a unit of measure is an accurate representation of the total amount of the biological agent present, followed by information on PSD. From a practical and economic point of view, the new unit of

measure should be able to be derived with current technology used in test chambers, ambient breeze tunnels, and field testing.

Key components of a unit of measure for bioaerosol testing and evaluation.

- *Live vs. dead agent is irrelevant since most detector technologies can not discriminate between the two states.*
- *The total number of agents present in a given volume of air is the most important measure of a bioaerosol.*
- *The particle size distribution of a bioaerosol can have a substantial impact on testing results and must be included in a unit of measure.*
- *The unit must be “measurable” in test chambers, ambient breeze tunnels, and in the field, using readily available technologies.*

Herein, we propose a new unit of measure, which combines Total Organisms per Liter of Air (TOLA) with PSD, to be represented as TOLAp. The logic for this unit of measure is straightforward. TOLAp contains the most important measure of a bioaerosol, the total amount of agent present, and describes the dissemination of that aerosol via the PSD. For T&E purposes, TOLAp can be calculated as long as one knows two things: the composition of what is disseminated, and the dynamics of the distribution, including PSD and flow rate. Crucially, both factors are within the control of the tester. The first requirement is to know how many organisms and how much inert material (e.g., filler) are being disseminated. Given a well designed sample preparation protocol, this information should be readily available. The second requirement is to know the PSD. For a solid powder, the PSD is largely dependent on the degree to which the sample has been milled and is readily available. From this point, the dissemination technique has little effect on the PSD. For liquid slurries, the calculation is more complex. Most liquid dissemination techniques are well characterized and generate a fairly consistent PSD. However, because the liquid component of a slurry will rapidly evaporate upon dissemination (leaving only solid components behind), the resulting PSD that is actually presented to a detector will be different. The PSD of this resulting aerosol can still be readily predicted or, in a well designed test chamber, measured directly assuming the composition of the starting material is well characterized. In fact some T&E facilities visited by the JISP have already created models that can make these particle size predictions. From an experimental point of view, it is preferable to measure PSDs directly via a particle sizer, as this method will account for any agglomeration or deagglomeration of particles after dissemination.

From here, it is relatively easy to conceptualize how TOLA would be calculated. Knowing the number of particles being distributed (preferably from direct measurement), the size of these particles (again, preferably from direct measurement), and their composition (from the sample preparation protocol), one can calculate the TOLA. A simplified example is provided in the table. A more formal description of TOLA calculations is provided in the Appendix.

Table. Simplified Conceptualization of the Calculation of TOLA.

No. of particles: 5 at 1 micron, 10 at 5 microns

Sampling rate: 1 liter per second

Sampling Time: 1 second

Total particles per liter of air: 5 at 1 micron, 10 at 5 microns

No. of organisms per particle: 1 for each 1 micron particle, 125 for each 5 micron particle

TOLA = number of organisms in 1 micron particles + number of organisms in 5 micron particles

TOLA = (1x5) + (10x125) = 1255

The number of particles of differing sizes (1 or 5 microns in this example) can be determined either through direct measurement using a particle sizer or from knowledge of the dissemination technique. From this value, the number of particles per liter of air can be computed using the sampling rate of the particle sizer (chosen as 1 liter per second for simplicity). Knowing the composition of these particles (from the sample preparation protocol), one can determine the number of agents per particle. By combining these values, the Total Organisms per Liter of Air (TOLA) can be calculated.

For the test paradigm to be relevant, the PSD must be controlled and applicable to real life biological warfare scenarios. For testing purposes, the PSD could be standardized within the respirable range, generally 1 -10 microns. Ideally, the PSD will match what is mostly likely to be experienced during a biological attack. Lacking this important piece of information, detectors could be tested at a variety of PSDs (i.e., tests could be conducted with 1-5 micron particles and separately with 5-10 micron particles). Beyond stating the range of the PSD, additional information should be recorded about the “shape” of the distribution. Again, the PSD “shape” stated in T&E requirements will ideally match the shape likely to be seen in a biological attack. Assuming this information is not forthcoming from the intelligence community, a reasonable assumption can be made that most aerosols will not be monodisperse particulates. As such, some arbitrary distribution shape may be necessary (i.e., a normal distribution centered at x with a standard deviation of y). Multiple well specified PSDs will be extremely important for testing standoff detectors, which may have vastly different responses, depending on the size of the particles. See Figure 2.

One can readily see that, within the limits of experimental error, the data required to compute the value for TOLA_p are available using equipment and procedures already in place in a sealed test chamber. More important, in many cases, one could go back into archival databases and perform these calculations on data from previous tests. Granted, PSDs were not specified or standardized in earlier tests, making direct comparisons of TOLA_p potentially problematic. However, even imperfect TOLA_p comparisons will be more useful than their ACPLA based counterparts.

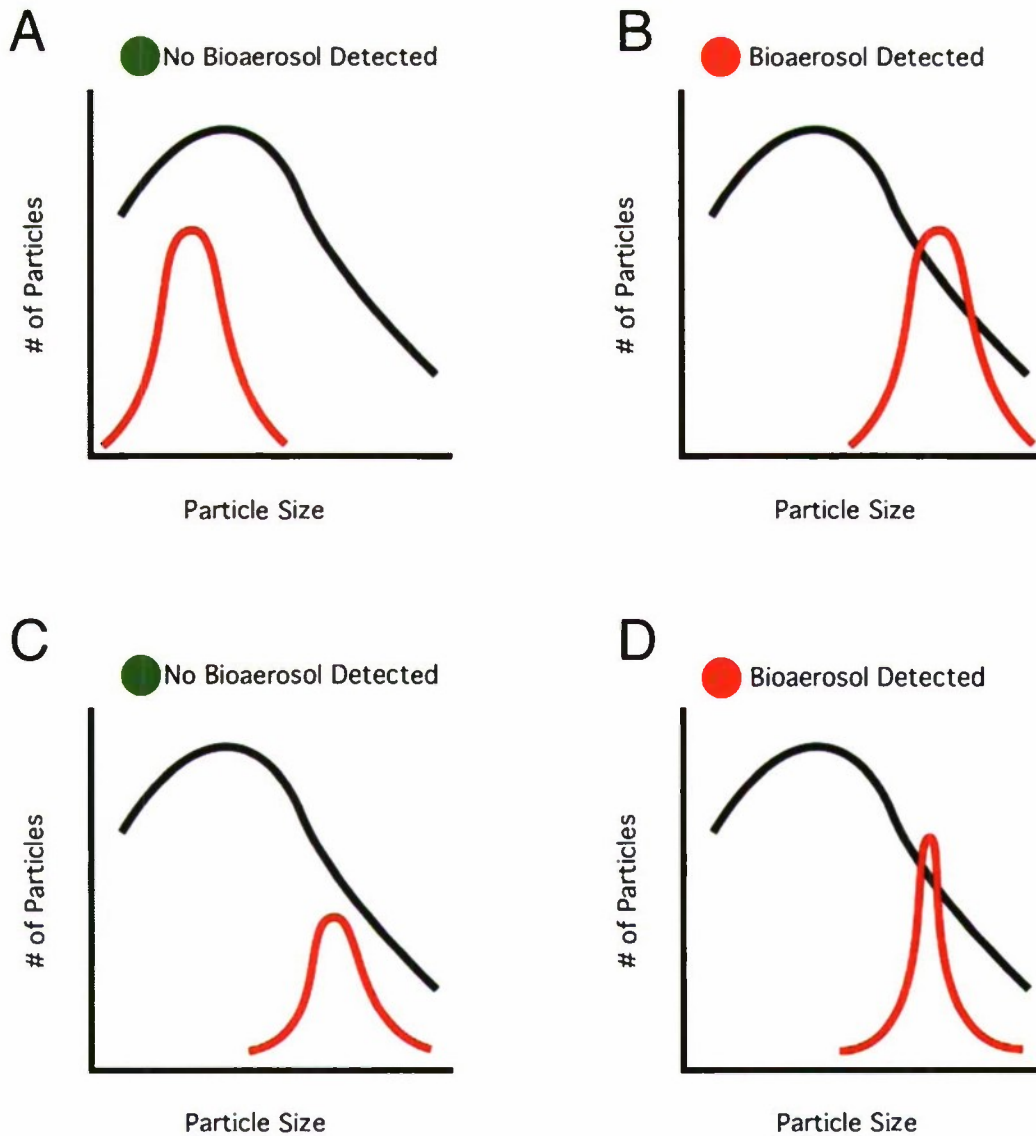


Figure 2. Particle size range and distribution “shape” vastly affect detector testing.

Standoff detectors have different detection thresholds at different particle sizes (depicted by the black lines above). Due to this variable sensitivity, different PSDs that contain an identical number of particles (the red lines) may or may not be detected [A,B]. Beyond the size range, the shape of this distribution can also affect detector performance as differently shaped distributions, which contain an identical range and number of particles and may or may not cross the detection threshold [C,D].

The progression from chambers to ambient breeze tunnels to large scale open air testing introduces additional variability and experimental error. Although particle sizing and binning is relatively straightforward in a chamber under well controlled conditions, outdoor testing introduces a considerable increase in background particulates (i.e., noise). The cleanest air in the desert around Dugway Proving Ground had background particulates of around 100 ppl; but, this can vary up to 5000 ppl even on a clear day. Some of this background can be readily subtracted from the overall particle count because they will not be in the particle sizes of

relevance to biological warfare (generally 1 to 10 microns). However, some of the background will fall within the 1-10 micron range, emphasizing the need for strict monitoring of the background at all times during the test. In breeze tunnel and field testing, the background particulates may far outnumber those of the bioaerosol such that simple background subtraction may not be possible. One potential technological fix would be to develop simple taggants for test aerosols that would allow particle sizers to discriminate between bioaerosol and background particles. Something as simple as green fluorescent protein (GFP) could act as a signal to a fluorescently gated particle sizer, indicating that a particular particle should be counted as part of the bioaerosol. GFP is a standard taggant in biological experiments and industrial scale fermentation processes and could readily be used in the environment without restriction. Notably, fluorescently enabled particle sizers are already commercially available.

5. FINDINGS AND RECOMMENDATIONS

JISP performed an extensive set of interviews with T&E personnel at multiple facilities across the country. By incorporating their comments, concerns, and experiences with the knowledge of the JISP subject matter experts, the JISP reached a consensus on a number of key findings.

a. Key Finding 1: From a T&E standpoint, viability of the organism in a bioaerosol is not a necessary component of a unit of measure.

Current detector technologies cannot differentiate between live and dead biological organisms. Therefore, these technologies are not directly compatible with a unit of measure that makes a distinction between live and dead organisms.

b. Key Finding 2: The most important aspect of a T&E unit of measure is the total number of organisms delivered to either a point or standoff detection system.

The main concern when testing and evaluating a biodetector is to determine its level of sensitivity. The most straightforward and robust way to measure this sensitivity is to determine the minimum number of organisms that can be detected in a given time frame. Notably, the numbers of organisms delivered to the detector are functions of known variables, such as the aerosol composition and the PSD, which are both within the control of the tester.

c. Key Finding 3: Improvements in the generation and dissemination of consistent, well characterized aerosols are necessary. In particular, the ability to present similar aerosols at all scales (test chamber, breeze tunnel, and field tests) is important for rigorous T&E.

To make accurate correlations and extrapolations between different scale tests, aerosols must be generated in a consistent, well characterized measure. Some facilities and T&E personnel indicated to the JISP that improvements were

necessary in this area. Improvements in aerosol generation at a large scale will be particularly important for standoff detector testing.

d. Key Finding 4: Background particulates can have important effects on detector testing and must be monitored and controlled.

Outside of a testing chamber, background particulates become a concern, particularly as detectors are tested at lower and lower levels of bioaerosol. During T&E of detectors, the background must be closely monitored. In field tests, and perhaps even in breeze tunnels, simulant aerosols could be fluorescently tagged, allowing referee particle sizers and other instruments to accurately count only the particles that are components of the bioaerosol (effectively subtracting out background particulates).

e. Key Finding 5: Standardization of testing facilities is not feasible; however, standardization of testing protocols and reagents provides many of the same benefits.

As long as testing chambers and facilities are well characterized, standardization of these facilities is not required. However, to make accurate comparisons across different test facilities and between detectors, the production and dissemination of test aerosols must be consistent. Several T&E personnel interviewed by the JISP indicated that the current lack of standardization had led to testing errors.

f. Key Finding 6: Additional research/information is required to accurately translate TOLAp, or any unit of measure, into an operation decision regarding health effects.

The main difficulty with the NRC's recommended unit of measure, BAULA, was that it required information such as LD50, amount of live agent, and health impacts of different PSDs. This information is not currently available and may not be available for many years to come. To make informed operational decisions, additional research must be conducted on infectivity of biological agents, likely dissemination techniques (which affect agent viability), and PSDs. Information on dissemination techniques and PSDs would serve a dual purpose by allowing more realistic testing of biodetectors.

g. Key Finding 7: T&E challenge level requirements should include an explicit sampling time component.

Many detector technologies collect samples over various lengths of time. The longer the technology sample collection takes, the higher the sensitivity. Several T&E community members stated concerns that challenge level requirements sometimes lacked a sampling time frame, or that the time requirements did not remain constant throughout the T&E process.

6. FINAL RECOMMENDATION TO THE JOINT T&E OFFICE

JISP recommends that a new unit of measure be introduced for test and evaluation (T&E) of point and standoff biotectors. This unit of measure, Total Organisms per Liter of Air with PSD TOLAp, contains all of the key components necessary to accurately test and evaluate point and standoff detectors. Conveniently, TOLAp applies to all types of agents, including spores, vegetative bacteria, and viruses. TOLAp can also be applied to toxins by conceptually classifying each molecule of toxin as an "organism." Thus, TOLAp can be used as a unit of measure for all agent classes specified by the Joint Test and Evaluation Office (JTEO). JISP recommends that challenge level requirements for biotectors be stated in TOLAp with a given PSD (or several different PSDs) and sampling time. Importantly, TOLAp is measureable with current referee equipment, and legacy data should be readily convertible to TOLAp.

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APPENDIX

MEASUREMENT OF TOLAp

Knowledge of the particle size distribution (PSD) is required to determine the total organisms per liter of air (TOLA); thus, TOLAp is readily generated while determining the TOLA. The following calculation assumes a particle counter, which provides the number of particles in a given size range (bin) as a function of particle size, taken here as the radius. This type of particle sizer is readily available and already in use in the bioaerosol testing facilities visited by the Joint Independent Science Panel. Although different particle sizers may operate on different principles (e.g., light scattering intensity, aerodynamics, etc.), they all provide the number of particles as a function of size (equivalent radius). If the particles are spherical, then all are essentially the same. Although disseminated biological aerosols (e.g., organisms, filler, surfactants, and/or other extraneous materials) may not always be strictly spherical, this source of error should fall within an acceptable range for T&E (which is an inherently variable process). Because many organisms are not spherical at all, their aggregates in the 1-10 micron size range aerosol will generally be spherical or nearly so.

Two parameters from the particle counter are needed: sampling flow rate (F , L/min) and the sampling time (t , min) used to obtain a given data set. Depending upon the instrument, F may or may not be under the experimenter's control, but will be known. The time t is usually under experimenter control, with larger sampling times leading to more precise PSDs. Depending on the sampling time of the detector, as well as the time course of the entire test, it is likely that a number of separate measurements will be taken during the course of the run. Clearly, multiple data sets can be suitably averaged, so only a single calculation will be used here. The data are normally collected numerically, and are displayed as a histogram in the figure. Here, N_i is the number of particles per liter of air in a bin of size ΔR centered at R_i .

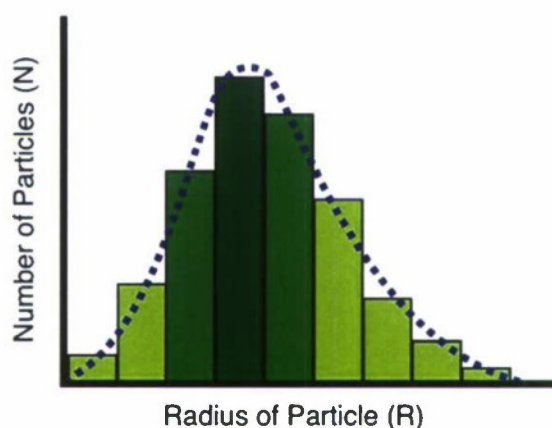


Figure. Hypothetical Output from a Particle Size Counter

Particle sizers “count” the number of particles of various hypothetical radii in various size bins (the green boxes). The various bins can be fit to a distribution curve (blue line), if necessary.

The actual data from the counter is the number of particles in the size bin N_i' (the number of particles collected by the detector in a given sampling period), which can be converted to N_i by dividing N' by Ft ($N_i = N'/(Ft)$). Although Ft is a constant, one could alternatively use N' in the calculation and then divide by Ft at the end.

Now, the total volume of particles contained in 1 liter of air (V) is given by $4/3\pi \sum N_i R_i^3$. (This sum is derived from the equation for the volume of a sphere: $4/3\pi r^3$). If v is the equivalent volume of one organism in the particle (i.e., volume of the organism, plus any surrounding filler and/or other material), then:

$$TOLA = V/v \quad (1)$$

The parameter V may be obtained from the composition of the disseminated aerosol, plus knowledge of the average volume of the organism (V_o). For a dry powder, where w is the weight fraction of the organisms in the powder, D is the bulk density of the powder, and D_o is the density of the organism, then $V = (D_o V_o)/(Dw)$. The values of w and D are known from the powder formulation and are under the control of either the experimenter or the tester. The values of D_o and V_o should be available for each organism, and can generally be treated as constants. The values of D_o are expected to be near 1 gram/cubic centimeter, and it may be that this value can be used for all organisms without introducing significant error. If an aqueous slurry is disseminated instead of a dry powder, the value of w to be used in the above expression must be corrected for the weight of water because it will evaporate after dissemination, leaving the dry aerosol. The value is corrected by dividing the weight fraction of agent (organisms) in the slurry by one minus the weight fraction of water in the slurry. To summarize then, in terms of the experimental (measured) parameters,

$$TOLA = (4\pi w D)/(3V_o D_o) \sum N_i R_i^3 \quad (2)$$

If the data from the particle counter can be approximated by an analytical function (e.g., normal, log normal, Poisson, etc.) as represented by the dotted line in the figure, then the summation can be replaced by an integral.

$$TOLA = (4\pi w D)/(D_o V_o) \int N(R) R^2 dR \quad (3)$$

A note on the “p” in $TOLA_p$; clearly, the PSD has been measured, and as stated in the body of this report, can be characterized in a number of ways. If a single parameter is desired, perhaps the best one to use is the volume weighted average radius because it reflects the average size containing the most particles. Finally, it may be noted that with the data collected, it is also possible to weight the distribution for inhalation effectiveness as a function of size if so desired, either now or at some future time.